ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2022 January 25; 11(1): 1-89

Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents

Bimonthly Volume 11 Number 1 January 25, 2022

World Journal of Virology

Bimonthly Volume 11 Number 1 January 25, 2022

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
January 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 1-19

DOI: 10.5501/wjv.v11.i1.1

ISSN 2220-3249 (online)

OPINION REVIEW

Heart failure in COVID-19 patients: Critical care experience

Kevin John John, Ajay K Mishra, Chidambaram Ramasamy, Anu A George, Vijairam Selvaraj, Amos Lal

ORCID number: Kevin John John 0000-0003-3382-0294; Ajay K Mishra 0000-0003-4862-5053; Chidambaram Ramasamy 0000-0002-0737-4000; Anu A George 0000-0002-6769-732X; Vijairam Selvaraj 0000-0002-8507-9891; Amos Lal 0000-0002-0021-2033.

Author contributions: John KJ, Lal A and Mishra AK were responsible for the conception and design of the work, screening of papers, data analysis and drafting the manuscript; Ramasamy C and George AA were responsible for the literature review; Selvaraj V, Lal A and Mishra AK reviewed and revised the preliminary draft; Lal A gave the final approval for the published version of the manuscript.

Conflict-of-interest statement: Authors claim no conflicts of interest.

Country/Territory of origin: United States

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C

Kevin John John, Department of Critical Care, Believers Church Medical College Hospital, Thiruvalla 689103, India

Ajay K Mishra, Chidambaram Ramasamy, Anu A George, Department of Internal Medicine, Division of Cardiovascular Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Vijairam Selvaraj, Division of Medicine, The Miriam Hospital and Warren Alpert Medical School of Brown University, Providence, RI 02906, United States

Amos Lal, Department of Medicine, Division of Pulmonary and Critical Care medicine, Mayo Clinic, Rochester, MN 55902, United States

Corresponding author: Amos Lal, FACP, MBBS, Assistant Professor, Department of Medicine, Division of Pulmonary and Critical Care medicine, Mayo Clinic, 200 First st, SW, Rochester, MN 55902, United States. lal.amos@mayo.edu

Abstract

Patients with heart failure (HF) may be at a higher risk of coronavirus disease 2019 (COVID-19) infection and may have a worse outcome due to their comorbid conditions and advanced age. In this narrative review, we aim to study the interaction between COVID-19 and HF from a critical care perspective. We performed a systematic search for studies that reported HF and critical care-related outcomes in COVID-19 patients in the PubMed and Medline databases. From a total of 1050 papers, we identified 26 that satisfied the eligibility criteria for our review. Data such as patient demographics, HF, intensive care unit (ICU) admission, management, and outcome were extracted from these studies and analyzed. We reported outcomes in heart-transplant patients with COVID-19 separately. In hospitalized patients with COVID-19, the prevalence of HF varied between 4% and 21%. The requirement for ICU admission was between 8% and 33%. HF patients with COVID-19 had an overall mortality rate between 20% and 40%. We identified that HF is an independent predictor of mortality in hospitalized COVID-19 patients, and patients with HF were more likely to require ventilation, ICU admission and develop complications. Patients with HF with reduced ejection fraction did worse than those with HF with midrange ejection fraction, and HF with preserved ejection fraction. COVID-19 patients with HF should be identified early and managed aggressively in an attempt to improve outcomes in this cohort of patients.

Key Words: Heart failure; COVID-19; Critical care; Intensive care; Mortality

Grade D (Fair): D
Grade E (Poor): 0

Received: March 19, 2021
Peer-review started: March 19, 2021
First decision: May 5, 2021
Revised: May 9, 2021
Accepted: November 25, 2021
Article in press: November 25, 2021
Published online: January 25, 2022

P-Reviewer: Barison A, Jha AK, Velikova TV
S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

Core Tip: Heart failure (HF) can lead to worse outcomes in coronavirus disease 2019 (COVID-19). Moreover, critically ill patients with COVID-19 can develop *de novo* HF. Patients with COVID-19 and HF are more likely to require ventilation, ICU admission and develop complications. HF is an independent predictor of mortality in hospitalized COVID-19 patients and therefore, HF should be identified early and managed aggressively in an attempt to improve outcomes in critically ill patients.

Citation: John KJ, Mishra AK, Ramasamy C, George AA, Selvaraj V, Lal A. Heart failure in COVID-19 patients: Critical care experience. *World J Virol* 2022; 11(1): 1-19
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.1

INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged from China in December of 2019 and continues to be a public health emergency of international concern. As of March 12, 2021, more than 118 million cases have been diagnosed worldwide with 29.3 million patients reported from the United States. Patients with pre-existing comorbidities, cardiac dysfunction and immunocompromised status continue to be at high risk of morbidity and mortality. The literature on COVID-19 infection in patients with heart failure (HF) is limited. Patients with HF may be at higher risk of COVID-19 infection and have a worse outcome due to their comorbid conditions and advanced age.

The currently available literature regarding the role of critical care and a multidisciplinary approach in treating patients with HF and COVID-19 infection, remains scarce. In this narrative review, we aim to study the interaction between COVID-19 and HF from a critical care perspective. We also aim to explore the various outcomes as reported in the literature in this subgroup of patients and to provide a summary of the current evidence and practices in the management of HF in COVID-19 patients in the intensive care unit (ICU).

In this review, we have attempted to summarize all the articles published on the presentation and management of patients with COVID-19 and HF. We searched the PubMed and Medline database for the MeSH terms "COVID-19", "heart failure" and" critical care". Studies published in English, including adults with HF and COVID-19 infection were eligible to be included in this review (Figure 1). All studies published before March 2021 were included. Studies that provided details on patient demographics, HF, ICU admission, management, and outcome were analyzed. Various treatment details including medications such as beta blockers, angiotensin converting enzyme inhibitors (ACEi), aldosterone receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNi), automatic implantable cardioverter-defibrillator, permanent pace-maker and cardiac resynchronization therapy were included. Critical care details that were obtained were the type of organ dysfunction, the requirement of non-invasive and invasive ventilation, administration of vasopressor support, extra-corporeal membrane oxygenation (ECMO) and outcome. Articles that did not have the patient's details, opinions, comments, letters, and articles not published in English were excluded from the analysis. Studies that included cardiac transplant patients were analyzed separately. Two independent clinicians reviewed all articles.

As of March 2021, a total of 1050 papers were identified (Figure 1). Among these, 26 satisfied the eligibility criteria for our study. One study was a prospective cohort study, while all others were retrospective studies. Studies were principally published from North American and European nations. There were significant differences in the study design, data collection and measured outcomes among the studies which made the comparison of data difficult. Therefore, we divided the studies into four categories and reported the outcomes separately. The four categories were: (1) Studies highlighting prevalence of HF, requirement of ICU level of care and outcomes in hospitalized COVID-19 patients; (2) Studies reporting outcomes in COVID-19 patients admitted to ICU; (3) Studies reporting outcomes in HF patients with COVID-19; and (4) Studies reporting outcomes in heart-transplant patients with COVID-19 (Figure 2).

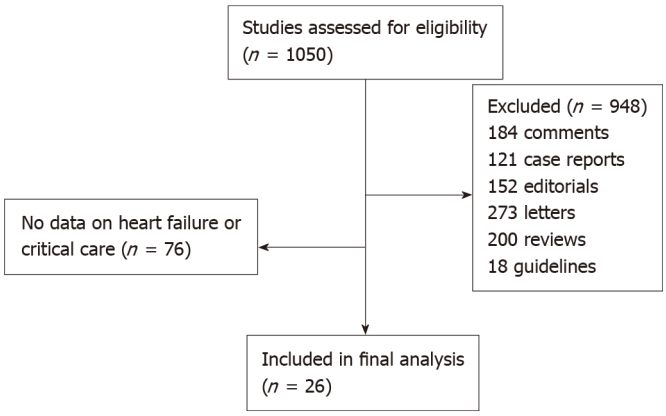


Figure 1 CONSORT diagram.

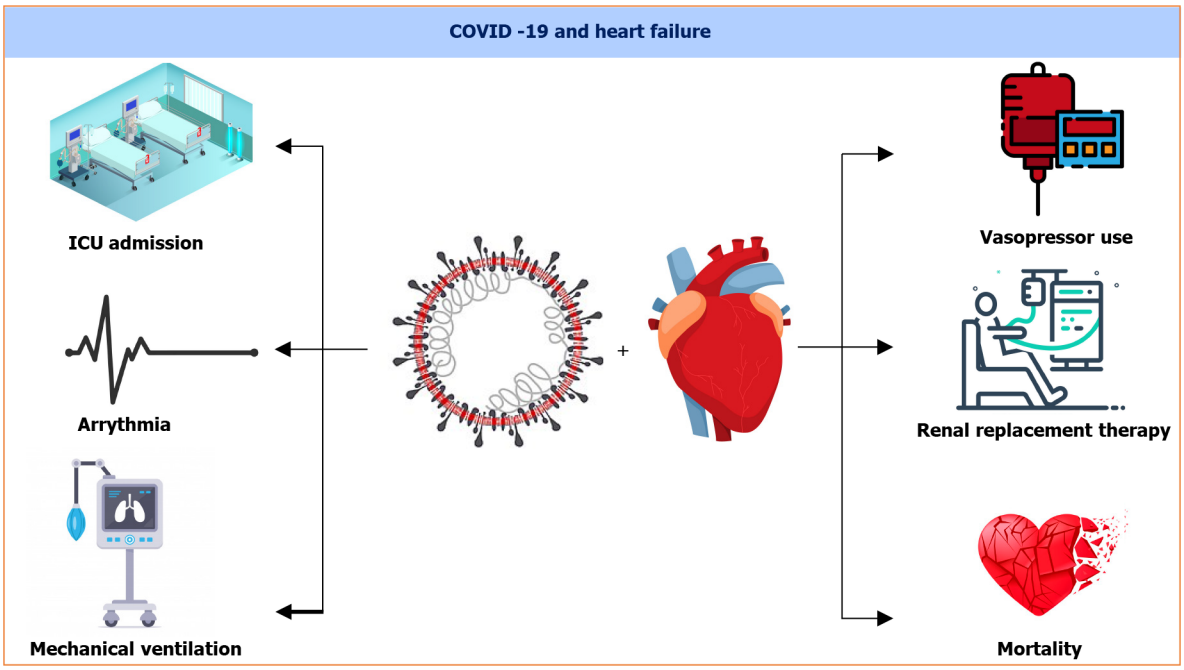


Figure 2 Coronavirus disease 2019 and heart failure.

INCREASED RISK OF HEART FAILURE IN COVID-19 PATIENTS

Among studies that reported outcomes in hospitalized patients with COVID-19, we found 11 studies that provided data on HF and ICU admission (Table 1)[1-11]. The total number of patients in this group was 9420, with studies from the United States contributing the maximum number of patents. The diagnosis of COVID-19 was uniformly established with reverse transcription polymerase chain reaction (RT-PCR) in all of the patients. The proportion of patients with pre-existing HF varied from 1% to 21%, which was almost ten times the community prevalence of HF, as reported by the Framingham study[12]. This suggests that patients with HF are more likely to require hospitalization for COVID-19. Zylla *et al*[3] reported that 3% of patients developed newly diagnosed (*de novo)* left ventricular (LV) dysfunction after admission, while Zhou *et al*[9] and Chen *et al*[10] reported a number close to 25%. This highlights the fact that HF can be both a risk factor, as well as a complication of COVID-19. Most studies reported a male preponderance with a mean age above 60 years. The requirement for ICU admission was between 8% and 33%. Patients with HF were more likely to require mechanical ventilation and develop complications such as thromboembolism, sepsis, stroke and acute kidney injury. The overall mortality rate for hospitalized patients with COVID-19 was between 4% and 40%. Inciardi *et al*[1] noted that chronic therapy with an ACEi, ARB, or ARNI had to be discontinued in 77% of cases

Table 1 Studies highlighting prevalence of heart failure, requirement of intensive care unit level of care and outcomes in hospitalized coronavirus disease 2019 patients, *n* (%)

No.	1	2	3	4	5	6	7	8	9	10	11
Ref.	Inciardi *et al*[1]	Singer *et al*[2]	Zylla *et al*[3]	Russo *et al*[4]	Bhatla *et al*[5]	Peltzer *et al*[6]	Lala *et al*[7]	Shi *et al*[8]	Zhou *et al*[9]	Chen *et al*[10]	Jarrett *et al*[11]
Country	Italy	United States	Germany	Italy	United States	United States	United States	China	China	China	United States
Total number of patients	99	737	166	414	700	1053	2736	416	191	274	2634 (all patients died)
Patients with chronic heart failure	21 (21)	39 (5)	-	46 (11.1)	88 (13)	79 (7.5)	276 (10.1)	17 (4.1)	-	1 (< 1)	291 (11.1)
Newly diagnosed LV dysfunction	-	-	5 (3)	-	-	-	-	-	44 (23)	43/176 (24)	-
Study type	RC, single centre	RC, single centre	RC,multicenter	RC, multicenter	RC, single centre	RC, multicenter	RC, multicenter	RC, single centre	RC, multicenter	RC, single center	RC of in-patients who died of COVID-19 in a single center
Age (mean ± SD)	67 ± 12	60 ± 18	64.1 ± 16.7	66.9 ± 15.0	50 ± 18	62 ± 17	66.4 (median)	64 (range: 21-95)	56 (IQR: 46-67)	62 (IQR: 44-70)	Range: 21-107
Male	8 (81)	423 (57)	108 (65.1)	253 (61.1)	315 (45)	653 (62)	1630 (59.5)	205 (49.3)	119 (62)	171 (62)	1664 (63.2)
LVEF, % (mean ± SD)	48 ± 14	-	53.0 ± 12.3	-	-	HFrEF: 41 (3.8)	-	-	-	-	-
ICU admission	12 (12)	59 (8)	65 (39.2)	-	79 (11.28)	349 (33.14)	-	-	50 (26)	-	1299 (49.3)
NIV	18 (19.1)	40 (5)	39 (23.5)	-	-	-	-	32 (7.7)	26 (14)	102 (37)	-
IV	2 (2)	149 (20.2)	37 (22.3)	-	-	327 (31.05)	307 (11.2)	51 (12.3)	32 (17)	17 (6)	140 (53.2)
ECMO/ICD/CRT/PPM	-	-	PPM:3 (1.8), ICD:2 (1.2), ECMO:3 (1.8)	-	-	-	-	-	ECMO: 3 (2)	ECMO: 1 (<m1)	-
Vasopressor	-	-	30 (18.1)	-	-	323 (30.67)	-	-	-	-	-
Hospital LOS, d, (mean ± SD)	11.4 ± 6.5	4.7 ± 3.0	10.5 (IQR 5-22 d)[ICU stay: 8 (IQR 4-22.5)]	-	-	-	5.75 (IQR :3.36-9.56)	-	11 (7–14) [ICU stay: 8 (4–12)]	-	-
Complications	Venous thrombo-embolism: 12 (12),	-	-	-	-	Bacteremia:100 (9.5), VTE: 54 (5.13),	Hospitalized at time ofstudy	CRRT: 2 (0.5), ARDS: 97 (23.3), Coagulation	RRT: 10 (5), sepsis:112 (59), respiratory failure: 103 (54),	AKI: 29 (11), CRRT: 3 (1),	-

	Arterial thrombo-embolism: 3 (3), septic shock/sepsis: 6 (6)					stroke/TIA:18 (1.71), AKI requiring RRT: 34 (3.23)	publication: 1098 (40.1)	disorders: 12 (2.9), hospitalized at end of study period:319 (76.7)	ARDS: 59 (31), septic shock: 38 (20), coagulopathy: 37 (19), secondary infection:28 (15)	sepsis: 179 (65), DIC: 21 (8), shock: 46 (17), ALI: 13 (5)	
Mortality	26 (26)	68 (9)	26 (15.7)	107 (25.8)	30 (4)	184 (17.47)	506 (18.5)	57 (13.7)	54 (28.2)	113 (40)	2634 (100)

- Signifies that the variable was not reported in the study.

LV: Left ventricle; RC: Retrospective cohort; LVEF: Left ventricle ejection fraction; HFrEF: Heart failure with reduced ejection fraction; ICU: Intensive care unit; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation; ICD: Implantable cardiovascular-defibrillator; CRT: Cardiac resynchronisation therapy; PPM: Permanent pacemaker; LOS: Length of stay; IQR: Inter-quartile range; VTE: Venous thrombo-embolism; TIA: Transient ischemic attack; AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; RRT: Renal replacement therapy; ARDS: Acute respiratory distress syndrome; ALI: Acute liver injury; DIC: Disseminated intravascular coagulation.

because of severe hypotension, and patients who died were more likely to have a history of HF. In the same study, the mortality rate remained higher in patients with cardiac disease compared to those without (26% *vs* 9%; $P = 0.039$), even after excluding patients who were denied intubation due to comorbidities or age. Another study used multivariate regression modelling to identify an increased risk of atrial fibrillation among COVID-19 patients with HF (RR 1.88; $P = 0.023$), which in-turn increased the odds of ICU or intermediate care ward admission (OR 2.37; 95%CI: 1.10-5.09; $P = 0.03$) [4,5]. HF was also linked to brady-arrhythmias (OR 9.75; 95%CI: 1.95-48.65) by a separate group of investigators[5]. Three separate meta-analysis identified that HF was independently associated with an increased risk of mortality in patients with COVID-19[13-15].

NEED FOR INTENSIVE CARE UNIT LEVEL OF CARE

We found six studies that reported HF data in COVID-19 patients who were admitted to the ICU, while excluding patients who were hospitalized without requiring ICU care (Table 2)[5,16-20]. These studies had a total patient number of 6539, with a major patient population contributed from the United States. The mean age in this group of patients was above 60 years and there were more men than women. Between 10% and 43% of these patients had pre-existing HF. This range was higher than what was observed among hospitalized patients overall. It was also noted that more patients developed *de-novo* HF in this group (up to 33%)[16]. The average ICU length of stay was between 2 to 5 weeks and a majority of patients required ventilatory assistance. In addition, advanced life-sustaining supportive interventions such as ECMO were also utilized by 3% to 15% of these patients. As a group, these patients had a higher mortality rate, which was as high as 52%. A cross-sectional observational multi-centre nationwide survey in Italy identified that obesity, chronic kidney disease and

Table 2 Studies reporting outcomes in coronavirus disease 2019 patients admitted to intensive care unit, *n* (%)

No.	1	2	3	4	5	6
Ref.	Zeng *et al*[16]	Petrilli *et al* [17]	Bhatla *et al* [5]	Hayek *et al*[18]	Iaccarino *et al* [19]	Arentz *et al*[20]
Country	China	United States	United States	United States	Italy	United States
Total number of patients in ICU	35	990	79	5019	395	21
Patients with chronic heart failure	NR	189 (19.1)	22 (28)	512 (10.20)	60 (15.2)	9 (42.9)
Newly diagnosed LV dysfunction/acute heart failure	5 (14)	-	-	166 (3.3)	-	7 (33.3)
Study type	Retrospective cohort, single centre	Prospective cohort, single centre	Retrospective cohort, single centre	Retrospective cohort, multicenter	Cross-sectional study, multicenter	Retrospective cohort, single centre
Age, (mean ± SD)	64.00 (59.50–68.00)	68 (58-78)	63 ± 16	60 ± 15, 63 ± 14[1]	68.9±0.7	70 (43-92) range
Male	23 (66)	656 (66.3)	40 (51)	3165 (63.06)	291 (73.7)	11 (52)
Risk factors	Hypertension: 13 (37), coronary artery disease: 2 (6), arrhythmia: 2 (6), valvular disease:1 (3), diabetes: 10 (29), COPD: 1 (3)	Diabetes: 389 (39.3), asthma or COPD: 169 (17.1), chronic kidney disease: 259 (26.2), cancer: 138 (13.9)	Coronary heart disease: 21 (27), diabetes mellitus :35 (44), hypertension: 62 (78), atrial fibrillation history: 5 (6), obstructive sleep apnea: 23 (29), COPD: 14 (18), liver disease: 14 (18), chronic kidney disease: 16 (20), current tobacco: 4 (5)	Current or former tobacco use: 2174 (43.31), diabetes mellitus: 2110 (42.04), hypertension:3086 (61.48), coronary artery disease:676 (13.46), chronic obstructive pulmonary disease: 43 (0.85), chronic or end stage kidney disease: 819 (16.31), active malignancy:227 (4.52)	Hypertension: 256 (65.3), obesity: 49 (12.4), diabetes: 90 (22.8), COPD: 41 (10.4), CKD: 34 (8.6), coronary artery disease: 62 (15.7)	Asthma: 2 (9.1), chronic obstructive pulmonary disease: 7 (33.3), diabetes: 7 (33.3), obstructive sleep apnea: 6 (28.6), chronic kidney disease: 10 (47.6), end-stage kidney disease: 2 (9.5), history of solid organ transplant: 2 (9.5), cirrhosis: 1 (4.8), immunosuppression: 3 (14.3)
HFrEF,	5 (14)	-	-	-	-	-
HFpEF	0 (0)	-	-	-	-	-
Drugs	-	-	-	-	ACE-inhibitors: 97 (24.6), ARB: 66 (16.7), beta-blockers: 96 (24.3), ca-antagonists: 31 (7.8), diuretics: 58 (14.7), alpha-blockers: 7 (1.8)	-
ICD	-	-	5 (6)	-	-	-
Ventilation	35 (100)	647 (65.35)	-	-	-	19 (90.5)
NIV	17 (49)	-	-	-	-	4 (19)
IV	18 (51)	647 (65.35)	-	3663 (72.98)	-	15 (71)
ECMO	5 (15)	-	-	176 (3.51)	-	-
Vasopressor	NR	-	-	1617 (32.22)	-	14 (67)
ICU stay duration in days	38 (33–47)	36 (32-40)	-	17 (9-30), 6 (4-10)[1]	-	-
Organ dysfunction	NR	-	-	Acute kidney injury requiring RRT: 1003	-	AKI: 4 (19.1), ALI: 3 (14.3)
Morbidity	acute cardiac injury: 21 (60), atrial or ventricular tachyarrhythmia:3 (9)	86 (8.68) patients being ventilated and 74 (7.47) patients still	-	Still in hospital 30 days after ICU admission: 169	-	Admitted in ICU at end of study: 8 (38.1)

		admitted at the end of study period				
Mortality	3 (9)	485 (49)	-	2043 (40.71)	-	11 (52.4)

[1]Baseline characteristics of patients who did not have cardiac arrest and those who had cardiac arrest respectively.
- Signifies that the variable was not reported in the study.
ICU: Intensive care unit; LV: Left ventricle; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; ICD: Implantable cardiovascular-defibrillator; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation; ECMO: Extra-corporeal membrane oxygenation; RRT: Renal replacement therapy; AKI: Acute kidney injury; ALI: Acute liver injury.

hypertension in men, and obesity (OR 2.564; 95%CI: 1.336-4.920; $P < 0.0001$) and HF (OR 1.775; 95%CI: 1.030-3.057) in women were associated with higher rate of ICU admission[19]. Similar observations were made from a single academic medical centre in New York City and Long Island which found that the strongest risk factors for critical illness besides age were HF (OR 1.9; 95%CI: 1.4-2.5), BMI > 40 (OR 1.5; 95%CI: 1.0-2.2), and male sex (OR 1.5; 95%CI: 1.3-1.8)[17].

OUTCOMES IN CRITICALLY ILL COVID-19 PATIENTS WITH PREEXISTING HEART FAILURE

There were five studies (from North America and Europe) that focused on the outcomes of COVID-19 infection in patients with pre-existing HF (Table 3)[21-25]. Three of them were from the United States, one was from Italy and the last one was from Denmark. Together, these studies included 9191 patients. Maximum number of patients were contributed by the study by Bhatt *et al*[21]. The mean age of patients in these studies were above 70 years, which was about 10 years higher than what was observed in the two previous groups. Two out of the five studies had more women than men. This was in contrast to the uniform male predominance observed in the two previous groups. ICU admission rates were reported by two studies and ranged between 23% and 29%. ECMO was used by three patients in one study[21]. An overall mortality rate between 20% to 40% was observed. Overall mortality variation in multinational studies have ranged from close to 30 % to over 90 %. There was also a significant inter-hospital variability in the outcome of critically ill patients which could not be attributed to the location or performance of the treating facility[26]. Tomasoni *et al*[24] reported more in-hospital complications such as acute HF (33.3% *vs* 5.1%, $P < 0.001$), acute renal failure (28.1% *vs* 12.9%, $P < 0.001$), multiorgan failure (15.9% *vs* 5.8%, $P = 0.004$) and sepsis (18.4% *vs* 8.9%, $P = 0.006$) in COVID-19 patients with a prior history of HF. This suggests that patients with HF and COVID-19 have a poorer outcome than the general population. When compared to hospital admissions for other causes, HF patients admitted for COVID-19 were older, more likely to identify as Black and/or Hispanic, had higher rates of diabetes and kidney disease and used more healthcare resources such as ICU beds (29% *vs* 15%), mechanical ventilation (17% *vs* 6%), and central venous catheter insertion (19% *vs* 7%; $P < 0.001$ for all)[21]. They also had higher in-hospital mortality (24.2% *vs* 2.6%) as well as higher skilled-nursing and rehabilitative care requirement among survivors (13% *vs* 41%)[21]. Similar conclusions were drawn by Alvarez-Garcia *et al*[22], who noted that the history of HF was an independent risk factor for the need for ICU care (adjusted OR 1.71; 95%CI: 1.25-2.34; $P = 0.001$), intubation and mechanical ventilation (adjusted OR 3.64; 95%CI: 2.56 -5.16; $P < 0.001$), and in-hospital mortality (adjusted OR 1.88; 95%CI: 1.27-2.78; $P = 0.002$). Furthermore, the former was the only study to look at outcomes stratified by left ventricular ejection fraction (LVEF) and found that cardiogenic shock (7.8% *vs* 2.3% *vs* 2%; $P = 0.019$) and HF-related causes for 30-day readmission (47.1% *vs* 0% *vs* 8.6%) were significantly higher in patients with HF with reduced ejection fraction (HFrEF) than in those with HF with midrange ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF)[22]. Multivariate cox regression identified older age, more severe HF [baseline New York Heart Association (NYHA) functional classes III and IV], previous mitral regurgitation, lower systolic blood pressure, lower oxygen saturation, lower lymphocyte count, and increased troponin concentrations as risk factors for in-hospital mortality in COVID-19 patients with HF[22].

Table 3 Studies reporting outcomes in heart failure patients with coronavirus disease 2019, *n* (%)

No.	1	2	3	4	5
Ref.	Bhatt *et all*[21]	Alvarez-Garcia *et al*[22]	Caraballo *et al*[23]	Tomasoni *et al*[24]	Andersson *et al*[25]
Country	United States	United States	United States	Italy	Denmark
Patient number	8383	422	206	90	90
Study type	Retrospective cohort, multicentre	Retrospective cohort, multicentre	Retrospective cohort, multicentre	Retrospective cohort, multicentre	Retrospective cohort. multicentre
Age, (mean±SD)	71.7 ± 13.2	72.5 ± 13.3	78 (IQR: 65-87)	73.0 ± 11.4	
Male	4178 (49.8)	236 (55.9)	93 (45.1)	66 (73.3)	
Risk factors	Obesity: 2461 (29.4), morbid obesity: 1425 (17.0), hypertension: 6997 (83.5), diabetes: 5107 (60.9), history of arrhythmia: 4548 (54.3), valvular disease: 1417 (16.9), kidney disease: 5020 (59.9), ESKD: 1689 (20.1), smoking: 3665 (43.7), pulmonary disease: 3539 (42.2), asthma: 628 (7.5), anemia: 628 (7.5), malignancy: 290 (3.5)	Obesity: 169 (40.0), hypertension: 382 (90.5), diabetes mellitus: 269 (63.7), dyslipidemia: 228 (54.0), CAD: 235 (55.7), stroke: 114 (27.0), atrial fibrillation: 160 (37.9), CKD: 177 (41.9), COPD: 94 (22.3), asthma: 58 (13.7), OSA: 57 (13.5)	Hypertension: 164 (79.6)COPD: 67 (32.5)CAD: 73 (35.4)Renal disease:7 9 (38.3)	Smoker: 42 (55.3), hypertension: 68 (75.6), dyslipidaemia: 56 (62.2), diabetes: 37 (41.1), atrial fibrillation: 42 (46.7), coronary artery disease: 55 (61.1), COPD: 22 (24.4), CKD: 49 (54.4)	
LVEF (%), (mean ± SD)	-	-	-	42.1 ± 13.1	-
HFrEF	3318 (39.6)	128 (30.3)	36 (17.5)	64 (71)	-
HFmrEF	-	44 (10.4)	-	-	-
HFpEF	3486 (41.6)	250 (59.3)	-	26 (29)	-
RV dysfunction	-	-	-	16 (28.6)	-
Drugs prior to hospitalization	-	RAAS inhibitors: 260 (61.6), beta-blockers: 354 (83.9), MRA: 60 (14.2), loop diuretics: 318 (75.4), thiazides: 64 (15.2), antiplatelet: 327 (77.5), anticoagulant: 175 (41.5), statins: 351 (83.2)	ACEi/ARB: 58 (28.2), beta-blocker: 94 (45.6), CCB: 69 (33.5), SGLT2i: 1 (0.5), warfarin: 16 (7.8), NOAC: 47 (22.8), diuretic: 99 (48.1), statin: 117 (56.8)	ACEi/ARBs/ARNI: 42 (50.0), MRAs: 23 (34.8), beta-blockers: 69 (81.2), direct oral anticoagulants: 17 (20.5), warfarin: 18 (21.6), statins: 47 (56.0)	-
ICD/CRT	-	-	-	ICD: 20 (22.2), CRT: 8 (8.9) (both prior to hospitalization)	-
ICU	2431 (29)	98 (23.2)	-	-	-
Ventilation	-	96 (22.8)	-	-	-
NIV	-	-	-	28 (31.1)	-
IV	-	96 (22.8)	-	5 (5.6)	-
ECMO	3 (0.04)	-	-	-	-
ICU stay duration	-	5 (2-11)	-	-	-
Mortality	2026 (24.2)	169 (40.0)	41 (20)	37 (41.1)	33 (27)

- Signifies that the variable was not reported in the study.

ESKD: End stage kidney disease; CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea; LVEF: Left ventricle ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; RV: Right ventricle; RAAS: Renin angiotensin aldosterone system; MRA: Mineralocorticoid receptor antagonist; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; SGLT: Sodium-glucose linked transporter; NOAC: Novel oral anticoagulants; ARNI: Angiotensin receptor II blocker – neprilysin inhibitor; ICD: Implantable cardiovascular-defibrillator; CRT: Cardiac resynchronisation therapy; ICU: Intensive care unit; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation.

DATA ON CARDIAC TRANSPLANT PATIENTS WITH COVID-19

We analyzed studies that included heart transplant patients separately because they are a distinct subset of patients who are likely to be on immunosuppressive therapy. We found five retrospective studies with a total of 99 patients (Table 4)[27-31]. This was a group of predominantly male patients with a mean age above 55 years and a wide variation in requirements for ICU level of care; ranging from 10.5% to 100%. The patients who were admitted to ICU were sicker as evidenced by increased requirement of vasopressors, mechanical ventilation, and renal replacement therapy (83% *vs* 38%) [28]. The mortality rate was between 18% and 37%. In one study, all patients who required ICU admission died[29]. This was higher than the mortality rate in the general population, but not much more than non-transplanted HF patients or patients in ICU. Bottio *et al*[31] reported that older age ($P = 0.002$), diabetes mellitus ($P = 0.040$), extracardiac arteriopathy ($P = 0.040$), previous percutaneous coronary intervention ($P = 0.040$), cardiac allograft vasculopathy score ($P = 0.039$), lower glomerular filtration rate ($P = 0.004$), and higher NYHA functional classes ($P = 0.023$) were all significantly associated with in-hospital mortality among heart-transplant patients with COVID-19 [31]. We know that steroids are beneficial in severe COVID-19, and cardiac transplant patients are often on multiple immunosuppressive medications that include steroids, calcineurin inhibitors and anti-metabolites[32]. Whether these immunosuppressive medications protected these patients from severe disease is a question that warrants further investigation.

In this review, we summarized the relationship between HF, COVID-19 and the role of intensive care in patients with COVID-19 and HF. Our review of literature revealed many interesting observations. The evidence suggests that patients with HF are more likely to be hospitalized after COVID-19 infection. Exact quantification of risk will require community-level studies and cannot be derived from the hospital-based studies included in this review. Also, patients with COVID-19 are at increased risk of developing *de novo* HF after admission to the hospital; a risk that increases substantially with admission to the ICU. The reversibility and long-term morbidity of COVID-19 related *de* novo HF is unclear at this point and will require future studies with longer durations of follow up. Patients with COVID-19 and HF had increased chance of requiring ICU admission, mechanical ventilation, vasopressors and renal replacement therapy. They also had more complications and a higher mortality rate when compared to non-HF patients. These differences may be due to the effect of additional organ injury and decreased physiologic reserve leading to faster decompensation. This may also be an indirect marker for variation in practices. While it is expected that patients admitted to the ICU are at increased risk for development of complications and mortality, what is interesting is that the presence of HF represents an additional independent risk factor for the same. Furthermore, due to the similarity in clinical presentation, HF in COVID-19 patients is probably underdiagnosed. Therefore, it stands to reason that the risk estimate from the studies reported thus far are lower than the true risk estimate. It was noteworthy that the outcomes in critically ill heart transplant patients with COVID-19 was not very different from critically ill non-heart transplant patients. Whether the immunosuppressive medications that heart transplant patients are on, provides them with a selective advantage in combating the 'cytokine storm' seen in COVID-19 is a question worth asking. What is clear from our analysis of the existing literature is that HF is inextricably linked with the outcomes of COVID-19 infection. What is not known is the exact mechanisms by which they are linked and therefore, this is a field with immense scope for future research. There are many reasons to study HF in COVID-19 patients. Heart-lung interactions dictate that insult to one organ, affects the other. Acute respiratory distress syndrome (ARDS) is the most common manifestation of severe COVID-19 disease. While hypoxia and positive pressure ventilation stresses the right heart, the left heart has to compensate for increased metabolic demand. These problems are compounded in patients with pre-existing HF. Therefore, it is vital that we investigate the interaction between HF and COVID-19 so that we have a better understanding of its pathophysiology, optimal management and outcome.

PATHOGENESIS OF HF IN COVID-19

Cardiac troponins were elevated in 8%-12% of COVID-19 cases and the percentage rose up to 23%-33% in critically ill patients[1,33,34]. COVID-19 is theorized to injure the myocardium indirectly and directly. The systemic inflammatory response and

Table 4 Studies reporting outcomes in heart-transplant patients with coronavirus disease 2019, *n* (%)

No.	1	2	3	4	5
Ref.	Latif *et al*[27]	Ketcham *et al*[28]	Singhvi *et al*[29]	Lima *et al*[30]	Bottio *et al*[31]
Country	United States	United States	United States	United States	Italy
Patient number	28	6	22	5	38
Study type	Retrospective observational	Retrospective observational	Retrospective observational	Retrospective observational	Retrospective observational
Age, (mean ± SD)	64 (53.5-70.5)	57 (34–73)[1]	58.6 (49.1–71.2)[2]	62 ± 9.8	64.9 ± 12.0
Male	22 (79)	6 (100)	14 (63.6)	4 (80)	31 (82)
Risk factors	Hypertension:20 (71), diabetes:17 (61), lung disease: 10 (36), malignancy: 5 (18), chronic kidney disease: 10 (36)	Chronic heart failure: 4 (67), chronic kidney disease: 4 (67), Chronic anemia: 3 (50), coronary artery disease: 4 (67), former tobacco smoker: 1 (17), diabetes mellitus: 4 (67), hypertension: 6 (100), obesity: 3 (50), obstructive sleep apnea: 3 (50)	Hypertension: 21 (95.5), diabetes: 12 (54.5), lung disease: 3 (13.6), chronic kidney disease stage ≥ III: 14 (63.6), end stage renal disease on dialysis: 3 (13.6), malignancy (excluding non-melanoma skin cancers): 6 (27.3), HIV: 1 (4.5), current smoker: 1 (4.5), former smoker: 7 (31.8), permanent pacemaker: 3 (13.6), charlson comorbidity index ≥ 5: 12 (54.5)	Ischemic cardiomyopathy (pre□ HTx): 2 (40), hypertension: 5 (100), hyperlipidemia: 3 (60), diabetes mellitus: 1 (20), obesity: 2 (40), post□ transplant renal insufficiency: 2 (40)	Obesity: 7 (18), arterial hypertension: 25 (66), dyslipidemia: 18 (47), diabetes mellitus: 7 (18), former smoker: 8 (21), peripheral vascular disease: 8 (21), COPD: 3 (8), stroke: 1 (2), malignancy: 3 (8), previous PCI: 11 (29)
NYHA class	-	-	-	-	I:27 (71), II:8 (21), III:3 (8), IV:0 (0)
ICU	7 (25)	6 (100)	4 (18.18)	2 (40)	4 (10.5)
Ventilation	7 (25)	5 (83)	7 (31.81)	2 (40)	17 (44)
NIV	-	0	3 (13.63)	0	15 (39.4)
IV	7 (25)	5 (83)	4 (18.18)	2 (40)	2 (5.2)
ECMO	-	0	-	0	0 (0)
Vasopressor	-	5 (83)	3 (13.63)	-	3 (7.9%)
ICU stay duration in days	-	8.25 (4-12.5)	7 (4-9)	-	-
Organ dysfunction	HD: 3 (10.71)	AKI requiring CRRT: 5 (83)	RRT: 3 (13.63)	AKI requiring HD: 1 (20)	-
Morbidity	4 (18) patients remained hospitalized at the end of study period	2 (33) patients still admitted at the end of the study period	-	One patient developed mild acute cellular rejection	Bacterial coinfection:5 (13), sepsis: 4 (10.5), neurological complication: 1 (2.6), gastrointestinal complication: 1 (2.6)
Mortality	7 (25)	2 (33)	4 (18.18)	0 (0)	14 (36.8)

[1]Range.
[2]IQR.
- signifies that the variable was not reported in the study. All patients had COVID-19 confirmed by RT-PCR.
HIV: Human immunodeficiency virus; Htx: Heart transplant; PCI: Percutaneous coronary intervention; COPD: Chronic obstructive pulmonary disease; NYHA: New York Heart Association; ICU: Intensive care unit; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation; HD: Hemodialysis; AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; RRT: Renal replacement therapy; AKI: Acute kidney injury.

cytokine storm increases blood viscosity and coagulability, which causes endothelial dysfunction[35,36]. The sympathetic activation, tachycardia, increased myocardial oxygen consumption and energy expenditure can also injure the myocardium. More cases of takotsubo cardiomyopathy are being diagnosed in patients with severe COVID-19[37]. Elevated positive end-expiratory pressure during mechanical ventilation in COVID-19 patients with severe ARDS increases right ventricular wall stress and can further reduce the cardiac output in a failing heart[38]. In a series of consecutive autopsy cases, Lindner and colleagues documented SARS-CoV-2 in 24 of

39 patients (61.5%), suggesting that direct viral myocardial damage is also possible [39]. SARS-CoV-2 attaches to human cells after binding with its spikes to the ACE2, which are upregulated in patients with cardiovascular disease, diabetes, and those treated with ACEi or ARB[40-42]. In light of this observation, role of ACE2 and ACEi in the pathogenesis of COVID-19 related myocardial injury has also been investigated from a therapeutic point of view.

While there are multiple factors contributing to HF in COVID-19, the incidence of true 'myocarditis' in COVID-19 in unclear[43]. Some authors estimate that myocarditis may account for up to 7% of COVID-19 deaths[44]. This estimate is fundamentally flawed because the diagnosis cannot be confirmed in a vast number of cases. Also, the presentation of acute coronary syndrome, sepsis-related cardiomyopathy and takotsubo cardiomyopathy can mimic myocarditis, making this a challenging diagnosis. Myocarditis, even when subclinical, can worsen patient outcomes. In the short term, it can increase the risk of arrythmias and precipitate decompensated HF, especially in patients with pre-existing chronic HF[45]. In the long term, the resultant myocardial fibrosis and negative remodeling can accelerate the decline of systolic function leading to a limitation of physical activity. Therefore, in the ICU, it is important to screen patients for subclinical myocarditis, by following the AHA recommendation of testing patients with signs consistent with myocarditis with one or more cardiac imaging methods such as echocardiogram or cardiovascular magnetic resonance[46].

SCREENING FOR HF IN THE ICU

Up to one-third of COVID-19 patients admitted to the ICU develop cardiomyopathy, and cohort studies from Wuhan have estimated the proportion of COVID-19 patients with cardiac injury to be between 20% and 28%[8,47]. Therefore, it would be prudent to screen all COVID-19 patients admitted to the ICU for HF. Critically ill patients in the ICU, are not able to communicate their complaints, and physical examination findings are often limited. A screening algorithm such as the one suggested by the Cardiac Society of Australia and New Zealand can be employed in the ICU[48]. Incorporation of such a screening algorithm into the treatment protocol will help identify more patients with HF and optimize treatment.

Although major society guidelines recommend the measurement of natriuretic peptides when the diagnosis of HF is uncertain, they should be interpreted in the context of other clinical information due to their high sensitivity and limited specificity [49,50]. In addition to its diagnostic value, natriuretic peptides also have prognostic significance with higher pro-brain natriuretic peptide (pro-BNP) values associated with increased mortality[51,52]. Therefore, natriuretic peptides can be used for risk stratification of COVID-19 patients with HF. Elevations in cardiac troponins have also been observed in COVID-19 patients and may indicate both coronary and non-coronary disease[53]. Acute coronary syndrome, microvascular ischemia, myocarditis, takotsubo cardiomyopathy and arrythmia are some of the reasons for an elevated troponin in COVID-19 patients[54]. While this makes the measurement of cardiac troponins less useful from the point of view of diagnosing HF, an elevated troponin level cannot be ignored as it may point towards underlying heart disease in an asymptomatic COVID-19 patient.

ROLE OF CARDIAC POINT OF CARE ULTRASOUND

The American Society of Echocardiography defines cardiac point of care ultrasound (POCUS) as 'focused exams with specific imaging protocols based upon suspicion of a specific disease' and differentiates it from ultrasound assisted physical examination [55]. POCUS has multiple uses in the diagnosis and management of HF in COVID-19 patients in the ICU. POCUS has the added benefit of reducing risk of exposure to the health-care worker, when compared to the use of stethoscopes[56]. Adhering to a set-protocol such as the one described by Huang *et al*[57], will reduce inter and intra-observer variability. Documenting POCUS findings is important and if possible, the images should be stored on the device or on a central server. As this technology is relatively new, using mannequins for standardized training in image acquisition and interpretation may be helpful[58].

ECHOCARDIOGRAPHY

The American Society of Echocardiography, in a statement endorsed by the American College of Cardiology, recommends that Transthoracic echocardiography should be performed if it is expected to provide clinical benefit[59]. In the ICU, this can be done at the bedside, with adequate airborne precautions[59]. Echocardiography (ECHO) can provide more information when compared to cardiac POCUS and can also be used to risk stratify patients to aid in follow up. A study of 75 hospitalized patients with COVID-19 showed a significant association between lower LVEF and mortality[60]. The mortality among the patients with LVEF < 50% was 65% compared to 26% in the group with LVEF ≥ 50%. The patients with LVEF < 50% also had higher troponin T and pro-BNP levels[60]. Stepwise modelling demonstrated that mechanical ventilation (OR 22.6; 95%CI: 3.0-170.4), LVEF < 50% (OR 8.2; 95%CI: 1.4-46.9), and pro-BNP above the cohort median value (OR 5.8; 95%CI: 1.4-23.9) were the strongest predictors of mortality[60]. Similar findings were reported by Alvarez-Garcia *et al*[22], as mentioned previously. Both left ventricular global longitudinal strain (HR 1.39; 95%CI: 1.11-1.76) and right ventricular longitudinal strain (HR 1.33; 95%CI: 1.15-1.53) were associated with increased mortality in COVID-19[61,62]. ECHO also allows for more detailed evaluation of right heart function, including tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio (HR 0.026; 95%CI: 0.01-0.579; P = 0.019) which was an independent predictor of mortality in one study[63].

MANAGEMENT OF ACUTE HEART FAILURE IN THE ICU

Management of acute HF in COVID-19 patients in the ICU should be done according to established guidelines and protocols. Although questions have been raised about the potential deleterious effects of ACEi and ARBs in COVID-19, a joint statement from the Heart Failure Society of America and American College of Cardiology/American Heart Association recommends continuation of these medications in patients with HF, if hemodynamics allow[64]. An effort must be made to identify HF due to takotsubo cardiomyopathy, which may masquerade as an acute coronary syndrome, but is increasingly being recognized in the context of COVID-19[37]. Since catecholamine-excess is considered to be part of the pathogenesis behind takotsubo cardiomyopathy, this subset of patients may benefit from restricting the use of catecholamine-inotropes such as dobutamine and dopamine and replacing them with non-catecholamine inotropes such as levosimendan and milrinone[65-67]. In patients who develop HF refractory to inotrope support, mechanical circulatory support, *e.g.*, veno-arterial ECMO or other cardiac assistive devices such as Impella (Abiomed, Danvers, MA, United States) may be used. These interventions are resource intensive and may not be available in all centres. In patients with suspected myocarditis or cytokine mediated injury, high dose corticosteroids, intravenous immunoglobulin and even selective cytokine blockade are options that can be considered on an experimental basis, given the absence of strong evidence of their benefit[68].

EXTRA-CORPOREAL MEMBRANE OXYGENATION

The World Health Organization has recommended that ECMO can be used in experienced centres for the management of critically ill COVID-19 patients with ARDS with or without HF[69]. The Extracorporeal Life Support Organization has emphasized that ECMO should be judiciously used as a rescue strategy in severely ill patients since it is a resource-intensive, highly specialized, and expensive form of life support with the potential for significant complications[70]. Key considerations while implementing ECMO include proper patient assessment and selection, personnel assignment, infection control measures before and during ECMO initiation as well as devising protocols for ECMO weaning, decannulation and rehabilitation[71]. Given the resource intensive nature of ECMO, some authors have raised the question of whether it is worth using during a pandemic[72]. Barbaro *et al*[73] used the data from the ELSO registry and determined that the mortality in COVID-19 patients who required ECMO was less than 40%. This shows that in the appropriate setting, ECMO is indeed beneficial in critically ill COVID-19 patients.

The role of ECMO after CPR (E-CPR) is unclear at this point, and as of February 3, 2021, the Extracorporeal Life Support Organization registry has reported 32 COVID-19 patients who underwent E-CPR[74]. Current guidelines recommend judicious use of

E-CPR and only in centres that already have experience in its use[70,75,76]. Candidate selection should be done with due consideration of the patients comorbidities, other organ function, short and long-term life expectancy, availability of ECMO resources and risk of infectious exposure during cannulation and bed-side management[71].

LEFT-VENTRICULAR ASSIST DEVICES

Literature on left ventricular assist devices and COVID-19 are scant. LVADs have been used with varying success in the management of HF in COVID-19. Valchanov *et al*[77] have described a case of a 43-year patient with severe COVID-19 ARDS and HF who was managed with veno-arterial ECMO and an Impella 5.0 ventricular assist device. The patient, however, succumbed to his illness after a 3-wk period. There are case-reports and case-series of patients on long-term LVAD who developed COVID-19[78-82]. It is important to recognize that COVID-19 patients with LVADs are particularly prone to thrombotic complications. This requires intensivists to walk a fine line between potential complications of bleeding and thrombosis. In recipients with COVID-19 infection, daily interrogation of LVAD parameters can help in the early recognition of early signs of hemodynamic compromise, pump thrombosis, right ventricular failure, vasoplegia associated with secondary infection, or innate device malfunction[83].

REHABILITATION OF HF PATIENTS WITH COVID-19 AFTER ICU DISCHARGE

Rehabilitation of COVID-19 survivors who were in the ICU is critical. In those who developed HF, this becomes even more important. COVID-19 survivors who were critically ill often develop respiratory sequelae, cognitive sequelae, deconditioning, critical-illness related myopathy and neuropathy, dysphagia, joint stiffness and pain and psychiatric problems[84,85]. An early physical medicine and rehabilitation consultation, will help identify and address these issues early on. Rehabilitation can be initiated while the patient is still in ICU. However, more holistic rehabilitation will require assessment of respiratory capacity, muscle strength, exercise capacity, gait speed, balance and activities of daily living[86]. This is preferably done in a dedicated rehabilitation facility, after the patient is discharged home[82]. A graded exercise-based cardiac rehabilitation strategy can be prescribed, in accordance with standard HF guidelines[87].

Home based cardiac rehabilitation programs with telemonitoring methods can also be considered[88]. Few authors have reported promising results with remote cardiac care during the COVID-19 pandemic with telemonitoring devices such as the V-LAP™ (Vectorious Medical Technologies, Ltd) device for monitoring left atrial pressure as well as the HeartLogic platform (Boston Scientific, Marlborough, Massachusetts)[89,90]. Although this technology is relatively new, we may soon see its integration into rehabilitation protocols for patients with HF, after ICU discharge.

LIMITATIONS

We identified that only very few studies discussed the medical management of sick patients with COVID-19 in the background of HF. While many studies reported prevalence of 'cardiovascular disease' and 'cardiac injury' (usually defined as troponin I above the 99th percentile upper reference limit or new abnormalities shown on electrocardiography and echocardiography) in COVID-19 patients, the number of studies that reported chronic and *de novo* HF in this cohort was limited. Part of the reason may be the similarity in presentation of severe COVID-19 ARDS and acute decompensated HF. This is particularly challenging in the ICU patients, in whom both conditions often coexist. Moreover, HF is both a risk factor and a complication of COVID-19. Moreover, studies included in this review were retrospective and lack granular details on the severity of the disease, medical treatment, comorbidities, drug interactions, and outcome. Details of COVID-19 infection on the management of HF and vice versa were also not uniformly addressed. Outcomes in different studies were different. Details of treatment of COVID-19, duration of therapy, length of hospital stay, the long-term outcome were not uniformly available. Details of intensive care

treatment, including mode of ventilation, pressors of choice, renal replacement therapies, the role of sedatives and paralytics on this subgroup of populations were also not discussed in all studies. However, the strength of the studies was that it included studies with patients having COVID-19 in the background of HF from all over the world. We also tried to identify the predictors of morbidity and the role of intensive care therapy in these patients, from the literature. More research focusing on this subset of patients is necessary to clarify the pathogenesis, improve screening methods and identify optimal therapeutic strategies.

CONCLUSION

In this review, we identified that HF is an independent predictor of mortality in hospitalized COVID-19 patients. Patients with HF were more likely to require ventilation, ICU admission and develop complications. Patients with HFrEF did worse than those with HFmrEF and HFpEF. COVID-19 patients with HF should be identified early and managed aggressively in an attempt to improve outcomes in this cohort of patients.

REFERENCES

1 **Inciardi RM**, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020; **41**: 1821-1829 [PMID: 32383763 DOI: 10.1093/eurheartj/ehaa388]

2 **Singer AJ**, Morley EJ, Meyers K, Fernandes R, Rowe AL, Viccellio P, Thode HC, Bracey A, Henry MC. Cohort of Four Thousand Four Hundred Four Persons Under Investigation for COVID-19 in a New York Hospital and Predictors of ICU Care and Ventilation. *Ann Emerg Med* 2020; **76**: 394-404 [PMID: 32563601 DOI: 10.1016/j.annemergmed.2020.05.011]

3 **Zylla MM**, Merle U, Vey JA, Korosoglou G, Hofmann E, Müller M, Herth F, Schmidt W, Blessing E, Göggelmann C, Weidner N, Fiedler MO, Weigand MA, Kälble F, Morath C, Leiner J, Kieser M, Katus HA, Thomas D. Predictors and Prognostic Implications of Cardiac Arrhythmias in Patients Hospitalized for COVID-19. *J Clin Med* 2021; **10** [PMID: 33401735 DOI: 10.3390/jcm10010133]

4 **Russo V**, Di Maio M, Mottola FF, Pagnano G, Attena E, Verde N, Di Micco P, Silverio A, Scudiero F, Nunziata L, Fele N, D'Andrea A, Parodi G, Albani S, Scacciatella P, Nigro G, Severino S. Clinical characteristics and prognosis of hospitalized COVID-19 patients with incident sustained tachyarrhythmias: A multicenter observational study. *Eur J Clin Invest* 2020; **50**: e13387 [PMID: 32813877 DOI: 10.1111/eci.13387]

5 **Bhatla A**, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, Moss J, Chahal AA, Anesi G, Denduluri S, Domenico CM, Arkles J, Abella BS, Bullinga JR, Callans DJ, Dixit S, Epstein AE, Frankel DS, Garcia FC, Kumareswaram R, Nazarian S, Riley MP, Santangeli P, Schaller RD, Supple GE, Lin D, Marchlinski F, Deo R. COVID-19 and cardiac arrhythmias. *Heart Rhythm* 2020; **17**: 1439-1444 [PMID: 32585191 DOI: 10.1016/j.hrthm.2020.06.016]

6 **Peltzer B**, Manocha KK, Ying X, Kirzner J, Ip JE, Thomas G, Liu CF, Markowitz SM, Lerman BB, Safford MM, Goyal P, Cheung JW. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19. *J Cardiovasc Electrophysiol* 2020; **31**: 3077-3085 [PMID: 33017083 DOI: 10.1111/jce.14770]

7 **Lala A**, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Mancini DM, Fuster V; Mount Sinai COVID Informatics Center. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* 2020; **76**: 533-546 [PMID: 32517963 DOI: 10.1016/j.jacc.2020.06.007]

8 **Shi S**, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802-810 [PMID: 32211816 DOI: 10.1001/jamacardio.2020.0950]

9 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736]

10 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: 32217556 DOI: 10.1136/bmj.m1091]

11 **Jarrett M**, Schultz S, Lyall J, Wang J, Stier L, De Geronimo M, Nelson K. Clinical Mortality in a

Large COVID-19 Cohort: Observational Study. *J Med Internet Res* 2020; **22**: e23565 [PMID: 32930099 DOI: 10.2196/23565]

12 **Ho KK**, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; **22**: 6A-13A [PMID: 8376698 DOI: 10.1016/0735-1097]

13 **Ssentongo P**, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. *PLoS One* 2020; **15**: e0238215 [PMID: 32845926 DOI: 10.1371/journal.pone.0238215]

14 **Chidambaram V**, Tun NL, Haque WZ, Majella MG, Sivakumar RK, Kumar A, Hsu AT, Ishak IA, Nur AA, Ayeh SK, Salia EL, Zil-E-Ali A, Saeed MA, Sarena APB, Seth B, Ahmadzada M, Haque EF, Neupane P, Wang KH, Pu TM, Ali SMH, Arshad MA, Wang L, Baksh S, Karakousis PC, Galiatsatos P. Factors associated with disease severity and mortality among patients with COVID-19: A systematic review and meta-analysis. *PLoS One* 2020; **15**: e0241541 [PMID: 33206661 DOI: 10.1371/journal.pone.0241541]

15 **Shoar S**, Hosseini F, Naderan M, Mehta JL. Meta-analysis of Cardiovascular Events and Related Biomarkers Comparing Survivors Versus Non-survivors in Patients With COVID-19. *Am J Cardiol* 2020; **135**: 50-61 [PMID: 32916148 DOI: 10.1016/j.amjcard.2020.08.044]

16 **Zeng JH**, Wu WB, Qu JX, Wang Y, Dong CF, Luo YF, Zhou D, Feng WX, Feng C. Cardiac manifestations of COVID-19 in Shenzhen, China. *Infection* 2020; **48**: 861-870 [PMID: 32725595 DOI: 10.1007/s15010-020-01473-w]

17 **Petrilli CM**, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; **369**: m1966 [PMID: 32444366 DOI: 10.1136/bmj.m1966]

18 **Hayek SS**, Brenner SK, Azam TU, Shadid HR, Anderson E, Berlin H, Pan M, Meloche C, Feroz R, O'Hayer P, Kaakati R, Bitar A, Padalia K, Perry D, Blakely P, Gupta S, Shaefi S, Srivastava A, Charytan DM, Bansal A, Mallappallil M, Melamed ML, Shehata AM, Sunderram J, Mathews KS, Sutherland AK, Nallamothu BK, Leaf DE; STOP-COVID Investigators. In-hospital cardiac arrest in critically ill patients with covid-19: multicenter cohort study. *BMJ* 2020; **371**: m3513 [PMID: 32998872 DOI: 10.1136/bmj.m3513]

19 **Iaccarino G**, Grassi G, Borghi C, Carugo S, Fallo F, Ferri C, Giannattasio C, Grassi D, Letizia C, Mancusi C, Minuz P, Perlini S, Pucci G, Rizzoni D, Salvetti M, Sarzani R, Sechi L, Veglio F, Volpe M, Muiesan ML; SARS-RAS Investigators. Gender differences in predictors of intensive care units admission among COVID-19 patients: The results of the SARS-RAS study of the Italian Society of Hypertension. *PLoS One* 2020; **15**: e0237297 [PMID: 33022004 DOI: 10.1371/journal.pone.0237297]

20 **Arentz M**, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; **323**: 1612-1614 [PMID: 32191259 DOI: 10.1001/jama.2020.4326]

21 **Bhatt AS**, Jering KS, Vaduganathan M, Claggett BL, Cunningham JW, Rosenthal N, Signorovitch J, Thune JJ, Vardeny O, Solomon SD. Clinical Outcomes in Patients With Heart Failure Hospitalized With COVID-19. *JACC Heart Fail* 2021; **9**: 65-73 [PMID: 33384064 DOI: 10.1016/j.jchf.2020.11.003]

22 **Alvarez-Garcia J**, Lee S, Gupta A, Cagliostro M, Joshi AA, Rivas-Lasarte M, Contreras J, Mitter SS, LaRocca G, Tlachi P, Brunjes D, Glicksberg BS, Levin MA, Nadkarni G, Fayad Z, Fuster V, Mancini D, Lala A. Prognostic Impact of Prior Heart Failure in Patients Hospitalized With COVID-19. *J Am Coll Cardiol* 2020; **76**: 2334-2348 [PMID: 33129663 DOI: 10.1016/j.jacc.2020.09.549]

23 **Caraballo C**, McCullough M, Fuery MA, Chouairi F, Keating C, Ravindra NG, Miller PE, Malinis M, Kashyap N, Hsiao A, Wilson FP, Curtis JP, Grant M, Velazquez EJ, Desai NR, Ahmad T. COVID-19 infections and outcomes in a live registry of heart failure patients across an integrated health care system. *PLoS One* 2020; **15**: e0238829 [PMID: 32997657 DOI: 10.1371/journal.pone.0238829]

24 **Tomasoni D**, Inciardi RM, Lombardi CM, Tedino C, Agostoni P, Ameri P, Barbieri L, Bellasi A, Camporotondo R, Canale C, Carubelli V, Carugo S, Catagnano F, Dalla Vecchia LA, Danzi GB, Di Pasquale M, Gaudenzi M, Giovinazzo S, Gnecchi M, Iorio A, La Rovere MT, Leonardi S, Maccagni G, Mapelli M, Margonato D, Merlo M, Monzo L, Mortara A, Nuzzi V, Piepoli M, Porto I, Pozzi A, Sarullo F, Sinagra G, Volterrani M, Zaccone G, Guazzi M, Senni M, Metra M. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. *Eur J Heart Fail* 2020; **22**: 2238-2247 [PMID: 33179839 DOI: 10.1002/ejhf.2052]

25 **Andersson C**, Gerds T, Fosbøl E, Phelps M, Andersen J, Lamberts M, Holt A, Butt JH, Madelaire C, Gislason G, Torp-Pedersen C, Køber L, Schou M. Incidence of New-Onset and Worsening Heart Failure Before and After the COVID-19 Epidemic Lockdown in Denmark: A Nationwide Cohort Study. *Circ Heart Fail* 2020; **13**: e007274 [PMID: 32482087 DOI: 10.1161/CIRCHEARTFAILURE.120.007274]

26 **Domecq JP**, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S, Bansal V, Harhay MO, Garcia MA, Kaufman M, Danesh V, Cheruku S, Banner-Goodspeed VM, Anderson HL 3rd, Milligan PS, Denson JL, St Hill CA, Dodd KW, Martin GS, Gajic O, Walkey AJ, Kashyap R; Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-

19 Registry Investigator Group. Outcomes of Patients With Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2021; **49**: 437-448 [PMID: 33555777 DOI: 10.1097/CCM.0000000000004879]

27 **Latif F**, Farr MA, Clerkin KJ, Habal MV, Takeda K, Naka Y, Restaino S, Sayer G, Uriel N. Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019. *JAMA Cardiol* 2020; **5**: 1165-1169 [PMID: 32402056 DOI: 10.1001/jamacardio.2020.2159]

28 **Ketcham SW**, Adie SK, Malliett A, Abdul-Aziz AA, Bitar A, Grafton G, Konerman MC. Coronavirus Disease-2019 in Heart Transplant Recipients in Southeastern Michigan: A Case Series. *J Card Fail* 2020; **26**: 457-461 [PMID: 32417380 DOI: 10.1016/j.cardfail.2020.05.008]

29 **Singhvi A**, Barghash M, Lala A, Mitter SS, Parikh A, Oliveros E, Rollins BM, Brunjes DL, Alvarez-Garcia J, Johnston E, Ryan K, Itagaki S, Moss N, Pinney SP, Anyanwu A, Mancini D. Challenges in heart transplantation during COVID-19: A single-center experience. *J Heart Lung Transplant* 2020; **39**: 894-903 [PMID: 32891266 DOI: 10.1016/j.healun.2020.06.015]

30 **Lima B**, Gibson GT, Vullaganti S, Malhame K, Maybaum S, Hussain ST, Shah S, Majure DT, Wallach F, Jang K, Bijol V, Esposito MJ, Williamson AK, Thomas RM, Bhuiya TA, Fernandez HA, Stevens GR. COVID-19 in recent heart transplant recipients: Clinicopathologic features and early outcomes. *Transpl Infect Dis* 2020; **22**: e13382 [PMID: 32583620 DOI: 10.1111/tid.13382]

31 **Bottio T**, Bagozzi L, Fiocco A, Nadali M, Caraffa R, Bifulco O, Ponzoni M, Lombardi CM, Metra M, Russo CF, Frigerio M, Masciocco G, Potena L, Loforte A, Pacini D, Faggian G, Onorati F, Sponga S, Livi U, Iacovoni A, Terzi A, Senni M, Rinaldi M, Boffini M, Marro M, Jorgji V, Carrozzini M, Gerosa G. COVID-19 in Heart Transplant Recipients: A Multicenter Analysis of the Northern Italian Outbreak. *JACC Heart Fail* 2021; **9**: 52-61 [PMID: 33309578 DOI: 10.1016/j.jchf.2020.10.009]

32 **Sterne JAC**, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Møller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; **324**: 1330-1341 [PMID: 32876694 DOI: 10.1001/jama.2020.17023]

33 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

34 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600]

35 **Tomasoni D**, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020; **22**: 957-966 [PMID: 32412156 DOI: 10.1002/ejhf.1871]

36 **Mishra AK**, Sahu KK, Lal A, Sargent J. Patterns of heart injury in COVID-19 and relation to outcome. *J Med Virol* 2020; **92**: 1747 [PMID: 32267000 DOI: 10.1002/jmv.25847]

37 **John K**, Lal A, Mishra A. A review of the presentation and outcome of takotsubo cardiomyopathy in COVID-19. *Monaldi Arch Chest Dis* 2021; **91** [PMID: 33759445 DOI: 10.4081/monaldi.2021.1710]

38 **Luecke T**, Pelosi P. Clinical review: Positive end-expiratory pressure and cardiac output. *Crit Care* 2005; **9**: 607-621 [PMID: 16356246 DOI: 10.1186/cc3877]

39 **Lindner D**, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Püschel K, Westermann D. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiol* 2020; **5**: 1281-1285 [PMID: 32730555 DOI: 10.1001/jamacardio.2020.3551]

40 **Yan R**, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 2020; **367**: 1444-1448 [PMID: 32132184 DOI: 10.1126/science.abb2762]

41 **Ferrario CM**, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; **111**: 2605-2610 [PMID: 15897343 DOI: 10.1161/CIRCULATIONAHA.104.510461]

42 **Mishra AK**, Sahu KK, Sargent J. Cardiac drugs and outcome in COVID-19. *QJM* 2020; **113**: 523-524 [PMID: 32289168 DOI: 10.1093/qjmed/hcaa127]

43 **Mishra AK**, Lal A, Sahu KK, Sargent J. Cardiovascular factors predicting poor outcome in COVID-19 patients. *Cardiovasc Pathol* 2020; **49**: 107246 [PMID: 32640385 DOI: 10.1016/j.carpath.2020.107246]

44 **Driggin E**, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, Brown TS, Der Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol* 2020; **75**: 2352-2371 [PMID: 32201335 DOI:

10.1016/j.jacc.2020.03.031]

45 **Siripanthong B**, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, Cooper LT Jr, Chahal CAA. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm* 2020; **17**: 1463-1471 [PMID: 32387246 DOI: 10.1016/j.hrthm.2020.05.001]

46 **Kociol RD**, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, Shah RV, Sims DB, Thiene G, Vardeny O; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Recognition and Initial Management of Fulminant Myocarditis: A Scientific Statement From the American Heart Association. *Circulation* 2020; **141**: e69-e92 [PMID: 31902242 DOI: 10.1161/CIR.0000000000000745]

47 **Guo T**, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 811-818 [PMID: 32219356 DOI: 10.1001/jamacardio.2020.1017]

48 **Lal S**, Hayward CS, De Pasquale C, Kaye D, Javorsky G, Bergin P, Atherton JJ, Ilton MK, Weintraub RG, Nair P, Rudas M, Dembo L, Doughty RN, Kumarasinghe G, Juergens C, Bannon PG, Bart NK, Chow CK, Lattimore JD, Kritharides L, Totaro R, Macdonald PS. COVID-19 and Acute Heart Failure: Screening the Critically Ill - A Position Statement of the Cardiac Society of Australia and New Zealand (CSANZ). *Heart Lung Circ* 2020; **29**: e94-e98 [PMID: 32418875 DOI: 10.1016/j.hlc.2020.04.005]

49 **Lindenfeld J**, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. Heart Failure Society of America. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010; **16**: e1-194 [PMID: 20610207 DOI: 10.1016/j.cardfail.2010.04.004]

50 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; Writing Committee Members. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: e240-e327 [PMID: 23741058 DOI: 10.1161/CIR.0b013e31829e8776]

51 **Maisel AS**, Duran JM, Wettersten N. Natriuretic Peptides in Heart Failure: Atrial and B-type Natriuretic Peptides. *Heart Fail Clin* 2018; **14**: 13-25 [PMID: 29153197 DOI: 10.1016/j.hfc.2017.08.002]

52 **Hsich EM**, Grau-Sepulveda MV, Hernandez AF, Eapen ZJ, Xian Y, Schwamm LH, Bhatt DL, Fonarow GC. Relationship between sex, ejection fraction, and B-type natriuretic peptide levels in patients hospitalized with heart failure and associations with inhospital outcomes: findings from the Get With The Guideline-Heart Failure Registry. *Am Heart J* 2013; **166**: 1063-1071.e3 [PMID: 24268222 DOI: 10.1016/j.ahj.2013.08.029]

53 **Gaze DC**. Clinical utility of cardiac troponin measurement in COVID-19 infection. *Ann Clin Biochem* 2020; **57**: 202-205 [PMID: 32255359 DOI: 10.1177/0004563220921888]

54 **Chapman AR**, Bularga A, Mills NL. High-Sensitivity Cardiac Troponin Can Be an Ally in the Fight Against COVID-19. *Circulation* 2020; **141**: 1733-1735 [PMID: 32251612 DOI: 10.1161/CIRCULATIONAHA.120.047008]

55 **Kirkpatrick JN**, Grimm R, Johri AM, Kimura BJ, Kort S, Labovitz AJ, Lanspa M, Phillip S, Raza S, Thorson K, Turner J. Recommendations for Echocardiography Laboratories Participating in Cardiac Point of Care Cardiac Ultrasound (POCUS) and Critical Care Echocardiography Training: Report from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2020; **33**: 409-422.e4 [PMID: 32122742 DOI: 10.1016/j.echo.2020.01.008]

56 **Buonsenso D**, Pata D, Chiaretti A. COVID-19 outbreak: less stethoscope, more ultrasound. *Lancet Respir Med* 2020; **8**: e27 [PMID: 32203708 DOI: 10.1016/S2213-2600]

57 **Huang G**, Vengerovsky A, Morris A, Town J, Carlbom D, Kwon Y. Development of a COVID-19 Point-of-Care Ultrasound Protocol. *J Am Soc Echocardiogr* 2020; **33**: 903-905 [PMID: 32624091 DOI: 10.1016/j.echo.2020.04.023]

58 **Sheehan FH**, Otto CM, Freeman RV. Echo simulator with novel training and competency testing tools. *Stud Health Technol Inform* 2013; **184**: 397-403 [PMID: 23400191 DOI: 10.3233/978-1-61499-209-7-397]

59 **Kirkpatrick JN**, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE Statement on Protection of Patients and Echocardiography Service Providers During the 2019 Novel Coronavirus Outbreak: Endorsed by the American College of Cardiology. *J Am Soc Echocardiogr* 2020; **33**: 648-653 [PMID: 32503700 DOI: 10.1016/j.echo.2020.04.001]

60 **Faridi KF**, Hennessey KC, Shah N, Soufer A, Wang Y, Sugeng L, Agarwal V, Sharma R, Sewanan LR, Hur DJ, Velazquez EJ, McNamara RL. Left Ventricular Systolic Function and Inpatient Mortality in Patients Hospitalized with Coronavirus Disease 2019 (COVID-19). *J Am Soc Echocardiogr* 2020; **33**: 1414-1415 [PMID: 32951969 DOI: 10.1016/j.echo.2020.08.016]

61 **Janus SE**, Hajjari J, Karnib M, Tashtish N, Al-Kindi SG, Hoit BD. Prognostic Value of Left Ventricular Global Longitudinal Strain in COVID-19. *Am J Cardiol* 2020; **131**: 134-136 [PMID: 32732008 DOI: 10.1016/j.amjcard.2020.06.053]

62 **Li Y**, Li H, Zhu S, Xie Y, Wang B, He L, Zhang D, Zhang Y, Yuan H, Wu C, Sun W, Li M, Cui L,

Cai Y, Wang J, Yang Y, Lv Q, Zhang L, Xie M. Prognostic Value of Right Ventricular Longitudinal Strain in Patients With COVID-19. *JACC Cardiovasc Imaging* 2020; **13**: 2287-2299 [PMID: 32654963 DOI: 10.1016/j.jcmg.2020.04.014]

63 **D'Alto M**, Marra AM, Severino S, Salzano A, Romeo E, De Rosa R, Stagnaro FM, Pagnano G, Verde R, Murino P, Farro A, Ciccarelli G, Vargas M, Fiorentino G, Servillo G, Gentile I, Corcione A, Cittadini A, Naeije R, Golino P. Right ventricular-arterial uncoupling independently predicts survival in COVID-19 ARDS. *Crit Care* 2020; **24**: 670 [PMID: 33256813 DOI: 10.1186/s13054-020-03385-5]

64 **Bozkurt B**, Kovacs R, Harrington B. Joint HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. *J Card Fail* 2020; **26**: 370 [PMID: 32439095 DOI: 10.1016/j.cardfail.2020.04.013]

65 **Veillet-Chowdhury M**, Hassan SF, Stergiopoulos K. Takotsubo cardiomyopathy: a review. *Acute Card Care* 2014; **16**: 15-22 [PMID: 24552225 DOI: 10.3109/17482941.2013.869346]

66 **Papanikolaou J**, Tsolaki V, Makris D, Zakynthinos E. Early levosimendan administration may improve outcome in patients with subarachnoid hemorrhage complicated by acute heart failure. *Int J Cardiol* 2014; **176**: 1435-1437 [PMID: 25147072 DOI: 10.1016/j.ijcard.2014.08.039]

67 **Mrozek S**, Srairi M, Marhar F, Delmas C, Gaussiat F, Abaziou T, Larcher C, Atthar V, Menut R, Fourcade O, Geeraerts T. Successful treatment of inverted Takotsubo cardiomyopathy after severe traumatic brain injury with milrinone after dobutamine failure. *Heart Lung* 2016; **45**: 406-408 [PMID: 27402629 DOI: 10.1016/j.hrtlng.2016.06.007]

68 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736]

69 **World Health Organization**. WHO interim guidance on the clinical management of COVID-19. [cited 10 January 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1

70 **Shekar K**, Badulak J, Peek G, Boeken U, Dalton HJ, Arora L, Zakhary B, Ramanathan K, Starr J, Akkanti B, Antonini MV, Ogino MT, Raman L, Barret N, Brodie D, Combes A, Lorusso R, MacLaren G, Müller T, Paden M, Pellegrino V; ELSO Guideline Working Group. Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: A Consensus Document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. *ASAIO J* 2020; **66**: 707-721 [PMID: 32604322 DOI: 10.1097/MAT.0000000000001193]

71 **Ramanathan K**, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med* 2020; **8**: 518-526 [PMID: 32203711 DOI: 10.1016/S2213-2600]

72 **Falcoz PE**, Monnier A, Puyraveau M, Perrier S, Ludes PO, Olland A, Mertes PM, Schneider F, Helms J, Meziani F. Extracorporeal Membrane Oxygenation for Critically Ill Patients with COVID-19-related Acute Respiratory Distress Syndrome: Worth the Effort? *Am J Respir Crit Care Med* 2020; **202**: 460-463 [PMID: 32543208 DOI: 10.1164/rccm.202004-1370LE]

73 **Barbaro RP**, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, Bartlett RH, Tonna JE, Hyslop R, Fanning JJ, Rycus PT, Hyer SJ, Anders MM, Agerstrand CL, Hryniewicz K, Diaz R, Lorusso R, Combes A, Brodie D; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020; **396**: 1071-1078. [PMID: 32987008 DOI: 10.1016/S0140-6736(20)32008-0]

74 **ELSO**. Full COVID-19 Registry Dashboard. [cited 10 January 202]. Available from: https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx

75 **Bartlett RH**, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, Stead CM, Rycus P, Fraser JF, Belohlavek J, Salazar L, Mehta Y, Raman L, Paden ML. Initial ELSO Guidance Document: ECMO for COVID-19 Patients with Severe Cardiopulmonary Failure. *ASAIO J* 2020; **66**: 472-474 [PMID: 32243267 DOI: 10.1097/MAT.0000000000001173]

76 **Rajagopal K**, Keller SP, Akkanti B, Bime C, Loyalka P, Cheema FH, Zwischenberger JB, El Banayosy A, Pappalardo F, Slaughter MS, Slepian MJ. Advanced Pulmonary and Cardiac Support of COVID-19 Patients: Emerging Recommendations From ASAIO-a Living Working Document. *Circ Heart Fail* 2020; **13**: e007175 [PMID: 32357074 DOI: 10.1161/CIRCHEARTFAILURE.120.007175]

77 **Valchanov K**, Krishnan U, Hoole SP, Davies WR, Pettit S, Jones N, Parmar J, Catarino P, Osman M, Berman M. COVID-19 patient with coronary thrombosis supported with ECMO and Impella 5.0 ventricular assist device: a case report. *Eur Heart J Case Rep* 2020; **4**: 1-6 [PMID: 33442588 DOI: 10.1093/ehjcr/ytaa342]

78 **Hodges K**, Mubashir M, Insler J, Estep J, Hsich E, Tong M, Insler S, Soltesz E. Successful management of COVID-19 and associated coagulopathy in a patient with durable left ventricular assist device. *J Card Surg* 2020; **35**: 3202-3204 [PMID: 32789890 DOI: 10.1111/jocs.14937]

79 **Chau VQ**, Oliveros E, Mahmood K, Singhvi A, Lala A, Moss N, Gidwani U, Mancini DM, Pinney SP, Parikh A. The Imperfect Cytokine Storm: Severe COVID-19 With ARDS in a Patient on Durable LVAD Support. *JACC Case Rep* 2020; **2**: 1315-1320 [PMID: 32292915 DOI: 10.1016/j.jaccas.2020.04.001]

80 **Singh R**, Domenico C, Rao SD, Urgo K, Prenner SB, Wald JW, Atluri P, Birati EY. Novel

Coronavirus Disease 2019 in a Patient on Durable Left Ventricular Assist Device Support. *J Card Fail* 2020; **26**: 438-439 [PMID: 32305569 DOI: 10.1016/j.cardfail.2020.04.007]

81 **Korada SKC**, Mann JA, Hasan AK, Baliga RR, Mokadam NA, Benza RL, Vallakati A. Management of COVID-19 in a durable left ventricular assist device recipient: A continuity of care perspective. *Heart Lung* 2020; **49**: 688-691 [PMID: 32861886 DOI: 10.1016/j.hrtlng.2020.08.012]

82 **Sobol I**, Yuzefpolskaya M, Roth Z, Colombo PC, Horn E, Takeda K, Sayer G, Uriel N, Naka Y. Characteristics and Outcomes of Patients With a Left Ventricular Assist Device With Coronavirus Disease-19. *J Card Fail* 2020; **26**: 895-897 [PMID: 32956813 DOI: 10.1016/j.cardfail.2020.09.011]

83 **Feldman D**, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J; International Society for Heart and Lung Transplantation. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant* 2013; **32**: 157-187 [PMID: 23352391 DOI: 10.1016/j.healun.2012.09.013]

84 **Carda S**, Invernizzi M, Bavikatte G, Bensmaïl D, Bianchi F, Deltombe T, Draulans N, Esquenazi A, Francisco GE, Gross R, Jacinto LJ, Moraleda Pérez S, O'dell MW, Reebye R, Verduzco-Gutierrez M, Wissel J, Molteni F. COVID-19 pandemic. What should Physical and Rehabilitation Medicine specialists do? *Eur J Phys Rehabil Med* 2020; **56**: 515-524 [PMID: 32434314 DOI: 10.23736/S1973-9087.20.06317-0]

85 **Lal A**, Mishra AK, John K, Akhtar J. Corticosteroids and rehabilitation in COVID-19 survivors. *J Formos Med Assoc* 2021; **120**: 1284-1285 [PMID: 33341350 DOI: 10.1016/j.jfma.2020.12.005]

86 **Smith JM**, Lee AC, Zeleznik H, Coffey Scott JP, Fatima A, Needham DM, Ohtake PJ. Home and Community-Based Physical Therapist Management of Adults With Post-Intensive Care Syndrome. *Phys Ther* 2020; **100**: 1062-1073 [PMID: 32280993 DOI: 10.1093/ptj/pzaa059]

87 **Long L**, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019; **1**: CD003331 [PMID: 30695817 DOI: 10.1002/14651858.CD003331.pub5]

88 **Schmidt C**, Magalhães S, Barreira A, Ribeiro F, Fernandes P, Santos M. Cardiac rehabilitation programs for heart failure patients in the time of COVID-19. *Rev Port Cardiol (Engl Ed)* 2020; **39**: 365-366 [PMID: 32680654 DOI: 10.1016/j.repc.2020.06.012]

89 **D'Amario D**, Restivo A, Canonico F, Rodolico D, Mattia G, Francesco B, Vergallo R, Trani C, Aspromonte N, Crea F. Experience of remote cardiac care during the COVID-19 pandemic: the V-LAP™ device in advanced heart failure. *Eur J Heart Fail* 2020; **22**: 1050-1052 [PMID: 32431021 DOI: 10.1002/ejhf.1900]

90 **Mitter SS**, Alvarez-Garcia J, Miller MA, Moss N, Lala A. Insights From HeartLogic Multisensor Monitoring During the COVID-19 Pandemic in New York City. *JACC Heart Fail* 2020; **8**: 1053-1055 [PMID: 33272384 DOI: 10.1016/j.jchf.2020.09.009]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 20-39

DOI: 10.5501/wjv.v11.i1.20

ISSN 2220-3249 (online)

REVIEW

COVID-19: A pluralistic and integrated approach for efficient management of the pandemic

Nouhoum Bouare, Daouda Kassim Minta, Abdoulaye Dabo, Christiane Gerard

ORCID number: Nouhoum Bouare 0000-0002-8362-6740; Daouda Kassim Minta 0000-0002-0333-5227; Abdoulaye Dabo 0000-0002-7238-3894; Christiane Gerard 0000-0002-9439-1692.

Author contributions: Bouare N contributed to manuscript drafting, reviewing and reading the final version; Minta DK and Dabo A contributed to manuscript reviewing and reading the final version; Gerard C contributed to manuscript drafting, reviewing and reading the final version.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: Mali

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Nouhoum Bouare, Biomedical Sciences Researcher, National Institute of Public Health, Bamako 1771, Mali

Daouda Kassim Minta, Department of Infectiology, CHU PointG, Bamako 333, Mali

Abdoulaye Dabo, Department Epidemiology & Infectiology Disease, Faculty Medicine & Dentistry, CNRST/Univ Bamako, Bamako 3052, Mali

Christiane Gerard, Formerly Responsible for the Blood Bank, CHU-Liège, University of Liège, Liège 4000, Belgium

Corresponding author: Nouhoum Bouare, DSc, PhD, Research Scientist, Biomedical Sciences Researcher, National Institute of Public Health, Hippodrome Rue Hamilcar Cabral, Bamako 1771, Mali. nouhoumsamakoro@yahoo.fr

Abstract

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which triggered the ongoing pandemic, was first discovered in China in late 2019. SARS-CoV-2 is a respiratory virus responsible for coronavirus disease 2019 (COVID-19) that often manifests as a pneumonic syndrome. In the context of the pandemic, there are mixed views on the data provided by epidemiologists and the information collected by hospital clinicians about their patients. In addition, the literature reports a large proportion of patients free of pneumonia *vs* a small percentage of patients with severe pneumonia among confirmed COVID-19 cases. This raises the issue of the complexity of the work required to control or contain the pandemic. We believe that an integrative and pluralistic approach will help to put the analyses into perspective and reinforce collaboration and creativity in the fight against this major scourge. This paper proposes a comprehensive and integrative approach to COVID-19 research, prevention, control, and treatment to better address the pandemic. Thus, this literature review applies a pluralistic approach to fight the pandemic.

Key Words: SARS-CoV-2; COVID-19; Pandemic; Pluralistic approach; Global approach; Efficient management

Received: April 21, 2021
Peer-review started: April 21, 2021
First decision: July 27, 2021
Revised: August 10, 2021
Accepted: December 28, 2021
Article in press: December 28, 2022
Published online: January 25, 2022

P-Reviewer: Pereira AA, Şehirli AÖ
S-Editor: Wang JJ
L-Editor: Webster JR
P-Editor: Wang JJ

Core Tip: Pandemic control requires optimal knowledge of the pathogen, infection routes, mode of transmission, and intervention strategies. The contagiousness of coronavirus disease 2019 (COVID-19) complicates pandemic control or containment because asymptomatic carriers, incubating patients, and recovered patients are all potentially contagious. This literature review proposes and justifies the value of a pluralistic and integrative approach to COVID-19 research, prevention, control and treatment.

Citation: Bouare N, Minta DK, Dabo A, Gerard C. COVID-19: A pluralistic and integrated approach for efficient management of the pandemic. *World J Virol* 2022; 11(1): 20-39
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/20.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.20

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of the ongoing pandemic, was first detected in late 2019 in Wuhan, Hubei Province, China. This novel respiratory virus causes the infectious coronavirus disease 2019 (COVID-19), which often manifests as pneumonia[1]. At least two previously identified coronaviruses, responsible for SARS-CoV and Middle East respiratory syndrome coronavirus, respectively, have accelerated the understanding of the epidemiology and pathogenesis of SARS-CoV-2[1-4]. Investigations are ongoing to determine the precise origin of the virus.

To control this global scourge, the scientific community and health professionals must invest in understanding the virus, the infection, its spread, the distribution, and its evolution to develop reliable strategies for prevention and/or response. However, public health professionals and/or infectious diseases specialists are often at the front line in the fight against outbreaks or pandemics. However, the statistics provided by epidemiologists often contrast with the information collected by practicing clinicians regarding their patients[5]. Although data collected from travelers coming from areas with a high incidence of COVID-19 may be useful for estimating the incidence, this risk measure is controversial. While epidemiologists use statistical methods or mathematical models to assess the magnitude of the epidemic in the community (*e.g.*, incidence), clinicians focus on patients based on the number of hospitalizations[5]. According to the literature, 80% of confirmed COVID-19 cases did not have pneumonia, approximately 15% had severe pneumonia, and approximately 6% were admitted to intensive care units (ICUs) for the treatment of respiratory failure, shock, or multiorgan damage[6]. Asymptomatic infected persons and incubating patients (potential sources of virus transmission) or patients who have recovered from COVID-19 without showing a reduced SARS-CoV-2 viral load by a factor of $1/10^6$ (*i.e.*, a 6-log reduction), can pose serious challenges for disease prevention and control[1,7].

This raises the issue of the complexity of pandemic control or containment. We believe that a pluralistic and integrated approach will put into perspective the specificities of each discipline and reinforce collaboration and creativity in the fight against this scourge. This paper proposes a collaborative approach of competencies to capitalize on expertise, an integrated strategy for interventions for the control of epidemic or chronic diseases, and a global patient management plan for disease and/or pandemic control.

METHODS

We analyzed the scientific literature according to six main areas of expertise. We searched the PubMed database to construct a clinical scientific bibliography. The basic search term used for the literature search was "covid+19," followed by one or other thematic terms, including virology, epidemiology, prevention, control, Africa, infection, and treatment. Preference was given to the "review" and "most recent" filters. The most appropriate articles for each thematic term were selected for the analysis and discussion. Table 1 summarizes the reference portals according to the corresponding target groups and disciplines. An additional search focused on the

Table 1 Documentary research by target groups and by specialty disciplines

Target groups	Documentary research links	Documentary search dates and periods	Main fields/remarks
Biologists	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+virology&filter=pubt.review	12/10/2020	Medical biology (virology, molecular biology, clinical biochemistry, hematology, immunology, *etc.*)
Public health professionals	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+epidemiology&filter=pubt.review	14/10/2020	Public health (epidemiology, community health, *etc.*)
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+prevention&filter=pubt.review	12/10/2020	
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+control&filter=pubt.review	13/10/2020	Communication (transversal)
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+Africa&filter=pubt.review	12/10/2020	
	https://eu.boell.org/en/2020/08/17/dr-congo-challenge-convincing-people-coronavirus-exists		
Clinicians	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+infection&filter=pubt.clinical study	12/10/2020	Medicine (infectiology, pneumology, cardiology, internal medicine, *etc.*)
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+treatment&filter=pubt.randomized controlled trial	13/10/2020	
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+vaccination&filter=pubt.review	14/02/2021	
Researchers	https://pubmed.ncbi.nlm.nih.gov/32230900/	January 2021	Research (transversal or universal character of science)
	https://www.ncbi.nlm.nih.gov/research/coronavirus/		
	http://www.health.belgium.be/eportal/disclaimer/		
	https://rega.kuleuven.be/if/corona_covid-19		
	https://covid19.sciensano.be/sites/default/files/Covid19/Covid19_fact_sheet_ENG.pdf		
Decision-makers	N/A		A pluralistic approach to inform and guide health policies

basic term "covid+19," followed by "vaccination" with "most recent" as the preferred filter. The PubMed literature search (including the additional vaccination search) was performed from October 12, 2020, to February 14, 2021 (Table 1). Figure 1 presents the flow chart of the search for articles and publications.

RESULTS AND DISCUSSION

Biology and virology

SARS-CoV-2 is a member of the coronaviridae family. It is a beta-coronavirus (subgroup B Sarbecovirus) enveloped with a large single-stranded RNA + that can infect animals and humans[8]. In humans, the structural (spike) protein of the viral envelope recognizes angiotensin-converting enzyme 2 (ACE2) as a receptor and preferentially infects pulmonary epithelial cells. The spike protein binding domain binds to ACE2; the host transmembrane protease serine 2 protease then cleaves the protein to expose fusion peptides that fuse the virus to cell membranes[2,9]. ACE2 is expressed in several human tissues, including the lung, small intestine, kidney, heart, thyroid and adipose tissues, which can be infected by SARS-CoV-2 and cause various symptoms[8,10].

The genome of SARS-CoV-2 is 96.2% and 79.5% identical to the sequences of RaTG13 (bat) CoV and SARS-CoV, respectively. Accordingly, bats are considered the natural host and a potential origin of the virus and may have transmitted the virus to humans through an unknown intermediary or directly *via* the aquatic wildlife market in Wuhan[8,11,12]. In the absence of strong evidence of pangolins as an intermediate host, some authors have suggested the need for coronavirus surveillance in these animals in the wild to minimize human exposure[13]. SARS-CoV-2 may also be transmitted by aerosols or vehicles (hands or soiled objects). Depending on the amount of inoculum, the virus can remain viable and infectious for hours in aerosols and days

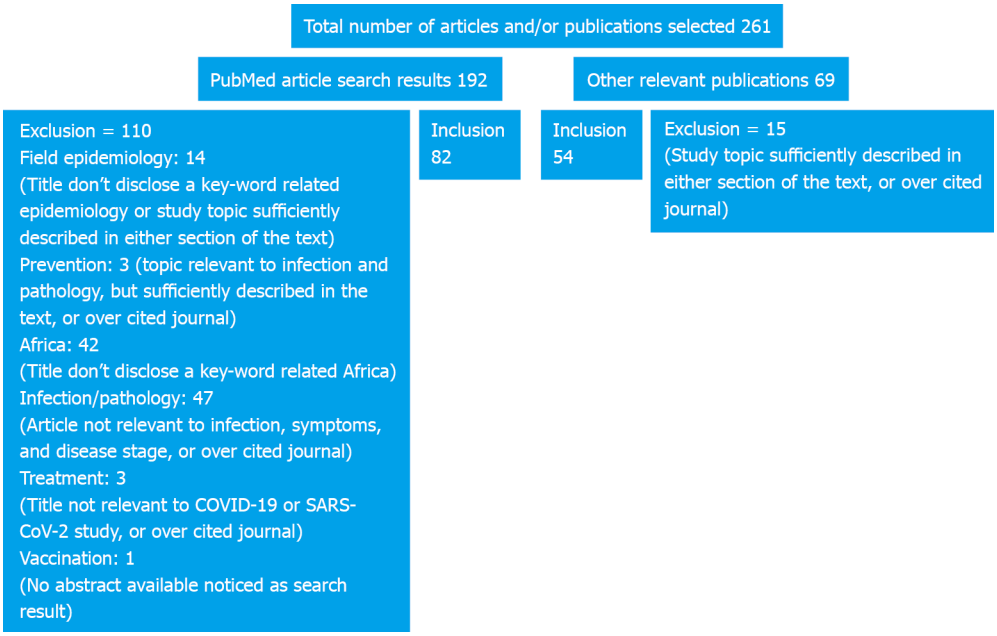


Figure 1 Flow chart of the search for articles and publications. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

on surfaces[14-16]. Longer SARS-CoV-2 and SARS-CoV-1 viabilities on stainless steel and plastic have been reported. The median half-life of SARS-CoV-2 was 6 h for stainless steel and 7 h for plastic[17]. Hence, universal hygiene precautions such as hand washing with soap and water, wearing masks, and cleaning surfaces have been recommended.

The pre-analytical phase is crucial. The quality of the analysis or results depends on the sample quality. Sputum samples may have viscous consistency due to mucus (purulent or not).

The effective extraction of viral nucleic acid requires the liquefaction of sputum to avoid false-negative results[18]. Moreover, the use of swabs made of non-compliant materials may inactivate the virus particles or inhibit polymerase chain reaction (PCR). For nasopharyngeal or oropharyngeal swabs, swabs (standard or flocked) with a flexible plastic shaft are recommended. Quantitative molecular tests (quantitative reverse transcription-PCR) are used to complement clinical, biological, and radiological investigation tools[19]. Although molecular tests are highly specific for the diagnosis of COVID-19, their sensitivity depends largely on parameters such as the specimen type, time of specimen collection, sampling technique, test quality, and technician qualification[20-23].

Immunoassays measure the levels of antibodies [circulating immunoglobulin M (IgM) and IgG] in patients with COVID-19. However, the usefulness of these tests as an epidemiological tool is questioned in terms of their sensitivity and specificity, since the results may vary depending on the serological window. This window must be neither too early nor too late to produce an interpretable result[24].

One study reported a higher sensitivity for the detection of IgA (about 4-25 d after disease onset), with IgG reportedly better for diagnosis in later stages of the disease [25]. A diagnosis of COVID-19 is suspected in cases in which the symptoms of respiratory infection occur within 14 d (consistent with the incubation time) in an asymptomatic person coming from an epidemic area[26]. The association of SARS-CoV-2 viral load relative to the nasopharyngeal specimen with COVID-19 severity has been reported, in which a higher viral load was associated with a lower lymphocyte count, greater organ damage, and longer time to molecular test negativity[27]. Higher viral loads were detected soon after symptom onset, with higher loads in the nose compared to throat swabs. The same study suggested that the kinetics of SARS-CoV-2 nucleic acid clearance resembled that of influenza and differed from that of SARS-CoV. In addition, the similarity of viral loads in symptomatic and asymptomatic patients suggests that minimally or asymptomatic people may potentially be infectious. Therefore, transmission may occur early during infection. Case detection and isolation may require strategies different from those previously used to control SARS-CoV. The identification of minimally or asymptomatic patients and modest

levels of viral RNA (detectable in the oropharynx) suggest the need for further investigation to determine the transmission dynamics and inform screening practices[28]. Furthermore, the implications of positive (or negative) test results in asymptomatic individuals remain undetermined, as well as the interpretation of these results for immune passports (detection of signals of past infection). The findings seem to contradict much of the popular literature on the use of the test as a tool for COVID-19 management. Although testing is an essential part of disease management, including COVID-19, its inappropriate use may have unintended adverse consequences[29]. Therefore, clinicians must consider other factors when interpreting a patient's test results. The Food and Drug Administration (FDA) issued approval to biotechnology firms to provide COVID-19 tests. One of the major areas of FDA intervention is to increase the availability of tests, treatments, and materials such as ventilators and personal protective equipment (PPE)[30,31]. The World Health Organization (WHO) regularly updates the list of qualified reference laboratories to confirm COVID-19 test results[32].

Epidemiology

To better control the epidemic, scientists are investigating how SARS-CoV-2 is transmitted and spread. Initial data from patients in China provided information on the mode of human-to-human transmission, mainly *via* the respiratory route, most likely through close contact[33,34]. Human-to-human transmission was demonstrated in the first confirmed cases of infection in Wuhan, China[28]. It is generally accepted that the more a person interacts with others and the longer this interaction lasts, the higher the risk of COVID-19 transmission. However, further investigations are needed to understand if and how different animals may be affected by this disease. Researchers at the Friedrich Loeffler Institute in Germany reported that raccoon dogs (*Nyctereutes procyonoides*), an invasive carnivorous animal used for fur, are a potential intermediate host in SARS-CoV-2 transmission. The researchers proposed that the farms where these animals are raised may serve as reservoirs for SARS-CoV-2 and that this risk should be mitigated by effective and continuous surveillance. In their opinion, while it is possible to control the virus on farms, spillover to susceptible wildlife and, in particular, to free-living raccoon dogs would be a major challenge to elimination[35]. Signs of respiratory pathology and increased mortality have also been described in farmed minks (*Neovison mink*) infected with SARS-CoV-2[36,37]. Evidence of animal transmission of SARS-CoV-2 to humans on mink farms was also reported in a phylogenetic study[38]. However, the authors indicated that some farm residents may have been infected within their households and not directly *via* the mink. They added that the survey did not identify common factors that could explain the spread among farms, probably *via* temporary workers not included in the tests. They were concerned that the fur production and trade sector not become a reservoir for the future re-emergence of SARS-CoV-2 in humans.

Globally, incidences ranging from 0.00 to 61.44 per 1000000 persons were reported for COVID-19 at the end of February 2020. Much lower incidences (perhaps due to weaknesses in reporting systems) were recorded in Africa (0.00 for Nigeria and 0.02 for Algeria). In contrast, higher incidences of 55.06 and 61.44 were reported in China and the Republic of Korea, respectively. The numbers of deaths per 1000000 people ranged from 0.00 in Nigeria to 1.97 in China[39]. Africa accounts for less than 1% of the global SARS-CoV-2 mortality[40].

A molecular study reported the early transmission of COVID-19 and a heterogeneous epidemic in South Africa[41]. The study sought to better understand the epidemic heterogeneity of SARS-CoV-2 strains and their introduction during the first month of the epidemic in that country. The early introduction of SARS-CoV-2 into Kwazulu Natal resulted in a localized outbreak in one hospital, which is a likely explanation for the initially high mortality rates in the province. The high rate of COVID-19 transmission in the Western and Eastern Cape highlights the critical need to strengthen local genomic surveillance in South Africa.

All 54 African countries officially reported cases of COVID-19. More than 3000000 people tested positive for COVID-19, with more than 99000 deaths (3.3%). These relatively low levels of mortality may be due to the rapid response in some countries, including South Africa, Uganda and Ethiopia. In addition to the rapid and insightful implementation of stringent response measures, the demographics of the continent (the youthfulness of the sub-Saharan African population) may have conferred some advantage, as a large fraction of deaths caused by COVID-19 occurs in patients over 70 years of age[42,43]. However, the hypothetical effectiveness of containment measures across this continent may be premature. Poor reporting quality, limited communication systems for patients and health professionals, and insufficiency of

surveillance and screening centers across the continent may also contribute to the low reported numbers. The registration rates of all deaths and their causes are incomplete in many African countries because accurate estimates are difficult to obtain, with coverage of registered deaths varying from 5% in Mozambique, 16% in Zambia, 25% in Botswana and Ghana, and 67% in South Africa[44]. In addition, COVID-19 may be confused with other infectious diseases, such as malaria, typhoid, human immunodeficiency virus (HIV)-AIDS, and tuberculosis[45]. These confounding factors can negatively impact the reporting of cases and deaths attributable to COVID-19[42]. Moreover, cultural challenges such as community stigmatization of infected patients, who consequently avoid medical assistance and consult traditional practitioners, further lead to underreporting. Country experience with pandemics and epidemics varies across the African continent, which may influence preparedness (*e.g.*, availability of testing and PPE). West African countries may be better able to respond given their recent experiences with Ebola. Similarly, East African countries have also gained critical epidemic experience from cholera, which has repeatedly affected the region in recent years[46].

The uncertainties regarding the impact of SARS-CoV-2 infection in Africa underscore the need for critical monitoring of the evolution of the pandemic and the factors affecting disease burden. Even in the absence of more effective vaccines and treatments, Africa can lead the fight against this scourge provided that appropriate containment intervention systems are put in place by addressing systematic challenges such as access to water, improved food systems, health education, bed capacity in intensive care hospitals, and increased funding and investment in health care[40].

Infection and pathology

The onset of clinical symptoms seems to favor contagiousness. In some individuals, contagiousness may occur several days before symptom onset. However, contagiousness is more marked in symptomatic persons during coughing. The average incubation period varies from 5 to 6 d, ranging from 2 to 14 d, which justifies the 14-d quarantine period[34]. The initial symptoms (headache, muscle pain and fatigue) are not specific and are followed 2 or 3 d later by fever and respiratory signs.

The clinical manifestations can be severe. Scientists are still seeking to understand COVID-19 severity. Preliminary descriptive studies of databases in China indicated an average time of 1 wk from symptom onset to hospital admission when the disease becomes severe. At this stage, the symptoms include fever, cough, chest pain, and respiratory discomfort. Chest computed tomography (CT) scans almost always show bilateral pneumonia[47]. Since the initial studies, other reported clinical signs include central nervous system involvement (*e.g.*, disorientation, especially in the elderly); sudden loss of taste and/or smell, which occur infrequently but allow confirmation of COVID-19 diagnosis[33,48]. Many patients with COVID-19 present neurological symptoms (including headache, myalgia, and altered consciousness), that are sugg-estive of the disease.

Some patients with SARS-CoV-2 present with symptoms suggestive of acute stroke, epilepsy, encephalopathy, and demyelinating neuropathies and without cough, fever, or other respiratory problems that could provide clues to the underlying pathology. Diagnosing and administering appropriate treatments to these patients is challenging and requires specialized neurologists, which are sorely lacking in Africa[42].

Real-time Assessment of CommunityTransmission-1 study data showed that chills, loss of appetite, headache, and muscle pain were the symptoms most strongly associated with infection, along with the four classic symptoms. The presence of one or more symptoms was associated with SARS-CoV-2 infection, with stronger associations with increasing numbers of symptoms. A loss or change of smell was less predictive of COVID-19 infection, while the proportion of people testing positive with a persistent new cough appeared to be increased[49].

The severity of clinical signs requires hospitalization in approximately 20% of patients, while 5% require admission to intensive care. The most severe forms are mainly observed in people who are vulnerable because of their age (over 70 years) or comorbidities (including diabetes and cardiovascular diseases)[47]. Patients with COVID-19 requiring ICU hospitalization are generally frail and have significant comorbidities. The outcomes in this group were generally poor and did not appear to be influenced by ICU admission. Symptoms of COVID-19 infection occurred during hospitalization for a different medical problem in 38% of the patients analyzed[50].

Observational and modeling studies have shown 30% to 60% of infected patients are asymptomatic (absence of clinical manifestations) or "paucisymptomatic" (presence of few symptoms)[47].

Determination of the clinical, laboratory, and radiological characteristics of patients suspected of COVID-19 infection are essential for early isolation, treatment, and contact tracing[51]. A positive COVID-19 test result in patients with hip fractures was associated with a 2.4-fold increase in 30-d mortality risk[52]. During the peak period of the COVID-19 epidemic in New York city, more than half of patients with emergent large vessel occlusion (ELVO) stroke were positive for COVID-19 and were younger, more likely to be male, and less likely to be white. These findings also suggested an increased incidence of ELVO stroke during the peak of the COVID-19 epidemic[53]. One study suggested that conditions (comorbidities, rheumatic diseases) and abnormal laboratory parameters such as C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), and increased serum ferritin levels were significantly associated with mortality, in contrast to a previous use of antirheumatic drugs. The authors suggested that inflammation was closely related to COVID-19 severity. Their key findings were as follows: (1) Most patients recovered from COVID-19 disease; (2) The use of antirheumatic drugs, corticosteroids, and biological agents did not increase the risk of mortality; and (3) Rheumatic disease activity may be associated with mortality[54].

Advanced age, diffuse distribution, and hypoxemia may help clinicians to identify COVID-19 patients with a poor prognosis. Similarly, aggregated social media data may also influence disease prognosis[55]. Higher troponin T levels and lower lymphocyte counts were predictive of disease progression. Early ventilation may be an effective treatment for severe cases[56]. Severe and consistent lymphopenia with significantly reduced lymphocyte subgroups with normal CD4/CD8 ratio has been reported in critically ill patients. In addition, extremely reduced transferrin saturation at ICU admission and a significant increase on days 3 to 6 with constant hyperferritinemia during the ICU stay have been reported[57]. More severe COVID-19 disease was observed in patients who were older, male, African-American, obese, diabetic, and with a higher overall comorbidity burden. Certain comorbidities paradoxically increased the risk in younger patients in most cases. Among inpatients, male sex was the primary determinant of the need for more intensive care. Further investigations are needed to understand the mechanisms underlying these findings[58]. A cohort study of COVID-19-related deaths in Ontario, Canada, reported a concentrated risk of mortality among residents of long-term care (LTC) facilities, which increased over a short time. A study on preventing the spread of COVID-19 between facilities reported the need for the early identification of risk, which necessitates screening and provision of PPE to staff as well as restructuring of LTC staff[59]. Patients with COVID-19 with an increased ST-segment myocardial infarction (STEMI) picture showed a favorable disease course to a high thrombotic burden and poor prognosis[60]. The authors suggested the need to determine the COVID-19 status in all STEMI cases. They also suggested the need for further work to understand the mechanism of increased thrombosis and identify aggressive antithrombotic therapy. An observational study reported the correlation of amino acid and fatty acid metabolism with COVID-19, providing information on the mechanism, potential markers of clinical severity, and potential therapeutic targets[61]. LDH and CRP may influence respiratory function and may be considered predictive of respiratory failure in patients with COVID-19. The authors suggested the usefulness of these biological markers for the early identification of patients requiring closer respiratory monitoring and more aggressive supportive therapies to avoid a poor prognosis[62]. One study observed that ischemic and hemorrhagic strokes complicated the course of COVID-19. In that series, these events occurred mainly in patients with severe pneumonia and multiorgan failure. Liver enzymes and LDH levels were markedly increased in all cases, and the prognosis was poorer[63]. Another study reported that more than half of the infected patients with cancer were susceptible to severe COVID-19. This risk was exacerbated by concurrent anticancer treatment and predicted poor survival despite COVID-19 treatment[64].

A transient twofold increase in the incidence of out-of-hospital cardiac arrest, associated with reduced survival, was observed during the pandemic, in contrast to data observed in a similar period during previous pandemic-free years. The authors proposed that this finding was partly related to COVID-19 but was also likely due to the indirect effects of the pandemic associated with lock-in and rehabilitation of healthcare services. They suggested that these factors should be considered when reviewing mortality data and public health strategies[65]. While the correlation between the prevalence of heterozygous beta-thalassemia and COVID-19 immunity has been reported, further investigations are required to confirm this finding[66].

Prevention, control, and communication

Communication strategies should focus on the routes of transmission (upper airways), modes of contamination (direct contact with respiratory secretions through airborne droplets and indirect contact through hands or soiled objects), and means of prevention. These strategies must be based on reliable and credible information and data. Prejudices and misinformation about the disease are often based on preliminary observations that are sometimes unreliable and speculative. However, this leads to confusion, panic, and anxiety among citizens[67]. This situation has been described as an "infodemic" by the WHO[68]. Clear and simple coherent messages based on the risk of transmission are preferred for good compliance with barrier measures[69]. Strict compliance with individual protective measures, combined with collective measures (containment, discouragement of gatherings), contributes synergistically to breaking the chain of transmission of both SARS-CoV-2 and other respiratory pathogens[70]. Measures such as containment and discouragement of gatherings help to reduce population density and, thus, reduce viral transmission.

Above all, distracting and/or annoying messages, as well as biased and sometimes unjustified measures, should be avoided. Anxiety-provoking messages should be avoided, as they cause panic and stress, emotional factors that weaken the immune system and, thus, expose the body to pathogens. Collective concerns can influence daily behaviors, economics, prevention strategies, and political decision-making of health organizations and medical centers, weakening COVID-19 control strategies, resulting in high morbidity and mental health needs worldwide[71].

The following means of protection and/or prevention are recommended: (1) Hand washing with soap and water; (2) Antiseptics (hydroalcoholic hand rubs); (3) Disinfection of soiled areas and materials using sodium hypochlorite or glutaraldehyde; (4) Wearing protective equipment (bibs, masks, gloves, lab coat, gowns, *etc.*); (5) Prohibition of activities that encourage gatherings to reduce the risk of viral spread; and (6) Home confinement if possible, especially during the outbreak[33,72-74].

However, frequent hand washing involves prolonged exposure to water and other chemical or physical agents, which results in pathophysiological variations. Undesirable dermatological effects such as excessive skin dryness or contact dermatitis (most often irritating and sometimes allergic), can occur, especially in people with a history of atopic dermatitis. These skin conditions are manageable with the application of a moisturizer immediately after hand washing or disinfectant use to prevent hand eczema[75].

It is important to remember certain public health concepts. The public health system (PHS) plays a key role in both patient management and disease prevention or control. In other words, achieving medico-social objectives requires an efficient, proactive PHS that is well adapted to the realities on the ground. Weak PHSs often face two main challenges in the management of an epidemic or a pandemic: The quality and/or the capacity of response and the compliance of people with the measures prescribed to cut the chain of transmission. Therefore, in the context of COVID-19, one study suggested strengthening the response capacity while recommending adequate prevention measures to avoid the risk of a resurgence of the epidemic[76].

The detection of more COVID-19-positive patients in the community along with compliance with adequate quarantine rules will reduce the number of secondary cases. This requires an increased testing capacity[77]. The limited availability of diagnostic tests makes it almost impossible to detect asymptomatic patients and adds to the uncertainty of the potential impact of SARS-CoV-2 infection in Africa, particularly concerning prevention strategies and economic impact[40]. The implementation of a robust prevention system along with compliance with individual or collective barrier measures (*e.g.*, containment, even if it appears more difficult to bear), is the most effective way to respond to the COVID-19 pandemic[78-80]. The WHO contributes to regularly updated guidelines for the home care of patients with COVID-19 with minor symptoms and the management of contacts, as well as operational guidelines for the management of patients in health facilities and communities, the quarantine of individuals in the context of COVID-19, the clinical management of severe acute respiratory infection when COVID-19 is suspected; and laboratory testing of suspected cases of COVID-19[81]. In addition, in the context of microbiological biosafety, the PPE guidelines are regularly updated[82]. In general, these guidelines are intended to provide information on PPE options in relation to safety and effectiveness to ensure better protection of healthcare workers and patients[74].

In addition to national and international guidelines, special attention must be paid to chemical or physical agents. Chemical agents exist in liquid or gaseous form; physical agents are, among others, heat, UV, and gamma rays. While chemical agents are used for antisepsis, disinfection, and/or sterilization, physical agents are generally

used for sterilization[83]. As PPE remains insufficient and decontamination methods are less cost-effective because they are complex, slow, expensive, and particularly unsuitable for low- and middle-income countries where the need is greatest, some researchers are investigating a new PPE decontamination option. They suggested a low-temperature, low-ambient humidity (WASP-D) decontamination method based on the 30-min or shorter half-life of SARS-CoV-2 (and other common pathogens) at temperatures > 45 °C, combined with the fact that most PPE is designed to be transported and stored safely at temperatures < 50 °C. They concluded that the decontamination of PPE at 12 h, 46 °C, and ambient humidity reduced the SARS-CoV-2 viral load by a factor of 10^{-6} (*e.g.*, $1/10^{6}$), without adversely affecting PPE materials or performance[84]. A test of three mask models purchased from supermarkets and drugstores showed that surgical masks, normally intended to be discarded after 4 h of use, retained very good filtration capacities after 10 machine washes at 60 °C. These masks also remained breathable enough to be worn for several hours without excessive discomfort. Finally, even after several washing cycles, these masks exceed the minimum requirements for fabric masks with an official filtration guarantee[85, 86]. Results in the literature showed that a universal face mask could help to reduce disease severity and strengthen the immunity of the wearer, since high doses of viral inoculum can overwhelm and deregulate the innate immune defenses, aggravating the disease[87]. While there has been apprehension regarding the accumulation of carbon dioxide during prolonged face mask wear, experimental studies have refuted this hypothesis. An observational clinical study reported that wearing face masks neither significantly restricted gas exchange (oxygen flow) nor contributed to carbon dioxide accumulation, even in individuals with pulmonary insufficiency. Nevertheless, prolonged use of face masks can negatively impact breathing, leading to heat stress, drowsiness, breathing difficulties (restricted flow of fresh air), and unusual heart rates. The discomfort experienced with the use of a surgical mask has also been attributed to neurological reactions or associated psychological phenomena such as anxiety, claustrophobia, or affective responses to a perceived difficulty in breathing. In addition, if a face mask is worn for a longer time, the filter becomes wet due to facial sweat and vapor from breathing, promoting particle clogging. Wearers may also experience a false sense of security, encouraging them to spend more time in public places. The other potential side effects of wearing face masks include skin irritation, discomfort from exhaled air entering the eyes, and speech quality and volume during conversations[87].

In addition to the classical measures (barriers or prevention), other factors can optimize COVID-19 prevention or control. Vitamin D is a promising agent for COVID-19 control, as it is involved in various pathophysiological mechanisms that occur during SARS-CoV-2 infection. High-dose vitamin D supplementation, particularly for at-risk groups, is recommended for the maintenance of serum levels between 40 and 60 ng/mL of 25-hydroxy vitamin D needed to prevent or treat COVID-19[88]. Vitamin supplementation or treatment of deficiency may be useful in areas with a high prevalence of hypovitamin D. The role of medicinal plants, including *Allium sativum, Camellia sinensis, Zingiber officinale, Nigella sativa, Echinacea spp., Hypericum perforatum, Glycyrrhiza glabra, and Scutellaria baicalensis*, in enhancing immunity has been reported. Terpenoids show promising effects in inhibiting viral replication, a finding that requires further study. Some alkaloids such as homoharringtonine, lycorine, and emetine have shown potent anti-coronavirus effects. Naturally occurring products such as emodin and baicalin can inhibit protein S production. Other enzymatic targets involved in coronavirus replication, included 3-chymotrypsin-like protease (3CLpro), papain-like protease, helicase, and RNA-dependent RNA polymerase, are inhibited by iguesterin, cryptotanshinone, silvestrol and sotetsuflavone. Consequently, natural products have been introduced as therapeutic agents against COVID-19[89]. A study reported the importance of essential nutrients in the diet for their beneficial effects on immune system function. The intake levels of relevant micronutrients (D, C, B12, and iron) were inversely associated with higher COVID-19 incidence or mortality, especially in subjects genetically predisposed to suboptimal micronutrient levels[90]. The nutrigenetic data obtained from the joint assessment of essential nutrients and the genetic factors that limit their bioavailability can serve as a fundamental tool to help strengthen the immune systems of individuals and prepare populations to fight infectious diseases such as COVID-19[90]. The multiple biological actions of hesperidin and vitamin C suggest that these two major citrus components that modulate systemic immunopathological phases, may be candidates to fight SARS-CoV-2 infections. Experimental studies are needed to corroborate the hypothesis that herbal or plant foods could contribute to COVID-19 prevention[91,92]. The beneficial role of Chinese medicine in the control of respiratory diseases, such as the common cold, has

been reported[93].

The "mandatory Bacillus Calmette-Guérin (BCG)" vaccination approach has shown a reducible effect on COVID-19 infection and mortality rates. Two immunological mechanisms; namely, the heterologous effects of adaptive and innate immunity induced by BCG vaccination, could explain host tolerance to COVID-19 infection. However, no direct evidence supports this biological background. Clinical trials related to BCG vaccination against COVID-19 are currently under investigation. In the absence of strong evidence, BCG cannot be recommended for COVID-19 prevention, although this is not an absolute contraindication[94].

Data suggest that people with epilepsy (PWE) have a low risk of being infected with SARS-CoV-2 and have less severe manifestations of COVID-19 due to their epileptic pathology alone[95]. The mechanisms of the activating effect of hyperventilation (HV), which causes deep and rapid breathing during seizures in PWE, are less well known. Although concrete evidence is lacking, if wearing a face mask can stimulate HV, at least to some extent, this practice should not be indiscriminately recommended to all PWE. However, in the absence of any proven COVID-19 treatment or vaccine, prevention is the best available strategy and it is probably not reasonable to suggest avoiding face masks in PWE under any circumstances[95]. Logically, this population does not need to wear a face mask most of the time, as long as there is no close contact with others, especially during intense physical activities. Instead, it is probably more beneficial to wear a face mask with intermittent breaks in crowded areas in safe, low-density areas[95].

Given the COVID-19 pandemic, there is emerging evidence that, compared to the general population, patients with cancer are particularly vulnerable to infection and adverse events, with correspondingly worse outcomes[64,96]. On admission or before initiating systemic therapy or radiotherapy, confirmation of COVID-19 status is recommended in asymptomatic or paucisymptomatic patients, especially those with high-risk features[23].

Regarding transfusion, the American Blood Bank Association and the Centers for Disease Control and Prevention (CDC) have made no specific recommendations regarding SARS-CoV-2[97].

Although no evidence of the transmission of SARS-CoV-2 through blood transfusion has yet been established, the blood supply has been affected by the COVID-19 pandemic[24,34].

The opportunity now exists for schools and academies to collaborate to advance science and potentially improve student outcomes[98].

SARS-CoV-2 has developed mutations in various parts of its nonstructural proteins (NSPs), particularly NSP2, NSP3, protein S, and RNA-dependent RNA polymerase. Because of the critical importance of mutations in SARS-CoV-2 pathogenicity and the development of serodiagnostics, antivirals, and vaccines, continuous molecular surveillance of the virus is recommended[99]. While seasonal changes, coordinated laboratory testing, isolation/quarantine, and school closures may help to control the COVID-19 pandemic, they are unlikely to stop SARS-CoV-2 transmission. Therefore, effective policies complementary to currently available control measures must be adopted to minimize the exponential spread of infection[100].

Achieving global goals, including the control of pandemics such as COVID-19, requires a strong commitment to impactful public policies and international collaborations, including universal vaccinations against COVID-19, with potential combination with both childhood and adult immunization programs and programs for the treatment of malaria, tuberculosis, HIV/AIDS, and neglected tropical diseases[101]. The core unit (public health office) of the Sri Lankan health system has earned the trust of the community because of its deep-rooted operations on the ground. It has expertise and extensive connectivity with the community. Thus, rigid prevention and control measures have been implemented in the geographical areas assigned to these health facilities. The managerial role of this unit should be further explored for future health system reforms[102] and effective strategies should be developed to strengthen the PHS at its core[103].

It is important to note that information may vary depending on the evolution of the epidemic and research findings[23]. In COVID-19, studies are progressing rapidly and knowledge is changing such that we must realize that today's truths may not be tomorrow's and that we must continue to increase our knowledge of this disease.

Treatment

To avoid patient harm, because of possible coinfections, a diagnosis should be made before starting possible anti-infectious probabilistic anti-influenza, oseltamivir, and/or antibiotic treatment[72]. Other drugs and/or vaccine candidates have been suggested

for treatment, although clinical studies are needed to provide solid evidence of their effectiveness[104].

Tocilizumab improved the clinical status of patients with severe COVID-19[105]. Corticosteroid therapy with high-dose methylprednisolone, followed by tocilizumab when necessary, rapidly restored respiratory function, decreased in-hospital mortality, and reduced the need for invasive mechanical ventilation in patients with COVID-19-associated "cytokine storm" syndrome. However, further investigation of these promising results is required[106]. The role of Chinese medicine as an adjunctive treatment for SARS-CoV-2-induced inflammation has also been reported. Yidu-toxicity could address SARS-CoV-2-induced inflammation by blocking pulmonary syndrome by eliminating inflammatory agents[107]. Moreover, Xuebijing injection effectively improved the levels of inflammatory markers and prognosis of patients with severe COVID-19[108].

Other conventional drugs have also been used. Ruxolitinib showed faster improvement in clinical status, significant improvement in heart tomography, faster normalization of lymphopenia, and a favorable side effect profile in patients with severe COVID-19. These results are informative for testing the efficacy of ruxolitinib in a larger population[109]. Colchicine showed a statistically significant improvement in the time to clinical deterioration in patients hospitalized with COVID-19; however, this result should be interpreted with caution because of the low statistical significance of the results[110]. Remdesivir (RDV) did not show a significant clinical outcome in patients with moderate COVID-19 compared to standard therapy[111]. However, this antiviral agent has shown efficacy against the severe form of COVID-19[111]. This drug also showed favorable pharmacokinetic (PK) and safety profiles in healthy volunteers who were administered the drug once daily[112]. These PK and clinical safety data and preliminary clinical data support further investigation of RDV in patients with COVID-19[112].

Drugs such as hydroxychloroquine are thought to be effective owing to their effects on the ACE2 receptors required for viral entry into the cell. While chronic treatment can lead to heart disease with impaired left ventricular function and conduction disorders with bradycardia, short-term treatment can also cause cardiac damage in some patients. It is important to consider parameters such as age, female sex, ionic disorders, renal insufficiency, and the combination of many products, which are risk factors for cardiac damage. Thus, it is prudent to follow recommendations for safe treatment with "chloroquine" to minimize damage and/or adverse reactions[24,113]. In patients with persistent (mild to moderate) COVID-19, the rate of negative conversion of hydroxychloroquine was comparable to that of standard treatment alone [113].

Regarding adverse drug reactions, a hospital-based pharmacovigilance study reported a high prevalence of adverse reactions in patients with COVID-19, a fortiori caused by drugs inducing gastrointestinal and hepatic disorders. The length of hospital stay, number of drugs used, and underlying diseases were risk factors for the occurrence of adverse reactions in patients with COVID-19[114].

Researchers believe that "the" treatment will require a combination of drugs to effectively control emerging diseases, including COVID-19, HIV, and hepatitis C infections[104]. Early triple antiviral therapy has shown superiority over lopinavir-ritonavir to suppress symptoms and shorten the duration of viral clearance and hospitalization in patients with mild to moderate COVID-19. Future investigation of dual antiviral therapies is warranted, with interferon beta-1b as the background regimen [115].

A ligand-protein interaction study in Africa reported that more than half of the 20 major alkaloids and terpenoids interacted favorably with 3CLpro, which controls coronavirus replication, and had higher binding affinities than those to lopinavir-ritonavir. The study identified substances such as 10-hydroxyusambarensine, cryptoquindoline (alkaloids), 6-oxoisoiguesterin, and 22-hydroxyhopan-3-one (terpenoids), which bind to the receptor and 3CLpro catalytic dyad of SARS-CoV-2. These compounds were identified by predictive analysis of the (absorption, distribution, metabolism, and excretion)/tox and Lipinski filters. However, further experimental analysis of these leads is required for the discovery of natural anti-COVID-19 therapeutic agents to combat the pandemic[116].

Immunotherapy *via* the administration of the plasma of people cured of COVID-19 may be a useful treatment method in countries in which this practice is possible[117].

A Jewish business news source reported that 96% of patients administered an innovative drug (EXO-CD24) were cured[118]. Testing of this technology in the first clinical phase in humans showed that 29 out of 30 patients with moderate to severe disease were discharged from the hospital within 3-5 d. EXO-CD24 is an innovative

preparation based on exosomes enriched with the CD24 protein. According to Nadir Arber, one of the leading physicians and researchers on the team that developed the drug, "Even if the vaccines work and no new mutations are produced, SARS-CoV-2 will stay with us". He adds that a drug was developed within 6 mo from the time the idea was conceived and the technology was developed until it was first tested in humans in the first clinical phase. The Ichilov Medical Center reported that EXO-CD24 uses exosomes - tiny carrier sacs that shuttle between cells - to deliver a protein called CD24 to the lungs and has been the subject of decades of research by Dr. Arber. CD24 is located on the cell surface and plays an important role in regulating the immune system. The protein helps to modulate the immune response and curb the lethal hyperreactivity of the immune system known as a cytokine storm. The administration of EXO-CD24 by direct aspiration into the lungs inhibited immune hyperreactivity resulting from cytokine amplification following SARS-CoV-2 infection[118]. Cytokine storms are a physiological reaction in humans, in which the innate immune system causes uncontrolled and excessive release of pro-inflammatory signaling molecules called cytokines. EXO-CD24 is moving into further testing phases[118].

Vaccination

Vaccination has generated significant interest among people in general, and researchers in particular. People with severe mental illness are at risk of SARS-CoV-2 infection because of the morbidity and mortality associated with COVID-19. Therefore, this population requires early access to safe and effective vaccines. However, further studies are needed to evaluate the efficacy, safety, and interactions of the vaccine with psychotropic drugs, specifically in patients with COVID-19, so that they can be properly informed about the benefits and risks of vaccination[119]. The rapid development of vaccines can have adverse effects, prompting long-term studies and years of post-vaccination treatment. However, for most treatments, the benefits outweigh the risks and many more people - and in most countries - need the vaccine, due to the collapse of economies and the subsequent crippling of livelihoods. With families losing large numbers of relatives to the virus, vaccination may help to restore the quality of life for hundreds of millions, if not billions, of people worldwide. Innovative strategies have improved the efficiency of processes within research models for novel therapies, ultimately accelerating the administration of potential novel treatments to patients [120]. Because the types or incidence of the side effects of COVID-19 vaccines in individuals with Parkinson's disease (PD) do not appear to differ from those observed in the general population, COVID-19 vaccination with approved vaccines can be recommended to patients with PD unless there is a specific contraindication. However, some caution is warranted in the vaccination of very frail and terminally ill elderly patients with PD living in LTC facilities[121].

The Standing Committee on Vaccination (STIKO) vaccination recommendations are recognized as medical standards. The current instructions for the vaccination of immunocompromised patients and the recommendation for COVID-19 vaccination, together with the scientific knowledge and rationale of STIKO, represent a valuable basis for medical action in the field of vaccination against infectious diseases[122]. To date, vaccine-related allergic reactions are rare. Current CDC reports suggest that anaphylactic reactions related to Pfizer-Bio-NTech mRNA vaccines may occur more frequently than with other vaccines. Therefore, to support large-scale COVID-19 vaccine delivery programs, allergists should offer clinical phenotyping, risk stratification, and clear recommendations based on reliable and credible information[123]. At present, there are insufficient data on COVID-19 co-infections with influenza or how these cases would evolve clinically, although they could place a significant burden on an already stressed healthcare system. Until an effective and proven COVID-19 vaccine is available, high influenza vaccination coverage should be the highest priority[124]. The obese population is vulnerable to COVID-19, requiring special attention during this pandemic to avoid complications. In the absence of COVID-19 vaccination, regular physical activity and a healthy diet are recommended, with special attention paid to mental health. Extended quarantine and prophylactic vitamin D administration should also be considered[125]. A study conducted in Australia reported that successful COVID-19 vaccination requires that the government consider elements in its vaccination policy such as the estimation of herd immunity thresholds, vaccine delivery strategies, vaccination clinic locations, provisions for health personnel and training, and strategies for prioritizing vaccines. Moreover, pharmacists should play a key role in the delivery of mass COVID-19 vaccination programs[126]. For the pediatric population, before a safe and effective COVID-19 vaccine is available, the focus should be on making the best use of already available childhood vaccines. Vulnerable or healthy children must be vaccinated according to

the recommended schedules to protect young patients and avoid future epidemics caused by vaccine-preventable diseases such as measles[127].

Independent groups of experts must be involved in life-saving actions to counter anti-vaccine propaganda and provide scientific information to the general public. If the pandemic is to be controlled to benefit the public interest, academic and medical societies and policymakers must speak the same language. Otherwise, the battle will be lost to those who oppose scientific evidence while offering no solution to the problem[128]. The key to success in promoting vaccine uptake is a strategic program, including local capacity building, to build and maintain trust. A critical factor in implementing such a confidence and demand-building approach is the need to invest in communication, especially related to influencing behaviors and the capacity for community engagement[129].

COVID-19 vaccines are expected to induce high-affinity neutralizing antibodies. They should also polarize the T-cell response towards type 1 immunity and avoid the stimulation of cytokines that induce T-helper 2 immunity. To avoid type 2 inflammatory responses, careful selection of the vector and antigen is mandatory. The addition of toll-like receptor ligands (TLRs) and other type 1 immunity-stimulating molecules could be useful for obtaining sufficient CD4+ T cells for antibody production as well as suppression of undesirable type 2 immunity leading to eosinophilia. However, it is only somewhat possible to predict vaccine efficacy and safety. Due to its urgency, COVID-19 vaccination should receive the highest priority[130].

Research

The COVID-19 outbreak is a striking reminder of the need for constant epidemiological surveillance, prompt diagnosis, and robust research[28]. Mapping of the structure of the SARS-CoV-2 spike protein at the atomic scale has allowed the development of therapies to combat the virus[131]. An international research effort is ongoing to understand the COVID-19 pandemic to answer questions regarding epidemiology, clinical epidemiology, biology, therapy, and vaccination. Researchers are also publishing the results of epidemiological, biological, and clinical trial studies in peer-reviewed journals. Moreover, clinical trials are underway to identify reliable, effective, and safe therapeutics[132-135]. Immunological and epidemiological data on endemic human coronaviruses (HCoV) showed that infection-blocking immunity wanes rapidly but that disease-reducing immunity is long-lived. In other words, anti-infectious immunity that prevents pathogen replication to render the host refractory to reinfection (*i.e.*, immune efficacy in relation to susceptibility), declines rapidly, while disease-reducing immunity due to reinfection and/or transmissibility-reducing immunity or infectiousness, with possible reinfection, lasts for a long time. This may be evidenced by the current severity of SARS-CoV-2 and the benign nature of HCoV, suggesting that once the endemic phase is reached and following primary exposure during childhood, SARS-CoV-2 may not be more virulent than the common cold. A different scenario is foreseeable for an emerging coronavirus capable of causing more severe disease in children. These results support the importance of behavioral compliance during pandemic vaccine use and suggest the need to evaluate scenarios for continued vaccination during the endemic phase[136].

CONCLUSION

The development of a robust prevention and/or response system relies on the capitalization and judicious use of knowledge in fields including epidemiology, infectious diseases, pathophysiology, biology, virology, in addition to scientific research. Hence, local or international collaboration in pluralistic teams may guarantee success. The dissemination of simple, coherent, and reliable messages reassures the population and reinforces compliance with individual or collective barrier measures (*e.g.*, confinement, even if it is difficult to bear). An integrative pluralistic approach coupled with efficient communication may be a more effective way of responding to an outbreak or pandemic, especially that caused by SARS-CoV-2. A pluralistic collaborative approach; in other words, the capitalization and judicious use of knowledge, will help to over-come the pandemic in the short or medium terms. Our results suggest the benefits of a pluralistic approach in managing COVID-19 a fortiori in relation to health and related fields. This work would be even more comprehensive if the search source was larger, the collaborative approach was more detailed, and the pluralistic approach extended to complementary disciplines such as biochemistry (vaccines), statistics, and mathematics, biomedical science and biotechnology, inventions (respirators, ven-

tilation equipment), physical therapy, *etc.*

ACKNOWLEDGEMENTS

We thank Prof. Hubner ROLAND from the Belgian High Committee of Health for his strong and continuing intellectual and technical support for this work. We thank Babri GALLEDOU, the Head of the DNP (National Head Office of Pedagogy), Mamadou BOUARE of the CDL (Center de Languages), and all the staff of the DNP/CDL for their generous support in the English translation of the French version of the manuscript text.

REFERENCES

1 **Jin Y**, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses* 2020; **12** [PMID: 32230900 DOI: 10.3390/v12040372]
2 **Vellas C**, Delobel P, de Souto Barreto P, Izopet J. COVID-19, Virology and Geroscience: A Perspective. *J Nutr Health Aging* 2020; **24**: 685-691 [PMID: 32744561 DOI: 10.1007/s12603-020-1416-2]
3 **Cui J**, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 2019; **17**: 181-192 [PMID: 30531947 DOI: 10.1038/s41579-018-0118-9]
4 **Li W**, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, Wong SK, Huang IC, Xu K, Vasilieva N, Murakami A, He Y, Marasco WA, Guan Y, Choe H, Farzan M. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. *EMBO J* 2005; **24**: 1634-1643 [PMID: 15791205 DOI: 10.1038/sj.emboj.7600640]
5 **INFO**. Coronavirus: épidémiologistes, virologues, infectiologues, pourquoi ils ne sont pas tous d'accord? [cited 18 April 2021]. Available from: https://www.rtbf.be/info/dossier/epidemie-de-coronavirus/detail_coronavirus-epidemiologistes-virologues-infectiologues-pourquoi-ils-ne-sont-pas-tous-d-accord?id=10589357
6 **Park SE**. Epidemiology, virology, and clinical features of severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). *Clin Exp Pediatr* 2020; **63**: 119-124 [PMID: 32252141 DOI: 10.3345/cep.2020.00493]
7 **Hoehl S**, Rabenau H, Berger A, Kortenbusch M, Cinatl J, Bojkova D, Behrens P, Böddinghaus B, Götsch U, Naujoks F, Neumann P, Schork J, Tiarks-Jungk P, Walczok A, Eickmann M, Vehreschild MJGT, Kann G, Wolf T, Gottschalk R, Ciesek S. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. *N Engl J Med* 2020; **382**: 1278-1280 [PMID: 32069388 DOI: 10.1056/NEJMc2001899]
8 **Mahmood Z**, Alrefai H, Hetta HF, A Kader H, Munawar N, Abdul Rahman S, Elshaer S, Batiha GE, Muhammad K. Investigating Virological, Immunological, and Pathological Avenues to Identify Potential Targets for Developing COVID-19 Treatment and Prevention Strategies. *Vaccines (Basel)* 2020; **8** [PMID: 32781571 DOI: 10.3390/vaccines8030443]
9 **Fehr AR**, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol* 2015; **1282**: 1-23 [PMID: 25720466 DOI: 10.1007/978-1-4939-2438-7_1]
10 **Wang M**, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; **30**: 269-271 [PMID: 32020029 DOI: 10.1038/s41422-020-0282-0]
11 **Guo YR**, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res* 2020; **7**: 11 [PMID: 32169119 DOI: 10.1186/s40779-020-00240-0]
12 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]
13 **Liu P**, Jiang JZ, Wan XF, Hua Y, Li L, Zhou J, Wang X, Hou F, Chen J, Zou J. Correction: Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)? *PLoS Pathog* 2021; **17**: e1009664 [PMID: 34106988 DOI: 10.1371/journal.ppat.1009664]
14 **Duguid JP**. The size and the duration of air-carriage of respiratory droplets and droplet-nuclei. *J Hyg (Lond)* 1946; **44**: 471-479 [PMID: 20475760 DOI: 10.1017/s0022172400019288]
15 **Asadi S**, Wexler AS, Cappa CD, Barreda S, Bouvier NM, Ristenpart WD. Aerosol emission and superemission during human speech increase with voice loudness. *Sci Rep* 2019; **9**: 2348 [PMID: 30787335 DOI: 10.1038/s41598-019-38808-z]
16 **Chao CYH**, Wan MP, Morawska L, Johnson GR, Ristovski ZD, Hargreaves M, Mengersen K, Corbett S, Li Y, Xie X, Katoshevski D. Characterization of expiration air jets and droplet size distributions immediately at the mouth opening. *J Aerosol Sci* 2009; **40**: 122-133 [PMID: 32287373 DOI: 10.1016/j.jaerosci.2008.10.003]

17 **Van Doremalen N**, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med* 2020; **382**: 1564-1567 [PMID: 32182409 DOI: 10.1056/NEJMc2004973]

18 **Centers for Disease Control and Prevention**. Interim Guidelines for Collecting and Handling of Clinical Specimens for COVID-19 Testing. [cited 18 April 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html

19 **Nabil A**, Uto K, Elshemy MM, Soliman R, Hassan AA, Ebara M, Shiha G. Current coronavirus (SARS-CoV-2) epidemiological, diagnostic and therapeutic approaches: An updated review until June 2020. *EXCLI J* 2020; **19**: 992-1016 [PMID: 32788913 DOI: 10.17179/excli2020-2554]

20 **Bullis SSM**, Crothers JW, Wayne S, Hale AJ. A cautionary tale of false-negative nasopharyngeal COVID-19 testing. *IDCases* 2020; **20**: e00791 [PMID: 32377507 DOI: 10.1016/j.idcr.2020.e00791]

21 **Li Y**, Yao L, Li J, Chen L, Song Y, Cai Z, Yang C. Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19. *J Med Virol* 2020; **92**: 903-908 [PMID: 32219885 DOI: 10.1002/jmv.25786]

22 **Xiao AT**, Tong YX, Zhang S. False negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence. *J Med Virol* 2020; **92**: 1755-1756 [PMID: 32270882 DOI: 10.1002/jmv.25855]

23 **Madariaga A**, McMullen M, Sheikh S, Kumar R, Liu FF, Zimmermann C, Husain S, Zadeh G, Oza AM. COVID-19 Testing in Patients with Cancer: Does One Size Fit All? *Clin Cancer Res* 2020; **26**: 4737-4742 [PMID: 32616498 DOI: 10.1158/1078-0432.CCR-20-2224]

24 **C**. Hermans. NUMÉRO SPÉCIAL COVID-19 MAI/JUIN 2020. Louvain: Elsevier, 2020: 139

25 **Ma H**, Zeng W, He H, Zhao D, Jiang D, Zhou P, Cheng L, Li Y, Ma X, Jin T. Serum IgA, IgM, and IgG responses in COVID-19. *Cell Mol Immunol* 2020; **17**: 773-775 [PMID: 32467617 DOI: 10.1038/s41423-020-0474-z]

26 **Ambassade De France en Macédoine du Nord**. Qu'est-ce que le coronavirus COVID-19? [cited 18 April 2021]. Available from: https://mk.ambafrance.org/Qu-est-ce-que-le-coronavirus-COVID-19

27 **Liu Y**, Liao W, Wan L, Xiang T, Zhang W. Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. *Viral Immunol* 2021; **34**: 330-335 [PMID: 32297828 DOI: 10.1089/vim.2020.0062]

28 **The New England Journal of Medicine**. A collection of articles and other resources on the Coronavirus (COVID-19) outbreak, including clinical reports, management guidelines, and commentary. [cited 18 April 2021]. Available from: https://www.nejm.org/coronavirus

29 **Stites EC**, Wilen CB. The Interpretation of SARS-CoV-2 Diagnostic Tests. *Med (N Y)* 2020; **1**: 78-89 [PMID: 32864639 DOI: 10.1016/j.medj.2020.08.001]

30 **Genome web**. FDA Dramatically Expands Enforcement Discretion to Speed COVID-19 Test Access. Available from: https://www.genomeweb.com/regulatory-news-fda-approvals/fda-dramatically-expands-enforcement-discretion-speed-covid-19-test#.YUwcLOzitPY]

31 **FDA**. FDA COVID-19 Response At-A-Glance Summary as of September 25, 2020. [cited 18 April 2021]. Available from: https://www.fda.gov

32 **WHO**. COVID-19 Reference Laboratory Network 29.4.20. [cited 18 April 2021]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-reference-laboratories-providing-confirmatory-testing-for-covid-19.pdf?sfvrsn=a03a01e6_4

33 **ABSA International**. SARS-CoV-2/COVID-19. [cited 15 April 2021]. Available from: https://absa.org/topic/covid19/

34 **Conseil Supérieur de la Santé**. Impact de la pandémie SARS-Cov-2 sur le système transfusionnel. [cited 15 April 2021]. Available from: https://www.health.belgium.be/fr/avis-9579-systeme-transfusionnel-covid19

35 **Freuling CM**, Breithaupt A, Müller T, Sehl J, Balkema-Buschmann A, Rissmann M, Klein A, Wylezich C, Höper D, Wernike K, Aebischer A, Hoffmann D, Friedrichs V, Dorhoi A, Groschup MH, Beer M, Mettenleiter TC. Susceptibility of Raccoon Dogs for Experimental SARS-CoV-2 Infection. *Emerg Infect Dis* 2020; **26**: 2982-2985 [PMID: 33089771 DOI: 10.3201/eid2612.203733]

36 **Oreshkova N**, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Hakze-van der Honing RW, Gerhards N, Tolsma P, Bouwstra R, Sikkema RS, Tacken MG, de Rooij MM, Weesendorp E, Engelsma MY, Bruschke CJ, Smit LA, Koopmans M, van der Poel WH, Stegeman A. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. *Euro Surveill* 2020; **25** [PMID: 32553059 DOI: 10.2807/1560-7917.ES.2020.25.23.2001005]

37 **Molenaar RJ**, Vreman S, Hakze-van der Honing RW, Zwart R, de Rond J, Weesendorp E, Smit LAM, Koopmans M, Bouwstra R, Stegeman A, van der Poel WHM. Clinical and Pathological Findings in SARS-CoV-2 Disease Outbreaks in Farmed Mink (*Neovison vison*). *Vet Pathol* 2020; **57**: 653-657 [PMID: 32663073 DOI: 10.1177/0300985820943535]

38 **Oude Munnink BB**, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, van der Spek A, Tolsma P, Rietveld A, Brouwer M, Bouwmeester-Vincken N, Harders F, Hakze-van der Honing R, Wegdam-Blans MCA, Bouwstra RJ, GeurtsvanKessel C, van der Eijk AA, Velkers FC, Smit LAM, Stegeman A, van der Poel WHM, Koopmans MPG. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. *Science* 2021; **371**: 172-177 [PMID: 33172935 DOI: 10.1126/science.abe5901]

39 **Lai CC**, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their

association with country healthcare resources and economic status. *Int J Antimicrob Agents* 2020; **55**: 105946 [PMID: 32199877 DOI: 10.1016/j.ijantimicag.2020.105946]

40 **Torti C**, Mazzitelli M, Trecarichi EM, Darius O. Potential implications of SARS-CoV-2 epidemic in Africa: where are we going from now? *BMC Infect Dis* 2020; **20**: 412 [PMID: 32536344 DOI: 10.1186/s12879-020-05147-8]

41 **Giandhari J**, Pillay S, Wilkinson E, Tegally H, Sinayskiy I, Schuld M, Lourenco J, Chimukangara B, Lessells R, Moosa Y, Gazy I, Fish M, Singh L, Khanyile KS, Fonseca V, Giovanetti M, Alcantara LC, Petruccione F, de Oliveira T. Early transmission of SARS-CoV-2 in South Africa: An epidemiological and phylogenetic report. *medRxiv* 2020 [PMID: 32511505 DOI: 10.1101/2020.05.29.20116376]

42 **Ayele BA**, Rizig M, Amogne W, Zenebe Y, Demissie H, Gams Massi D, El-Sadig S, Charway-Felli A, Abd-Allah F. COVID-19 and the state of African neurology. *Eur J Neurol* 2020; **27**: e48-e49 [PMID: 32558138 DOI: 10.1111/ene.14404]

43 **Worldometers**. COVID-19 CORONAVIRUS PANDEMIC. [cited 15 April 2021]. Available from: https://www.worldometers.info/coronavirus/?%22

44 **Rao C**, Bradshaw D, Mathers CD. Improving death registration and statistics in developing countries: Lessons from sub-Saharan Africa. *SAJ Dem* 2004; **9**: 81-99

45 **Bouare N**. La maladie de SARS-CoV2 (COVID-19): une réflexion contributive à la prévention et/ou la riposte contre la pandémie. 2020 [DOI: 10.13140/RG.2.2.27071.25769]

46 **Kapata N**, Ihekweazu C, Ntoumi F, Raji T, Chanda-Kapata P, Mwaba P, Mukonka V, Bates M, Tembo J, Corman V, Mfinanga S, Asogun D, Elton L, Arruda LB, Thomason MJ, Mboera L, Yavlinsky A, Haider N, Simons D, Hollmann L, Lule SA, Veas F, Abdel Hamid MM, Dar O, Edwards S, Vairo F, McHugh TD, Drosten C, Kock R, Ippolito G, Zumla A. Is Africa prepared for tackling the COVID-19 (SARS-CoV-2) epidemic. Lessons from past outbreaks, ongoing pan-African public health efforts, and implications for the future. *Int J Infect Dis* 2020; **93**: 233-236 [PMID: 32119980 DOI: 10.1016/j.ijid.2020.02.049]

47 **Institut Pasteur**. Tout sur SARS-CoV-2/COVID-19 à l'Institut Pasteur. [cited 18 April 2021]. Available from: https://www.pasteur.fr/fr/sars-cov-2-covid-19-institut-pasteur

48 **WHO**. WHO COVID-19: Case Definitions. Updated in Public health surveillance for COVID-19, published 7 August 2020. [cited 18 April 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/333912/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1-eng.pdf?sequence=1&isAllowed=y

49 **Joshua Elliott**, Matthew Whitaker, Barbara Bodinier, Steven Riley, Helen Ward, Graham Cooke, Ara Darzi, Marc Chadeau-Hyam, Paul Elliott. Symptom reporting in over 1 million people: community detection of COVID-19. 2021 Preprint. Available from: https://www.medrxiv.org/content/10.1101/2021.02.10.21251480v1 [DOI: 10.1101/2021.02.10.21251480]

50 **Kokoszka-Bargiel I**, Cyprys P, Rutkowska K, Madowicz J, Knapik P. Intensive Care Unit Admissions During the First 3 Months of the COVID-19 Pandemic in Poland: A Single-Center, Cross-Sectional Study. *Med Sci Monit* 2020; **26**: e926974 [PMID: 32979262 DOI: 10.12659/MSM.926974]

51 **Sisó-Almirall A**, Kostov B, Mas-Heredia M, Vilanova-Rotllan S, Sequeira-Aymar E, Sans-Corrales M, Sant-Arderiu E, Cayuelas-Redondo L, Martínez-Pérez A, García-Plana N, Anguita-Guimet A, Benavent-Àreu J. Prognostic factors in Spanish COVID-19 patients: A case series from Barcelona. *PLoS One* 2020; **15**: e0237960 [PMID: 32822413 DOI: 10.1371/journal.pone.0237960]

52 **Thakrar A**, Chui K, Kapoor A, Hambidge J. Thirty-Day Mortality Rate of Patients With Hip Fractures During the COVID-19 Pandemic: A Single Centre Prospective Study in the United Kingdom. *J Orthop Trauma* 2020; **34**: e325-e329 [PMID: 32815846 DOI: 10.1097/BOT.0000000000001889]

53 **Majidi S**, Fifi JT, Ladner TR, Lara-Reyna J, Yaeger KA, Yim B, Dangayach N, Oxley TJ, Shigematsu T, Kummer BR, Stein LK, Weinberger J, Fara MG, De Leacy R, Dhamoon MS, Tuhrim S, Mocco J. Emergent Large Vessel Occlusion Stroke During New York City's COVID-19 Outbreak: Clinical Characteristics and Paraclinical Findings. *Stroke* 2020; **51**: 2656-2663 [PMID: 32755349 DOI: 10.1161/STROKEAHA.120.030397]

54 **Santos CS**, Morales CM, Álvarez ED, Castro CÁ, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. *Clin Rheumatol* 2020; **39**: 2789-2796 [PMID: 32720259 DOI: 10.1007/s10067-020-05301-2]

55 **Liu D**, Wang Y, Wang J, Liu J, Yue Y, Liu W, Zhang F, Wang Z. Characteristics and Outcomes of a Sample of Patients With COVID-19 Identified Through Social Media in Wuhan, China: Observational Study. *J Med Internet Res* 2020; **22**: e20108 [PMID: 32716901 DOI: 10.2196/20108]

56 **Huang M**, Yang Y, Shang F, Zheng Y, Zhao W, Luo L, Han X, Lin A, Zhao H, Gu Q, Shi Y, Li J, Xu X, Liu K, Deng Y, Cao Q, Wang W. Clinical Characteristics and Predictors of Disease Progression in Severe Patients with COVID-19 Infection in Jiangsu Province, China: A Descriptive Study. *Am J Med Sci* 2020; **360**: 120-128 [PMID: 32709280 DOI: 10.1016/j.amjms.2020.05.038]

57 **Bolondi G**, Russo E, Gamberini E, Circelli A, Meca MCC, Brogi E, Viola L, Bissoni L, Poletti V, Agnoletti V. Iron metabolism and lymphocyte characterisation during Covid-19 infection in ICU patients: an observational cohort study. *World J Emerg Surg* 2020; **15**: 41 [PMID: 32605582 DOI: 10.1186/s13017-020-00323-2]

58 **Ebinger JE**, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, Nguyen TT, Luong E, Kim EH,

Park E, Liu Y, Rosenberry R, Matusov Y, Zhao S, Pedraza I, Zaman T, Thompson M, Raedschelders K, Berg AH, Grein JD, Noble PW, Chugh SS, Bairey Merz CN, Marbán E, Van Eyk JE, Solomon SD, Albert CM, Chen P, Cheng S. Pre-existing traits associated with Covid-19 illness severity. *PLoS One* 2020; **15**: e0236240 [PMID: 32702044 DOI: 10.1371/journal.pone.0236240]

59 **Fisman DN**, Bogoch I, Lapointe-Shaw L, McCready J, Tuite AR. Risk Factors Associated With Mortality Among Residents With Coronavirus Disease 2019 (COVID-19) in Long-term Care Facilities in Ontario, Canada. *JAMA Netw Open* 2020; **3**: e2015957 [PMID: 32697325 DOI: 10.1001/jamanetworkopen.2020.15957]

60 **Choudry FA**, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, Woldman S, Jain AK, Knight CJ, Baumbach A, Mathur A, Jones DA. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol* 2020; **76**: 1168-1176 [PMID: 32679155 DOI: 10.1016/j.jacc.2020.07.022]

61 **Thomas T**, Stefanoni D, Reisz JA, Nemkov T, Bertolone L, Francis RO, Hudson KE, Zimring JC, Hansen KC, Hod EA, Spitalnik SL, D'Alessandro A. COVID-19 infection alters kynurenine and fatty acid metabolism, correlating with IL-6 levels and renal status. *JCI Insight* 2020; **5** [PMID: 32559180 DOI: 10.1172/jci.insight.140327]

62 **Poggiali E**, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, Nuccetelli M, Vadacca GB, Guidetti D, Vercelli A, Magnacavallo A, Bernardini S, Terracciano C. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. *Clin Chim Acta* 2020; **509**: 135-138 [PMID: 32531257 DOI: 10.1016/j.cca.2020.06.012]

63 **Morassi M**, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, Vogrig A. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol* 2020; **267**: 2185-2192 [PMID: 32436105 DOI: 10.1007/s00415-020-09885-2]

64 **Zhang H**, Wang L, Chen Y, Wu Q, Chen G, Shen X, Wang Q, Yan Y, Yu Y, Zhong Y, Wang X, Chua MLK, Xie C. Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. *Cancer* 2020; **126**: 4023-4031 [PMID: 32573776 DOI: 10.1002/cncr.33042]

65 **Marijon E**, Karam N, Jost D, Perrot D, Frattini B, Derkenne C, Sharifzadehgan A, Waldmann V, Beganton F, Narayanan K, Lafont A, Bougouin W, Jouven X. Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study. *Lancet Public Health* 2020; **5**: e437-e443 [PMID: 32473113 DOI: 10.1016/S2468-2667(20)30117-1]

66 **Lansiaux E**, Pébaÿ PP, Picard JL, Son-Forget J. COVID-19: beta-thalassemia subjects immunised? *Med Hypotheses* 2020; **142**: 109827 [PMID: 32447232 DOI: 10.1016/j.mehy.2020.109827]

67 **Patel MP**, Kute VB, Agarwal SK; COVID-19 Working Group of Indian Society of Nephrology. "Infodemic" COVID 19: More Pandemic than the Virus. *Indian J Nephrol* 2020; **30**: 188-191 [DOI: 10.4103/ijn.IJN_216_20]

68 **Sulaimani MF**, Bagadood NH. Implication of coronavirus pandemic on obsessive-compulsive-disorder symptoms. *Rev Environ Health* 2021; **36**: 1-8 [PMID: 32866131 DOI: 10.1515/reveh-2020-0054]

69 **Wadoum REG**, Clarke A. How prepared is Africa to face COVID-19? *Pan Afr Med J* 2020; **35**: 1 [PMID: 32528612 DOI: 10.11604/pamj.supp.2020.35.2.22665]

70 **Antony SJ**, Almaghlouth NK, Heydemann EL. Are coinfections with COVID-19 and influenza low or underreported? *J Med Virol* 2020; **92**: 2489-2497 [PMID: 32530531 DOI: 10.1002/jmv.26167]

71 **Torales J**, O'Higgins M, Castaldelli-Maia JM, Ventriglio A. The outbreak of COVID-19 coronavirus and its impact on global mental health. *Int J Soc Psychiatry* 2020; **66**: 317-320 [PMID: 32233719 DOI: 10.1177/0020764020915212]

72 **Mission COREB nationale**. Repérer et prendre en charge un patient suspect d'infection à nouveau Coronavirus 2019 INFORMATION pour SAMU et soignants de 1ère ligne. [cited 18 April 2021]. Available from: https://solidarites-sante.gouv.fr/IMG/pdf/2019-ncov-fichesoignants22janv-vf.pdf

73 **Bhole RP**, Sarode VI, Bonde CG. Understanding and implementing alternative solutions to address the COVID-19 pandemic in the sense of public health emergencies. *Eur Rev Med Pharmacol Sci* 2020; **24**: 7485-7493 [PMID: 32706088 DOI: 10.26355/eurrev_202007_21920]

74 **Pradhan D**, Biswasroy P, Kumar Naik P, Ghosh G, Rath G. A Review of Current Interventions for COVID-19 Prevention. *Arch Med Res* 2020; **51**: 363-374 [PMID: 32409144 DOI: 10.1016/j.arcmed.2020.04.020]

75 **Beiu C**, Mihai M, Popa L, Cima L, Popescu MN. Frequent Hand Washing for COVID-19 Prevention Can Cause Hand Dermatitis: Management Tips. *Cureus* 2020; **12**: e7506 [PMID: 32373409 DOI: 10.7759/cureus.7506]

76 **Science et Avenir audio**. COVID-19: "Il suffit d'un très léger relâchement" pour lancer une seconde vague. [cited 18 April 2021]. Available from: https://www.sciencesetavenir.fr/sante/covid-19-il-suffit-d-un-tres-leger-relachement-pour-lancer-une-seconde-vague_144884

77 **Güner R**, Hasanoğlu I, Aktaş F. COVID-19: Prevention and control measures in community. *Turk J Med Sci* 2020; **50**: 571-577 [PMID: 32293835 DOI: 10.3906/sag-2004-146]

78 **Basnet S**, Koirala S, Pandey B, Koirala J. COVID-19 Containment Efforts of a Low-Resource Nation: The First Four Months in Nepal. *Cureus* 2020; **12**: e8946 [PMID: 32765991 DOI: 10.7759/cureus.8946]

79 **Peng F**, Tu L, Yang Y, Hu P, Wang R, Hu Q, Cao F, Jiang T, Sun J, Xu G, Chang C. Management and Treatment of COVID-19: The Chinese Experience. *Can J Cardiol* 2020; **36**: 915-930 [PMID: 32439306 DOI: 10.1016/j.cjca.2020.04.010]

80 **Gabutti G**, d'Anchera E, Sandri F, Savio M, Stefanati A. Coronavirus: Update Related to the Current Outbreak of COVID-19. *Infect Dis Ther* 2020; 1-13 [PMID: 32292686 DOI: 10.1007/s40121-020-00295-5]

81 **WHO**. Country & Technical Guidance - Coronavirus disease (COVID-19). [cited 18 April 2021]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance

82 **CDC**. Biosafety in Microbiological and Biomedical Laboratories. 5th ed. Health and Human Services, 2009

83 **Nouhoum B**. Prévention de la fièvre hémorragique virale (Ebola) au Mali. [cited 18 April 2021]. Available from: https://www.researchgate.net/publication/277649015_Prevention_de_la_fievre_hemorragique_virale_Ebola_au_Mali_une_reflexion_contributive

84 **Jesse J**. Kwiek, Christopher R. Pickett, Chloe A. Flanigan, Marcia V. Lee, Linda J. Saif Jeff Jahnes, Greg Blonder. A practical PPE decontamination method using warm air and ambient humidity. 2020 Preprint. Available from: https://doi.org/10.1101/2020.11.12.380196 [DOI: 10.1101/2020.11.12.380196]

85 **UFC-QUE CHOISIR**. Masques chirurgicaux. Que choisir? [cited 18 April 2021]. Available from: https://www.quechoisir.org/actualite-masques-chirurgicaux-vous-pouvez-les-laver-et-les-reutiliser-n85015/

86 **Futura Sciences**. Coronavirus: Masques chirurgicaux. [cited 18 April 2021]. Available from: https://www.futura-sciences.com/sante/breves/coronavirus-masques-chirurgicaux-sont-lavables-reutilisables-moins-10-fois-3267/ [DOI: 10.1016/s0038-0814(21)00143-2]

87 **Kumar S**, Lee HP. The perspective of fluid flow behavior of respiratory droplets and aerosols through the facemasks in context of SARS-CoV-2. *Phys Fluids (1994)* 2020; **32**: 111301 [PMID: 33281434 DOI: 10.1063/5.0029767]

88 **Bleizgys A**. Vitamin D and COVID-19: It is time to act. *Int J Clin Pract* 2021; **75**: e13748 [PMID: 33012103 DOI: 10.1111/ijcp.13748]

89 **Boozari M**, Hosseinzadeh H. Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies. *Phytother Res* 2021; **35**: 864-876 [PMID: 32985017 DOI: 10.1002/ptr.6873]

90 **Galmés S**, Serra F, Palou A. Current State of Evidence: Influence of Nutritional and Nutrigenetic Factors on Immunity in the COVID-19 Pandemic Framework. *Nutrients* 2020; **12** [PMID: 32911778 DOI: 10.3390/nu12092738]

91 **Bellavite P**, Donzelli A. Hesperidin and SARS-CoV-2: New Light on the Healthy Function of Citrus Fruits. *Antioxidants (Basel)* 2020; **9** [PMID: 32823497 DOI: 10.3390/antiox9080742]

92 **Panyod S**, Ho CT, Sheen LY. Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective. *J Tradit Complement Med* 2020; **10**: 420-427 [PMID: 32691006 DOI: 10.1016/j.jtcme.2020.05.004]

93 **Yan BH**, Jiang ZW, Zeng JP, Tang JY, Ding H, Xia JL, Qin SR, Jin SC, Lu Y, Zhang N, Wang ZH, Li HY, Sang XY, Wu LN, Tang SY, Li Y, Tao MY, Wang QL, Wang JD, Xie HY, Chen QY, Yang SW, Hu NS, Yang JQ, Bao XX, Zhang Q, Yang XL, Jiang CY, Luo HY, Cai ZH, Yu SG. [Large-scale prospective clinical study on prophylactic intervention of COVID-19 in community population using Huoxiang Zhengqi Oral Liquid and Jinhao Jiere Granules]. *Zhongguo Zhong Yao Za Zhi* 2020; **45**: 2993-3000 [PMID: 32726003 DOI: 10.19540/j.cnki.cjcmm.20200430.501]

94 **Charoenlap S**, Piromsopa K, Charoenlap C. Potential role of Bacillus Calmette-Guérin (BCG) vaccination in COVID-19 pandemic mortality: Epidemiological and Immunological aspects. *Asian Pac J Allergy Immunol* 2020; **38**: 150-161 [PMID: 32686943 DOI: 10.12932/AP-310520-0863]

95 **Asadi-Pooya AA**, Cross JH. Is wearing a face mask safe for people with epilepsy? *Acta Neurol Scand* 2020; **142**: 314-316 [PMID: 32654134 DOI: 10.1111/ane.13316]

96 **Williams M**, Le Calvez K, Mi E, Chen J, Dadhania S, Pakzad-Shahabi L. Estimating the risks from COVID-19 infection in adult chemotherapy patients. 2020 Preprint. Available from: https://doi.org/10.1101/2020.03.18.20038067 [DOI: 10.1101/2020.03.18.20038067]

97 **Cho HJ**, Koo JW, Roh SK, Kim YK, Suh JS, Moon JH, Sohn SK, Baek DW. COVID-19 transmission and blood transfusion: A case report. *J Infect Public Health* 2020; **13**: 1678-1679 [PMID: 32405329 DOI: 10.1016/j.jiph.2020.05.001]

98 **Hale JM**. Engaging the next generation of plant geneticists through sustained research: an overview of a post-16 project. *Heredity (Edinb)* 2020; **125**: 431-436 [PMID: 32943768 DOI: 10.1038/s41437-020-00370-0]

99 **Abdullahi IN**, Emeribe AU, Ajayi OA, Oderinde BS, Amadu DO, Osuji AI. Implications of SARS-CoV-2 genetic diversity and mutations on pathogenicity of the COVID-19 and biomedical interventions. *J Taibah Univ Med Sci* 2020; **15**: 258-264 [PMID: 32837505 DOI: 10.1016/j.jtumed.2020.06.005]

100 **Abdullahi IN**, Emeribe AU, Mustapha JO, Fasogbon SA, Ofor IB, Opeyemi IS, Obi-George C, Sunday AO, Nwofe J. Exploring the genetics, ecology of SARS-COV-2 and climatic factors as possible control strategies against COVID-19. *Infez Med* 2020; **28**: 166-173 [PMID: 32275258]

101 **Rojelio Mejia**, Peter Hotez and Maria Elena Bottazzi. Current Tropical Medicine Reports. In: Rojelio Mejia, Peter Hotez, Maria Elena Bottazzi. Global COVID-19 Efforts as the Platform to Achieving the Sustainable Development Goals. Springer Nature Switzerland AG, 2020: 99-103 [DOI: 10.1007/s40475-020-00209-y]

102 **Adikari PS**, Pathirathna K, Kumarawansa W, Koggalage PD. Role of MOH as a grassroots public

health manager in preparedness and response for COVID-19 pandemic in Sri Lanka. *AIMS Public Health* 2020; **7**: 606-619 [PMID: 32968681 DOI: 10.3934/publichealth.2020048]

103 **Tran BX**, Hoang MT, Pham HQ, Hoang CL, Le HT, Latkin CA, Ho CS, Ho RC. The operational readiness capacities of the grassroots health system in responses to epidemics: Implications for COVID-19 control in Vietnam. *J Glob Health* 2020; **10**: 011006 [PMID: 32566168 DOI: 10.7189/jogh.10.011006]

104 **CLINICAL TRIALS & RESEARCH NEWS**, Former SARS, MERS Drug Could Treat COVID-19 Patients. 2020 May 5 [cited 18 April 2021]. In: Twitter [Internet]. Available from: https://pharmanewsintel.com/news/former-sars-mers-vaccine-could-treat-covid-19-patients

105 **Xu X**, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020; **117**: 10970-10975 [PMID: 32350134 DOI: 10.1073/pnas.2005615117]

106 **Ramiro S**, Mostard RLM, Magro-Checa C, van Dongen CMP, Dormans T, Buijs J, Gronenschild M, de Kruif MD, van Haren EHJ, van Kraaij T, Leers MPG, Peeters R, Wong DR, Landewé RBM. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. *Ann Rheum Dis* 2020; **79**: 1143-1151 [PMID: 32719045 DOI: 10.1136/annrheumdis-2020-218479]

107 **Zhao J**, Yang X, Wang C, Song S, Cao K, Wei T, Ji Q, Zheng W, Li J, Zhou X, Liu J. Yidu-toxicity blocking lung decoction ameliorates inflammation in severe pneumonia of SARS-COV-2 patients with Yidu-toxicity blocking lung syndrome by eliminating IL-6 and TNF-a. *Biomed Pharmacother* 2020; **129**: 110436 [PMID: 32768938 DOI: 10.1016/j.biopha.2020.110436]

108 **Wen L**, Zhou Z, Jiang D, Huang K. [Effect of Xuebijing injection on inflammatory markers and disease outcome of coronavirus disease 2019]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020; **32**: 426-429 [PMID: 32527346 DOI: 10.3760/cma.j.cn121430-20200406-00386]

109 **Cao Y**, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Wang N, Zhou X, Luo H, Mao Z, Chen X, Xie J, Liu J, Cheng H, Zhao J, Huang G, Wang W, Zhou J. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020; **146**: 137-146.e3 [PMID: 32470486 DOI: 10.1016/j.jaci.2020.05.019]

110 **Deftereos SG**, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, Metallidis S, Sianos G, Baltagiannis S, Panagopoulos P, Dolianitis K, Randou E, Syrigos K, Kotanidou A, Koulouris NG, Milionis H, Sipsas N, Gogos C, Tsoukalas G, Olympios CD, Tsagalou E, Migdalis I, Gerakari S, Angelidis C, Alexopoulos D, Davlouros P, Hahalis G, Kanonidis I, Katritsis D, Kolettis T, Manolis AS, Michalis L, Naka KK, Pyrgakis VN, Toutouzas KP, Triposkiadis F, Tsioufis K, Vavouranakis E, Martinèz-Dolz L, Reimers B, Stefanini GG, Cleman M, Goudevenos J, Tsiodras S, Tousoulis D, Iliodromitis E, Mehran R, Dangas G, Stefanadis C; GRECCO-19 investigators. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. *JAMA Netw Open* 2020; **3**: e2013136 [PMID: 32579195 DOI: 10.1001/jamanetworkopen.2020.13136]

111 **Spinner CD**, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, Chai LYA, Roestenberg M, Tsang OTY, Bernasconi E, Le Turnier P, Chang SC, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wang H, Gaggar A, Brainard DM, McPhail MJ, Bhagani S, Ahn MY, Sanyal AJ, Huhn G, Marty FM; GS-US-540-5774 Investigators. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**: 1048-1057 [PMID: 32821939 DOI: 10.1001/jama.2020.16349]

112 **Humeniuk R**, Mathias A, Cao H, Osinusi A, Shen G, Chng E, Ling J, Vu A, German P. Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID-19, in Healthy Subjects. *Clin Transl Sci* 2020; **13**: 896-906 [PMID: 32589775 DOI: 10.1111/cts.12840]

113 **Tang W**, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020; **369**: m1849 [PMID: 32409561 DOI: 10.1136/bmj.m1849]

114 **Sun J**, Deng X, Chen X, Huang J, Huang S, Li Y, Feng J, Liu J, He G. Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System. *Clin Pharmacol Ther* 2020; **108**: 791-797 [PMID: 32324898 DOI: 10.1002/cpt.1866]

115 **Hung IF**, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, Ng YY, Lo J, Chan J, Tam AR, Shum HP, Chan V, Wu AK, Sin KM, Leung WS, Law WL, Lung DC, Sin S, Yeung P, Yip CC, Zhang RR, Fung AY, Yan EY, Leung KH, Ip JD, Chu AW, Chan WM, Ng AC, Lee R, Fung K, Yeung A, Wu TC, Chan JW, Yan WW, Chan JF, Lie AK, Tsang OT, Cheng VC, Que TL, Lau CS, Chan KH, To KK, Yuen KY. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; **395**: 1695-1704 [PMID: 32401715 DOI: 10.1016/S0140-6736(20)31042-4]

116 **Gyebi GA**, Ogunro OB, Adegunloye AP, Ogunyemi OM, Afolabi SO. Potential inhibitors of coronavirus 3-chymotrypsin-like protease ($3CL^{pro}$): an *in silico* screening of alkaloids and terpenoids from African medicinal plants. *J Biomol Struct Dyn* 2021; **39**: 3396-3408 [PMID: 32367767 DOI:

10.1080/07391102.2020.1764868]
117 **Martine Denis**, Valerie Vandeweerd, Rein Verbeeke, Anne Laudisoit, Tristan Reid, Emma C Hobbs, Laure wynants, Diane Van der Vliet. Covipendium: information available to support the development of medical countermeasures and interventions against COVID-19. *Transdisciplinary Insights* 2021; **4**: 1-296 [DOI: 10.11116/TDI2020.4.10.SI.Covipendium]
118 **Gali R**. Israel Is Leading In The Development Of A Cure For Coronavirus Coronavirus cure. *Life Science* 2021
119 **Mazereel V**, Van Assche K, Detraux J, De Hert M. COVID-19 vaccination for people with severe mental illness: why, what, and how? *Lancet Psychiatry* 2021; **8**: 444-450 [PMID: 33548184 DOI: 10.1016/S2215-0366(20)30564-2]
120 **Daou A**. COVID-19 Vaccination: From Interesting Agent to the Patient. *Vaccines (Basel)* 2021; **9** [PMID: 33546347 DOI: 10.3390/vaccines9020120]
121 **Bloem BR**, Trenkwalder C, Sanchez-Ferro A, Kalia LV, Alcalay R, Chiang HL, Kang UJ, Goetz C, Brundin P, Papa SM. COVID-19 Vaccination for Persons with Parkinson's Disease: Light at the End of the Tunnel? *J Parkinsons Dis* 2021; **11**: 3-8 [PMID: 33523021 DOI: 10.3233/JPD-212573]
122 **Bogdan C**. [STIKO vaccination recommendations: Vaccination of immunodeficient patients and vaccination against COVID-19]. *Hautarzt* 2021; **72**: 92-99 [PMID: 33462654 DOI: 10.1007/s00105-021-04761-0]
123 **Banerji A**, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, Wolfson AR, Williams P, Khan DA, Phillips E, Blumenthal KG. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *J Allergy Clin Immunol Pract* 2021; **9**: 1423-1437 [PMID: 33388478 DOI: 10.1016/j.jaip.2020.12.047]
124 **Khan MS**, Shahid I, Anker SD, Solomon SD, Vardeny O, Michos ED, Fonarow GC, Butler J. Cardiovascular implications of COVID-19 versus influenza infection: a review. *BMC Med* 2020; **18**: 403 [PMID: 33334360 DOI: 10.1186/s12916-020-01816-2]
125 **Cuschieri S**, Grech S. Obesity population at risk of COVID-19 complications. *Glob Health Epidemiol Genom* 2020; **5**: e6 [PMID: 33282327 DOI: 10.1017/gheg.2020.6]
126 **Lee L**, Peterson GM, Naunton M, Jackson S, Bushell M. Protecting the Herd: Why Pharmacists Matter in Mass Vaccination. *Pharmacy (Basel)* 2020; **8** [PMID: 33114654 DOI: 10.3390/pharmacy8040199]
127 **Eberhardt CS**, Siegrist CA. Is there a role for childhood vaccination against COVID-19? *Pediatr Allergy Immunol* 2021; **32**: 9-16 [PMID: 33113210 DOI: 10.1111/pai.13401]
128 **Rzymski P**, Borkowski L, Drąg M, Flisiak R, Jemielity J, Krajewski J, Mastalerz-Migas A, Matyja A, Pyrć K, Simon K, Sutkowski M, Wysocki J, Zajkowska J, Fal A. The Strategies to Support the COVID-19 Vaccination with Evidence-Based Communication and Tackling Misinformation. *Vaccines (Basel)* 2021; **9** [PMID: 33535716 DOI: 10.3390/vaccines9020109]
129 **French J**, Deshpande S, Evans W, Obregon R. Key Guidelines in Developing a Pre-Emptive COVID-19 Vaccination Uptake Promotion Strategy. *Int J Environ Res Public Health* 2020; **17** [PMID: 32823775 DOI: 10.3390/ijerph17165893]
130 **Simon HU**, Karaulov AV, Bachmann MF. Strategies to Prevent SARS-CoV-2-Mediated Eosinophilic Disease in Association with COVID-19 Vaccination and Infection. *Int Arch Allergy Immunol* 2020; **181**: 624-628 [PMID: 32544911 DOI: 10.1159/000509368]
131 **ScienceDaily**. Drug discovery. [cited 18 April 2021]. Available from: https://www.sciencedaily.com/terms/drug_discovery.htm
132 **Maskin LP**, Olarte GL, Palizas F Jr, Velo AE, Lurbet MF, Bonelli I, Baredes ND, Rodríguez PO. High dose dexamethasone treatment for Acute Respiratory Distress Syndrome secondary to COVID-19: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; **21**: 743 [PMID: 32843098 DOI: 10.1186/s13063-020-04646-y]
133 **Kharma N**, Roehrig S, Shible AA, Elshafei MS, Osman D, Elsaid IM, Mustafa SF, Aldabi A, Smain OAM, Lance MD. Anticoagulation in critically ill patients on mechanical ventilation suffering from COVID-19 disease, The ANTI-CO trial: A structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; **21**: 769 [PMID: 32895056 DOI: 10.1186/s13063-020-04689-1]
134 **Johansson PI**, Bestle M, Søe-Jensen P, Kristiansen KT, Stensballe J, Clausen NE, Perner A. The effect of prostacyclin (Iloprost) infusion at a dose of 1 ng/kg/min for 72 hours compared to placebo in mechanically ventilated patients with COVID-19: A structured summary of a study protocol for a randomized controlled trial. *Trials* 2020; **21**: 746 [PMID: 32847626 DOI: 10.1186/s13063-020-04696-2]
135 **Liu F**, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. *BMJ Open* 2020; **10**: e039519 [PMID: 32641343 DOI: 10.1136/bmjopen-2020-039519]
136 **Lavine JS**, Bjornstad ON, Antia R. Immunological characteristics govern the transition of COVID-19 to endemicity. *Science* 2021; **371**: 741-745 [PMID: 33436525 DOI: 10.1126/science.abe6522]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 40-56

DOI: 10.5501/wjv.v11.i1.40

ISSN 2220-3249 (online)

REVIEW

Animal models for SARS-CoV-2 and SARS-CoV-1 pathogenesis, transmission and therapeutic evaluation

Udhaya Bharathy Saravanan, Mayurikaa Namachivayam, Rajesh Jeewon, Jian-Dong Huang, Siva Sundara Kumar Durairajan

ORCID number: Udhaya Bharathy Saravanan 0000-0001-9032-1307; Mayurikaa Namachivayam 0000-0002-9856-1257; Rajesh Jeewon 0000-0002-8563-957X; Jian-Dong Huang 0000-0001-7531-2816; Siva Sundara Kumar Durairajan 0000-0001-7376-7163.

Author contributions: Durairajan SSK, and Huang JD conceptualized, designed, and contributed to the outline of the review article; Saravanan UB, Durairajan SSK, Jeewon R, and Namachivayam M contributed to drafting, editing, and formatting of the manuscript; Saravanan UB, and Namachivayam M contributed to the illustration; Durairajan SSK secured the funding of the study; Durairajan SSK, and Huang JD are joint senior authors.

Conflict-of-interest statement: Nothing to disclosed.

Supported by COVID Therapeutics, Department of Biotechnology, Government of India, Ref. No. BT/PR4094/COT/142/20/2021.

Country/Territory of origin: India

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer

Udhaya Bharathy Saravanan, Mayurikaa Namachivayam, Siva Sundara Kumar Durairajan, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Tiruvarur 610005, India

Rajesh Jeewon, Department of Health Sciences, Faculty of Medicine and Health Sciences, University of Mauritius, Reduit 80837, Mauritius

Jian-Dong Huang, School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

Jian-Dong Huang, CAS Key Laboratory of Quantitative Engineering Biology, Shenzhen Institute of Synthetic Biology, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, Guangdong Province, China

Corresponding author: Siva Sundara Kumar Durairajan, MSc, M.Tech, PhD, Associate Professor, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Neelakudi, Tiruvarur 610005, India. d.sivasundarakumar@cutn.ac.in

Abstract

There is a critical need to develop animal models to alleviate vaccine and drug development difficulties against zoonotic viral infections. The coronavirus family, which includes severe acute respiratory syndrome coronavirus 1 and severe acute respiratory syndrome coronavirus 2, crossed the species barrier and infected humans, causing a global outbreak in the 21stcentury. Because humans do not have pre-existing immunity against these viral infections and with ethics governing clinical trials, animal models are therefore being used in clinical studies to facilitate drug discovery and testing efficacy of vaccines. The ideal animal models should reflect the viral replication, clinical signs, and pathological responses observed in humans. Different animal species should be tested to establish an appropriate animal model to study the disease pathology, transmission and evaluation of novel vaccine and drug candidates to treat coronavirus disease 2019. In this context, the present review summarizes the recent progress in developing animal models for these two pathogenic viruses and highlights the utility of these models in studying SARS-associated coronavirus diseases.

Key Words: Animal models; SARS-CoV-1; SARS-CoV-2; COVID-19; Mice; Hamster;

reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: June 24, 2021
Peer-review started: June 24, 2021
First decision: July 31, 2021
Revised: August 22, 2021
Accepted: November 24, 2021
Article in press: November 24, 2021
Published online: January 25, 2022

P-Reviewer: Coelho AC, Seki M
S-Editor: Fan JR
L-Editor: Kerr C
P-Editor: Fan JR

Non-human primates; Pathogenesis; Transmission; Therapeutics

Core tip: In this review we discuss the importance of various animal models of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). SARS-CoV-2 is the causal agent of coronavirus disease 2019 (COVID-19) and the World Health Organization declared the outbreak of COVID-19 as a public health emergency of concern. Due to the inadequate knowledge in analyzing the mode of action of COVID-19 infection, we must be thoroughly familiarized with the available animal models. Therefore, we discuss the pros and cons of various animal models, and emphasize the use of humanized mice to study the biology of viral diseases because it is convenient to mimic the human immune system in humanized mice.

Citation: Saravanan UB, Namachivayam M, Jeewon R, Huang JD, Durairajan SSK. Animal models for SARS-CoV-2 and SARS-CoV-1 pathogenesis, transmission and therapeutic evaluation. *World J Virol* 2022; 11(1): 40-56
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/40.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.40

INTRODUCTION

The World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) outbreak as an epidemic in November 2002 in China, where 8098 confirmed cases were reported, with 774 total deaths. Recently, a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak in December 2019 in China. At the end of January 2020, WHO announced that SARS-CoV-2 was responsible for the coronavirus disease 2019 (COVID-19) pandemic, leading to a global health emergency of international significance. According to WHO, as of November 5, 2021, 249.48 million SARS-CoV-2 cases were confirmed in 223 countries with 5.05 million confirmed deaths, with a case mortality ratio of 2.2% and differential transmissibility rate R_0 was 1.5–5.5. Although the overall SARS-CoV-2 mortality rate is still low (3%), it has become one of the most rapidly spreading pandemics globally. The Coronaviridae family of viruses affects a wide range of animal species, and the infection range depends upon the type of host getting infected. There have been two major outbreaks caused by viruses belonging to the Coronaviridae family, SARS-CoV-1 and SARS-CoV-2. These viruses crossed the species barrier, adapted themselves to infect humans, resulting in an unprecedented and unexpected high fatality rate. SARS-CoV-1 and SARS-CoV-2 cause respiratory tract syndromes and can cause severe pneumonia among older adults[1]. Although both viruses share a similar mode of transmission and cause similar clinical symptoms [2], SARS-CoV-1 has a higher pathogenicity and mortality rate, whereas SARS-CoV-2 infection has a lesser mortality rate but is more contagious because of its high transmissibility[3]. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the cells and infects the upper respiratory tract, and the infection then spreads to the lower respiratory tract. Viral replication continues, resulting in apoptosis of host cells, with loss of type I and II pneumocytes. The damage of alveolar epithelial cells leads to acute respiratory distress syndrome (ARDS). The infection results in a cytokine storm, and other immune cells are attracted as a host defense mechanism to clear the virus[4]. The complex pathophysiology of COVID-19 can only be understood by reproducing tissue-specific and systemic virus–host interactions, which can be studied using animal models.

Animal models are required to completely understand virus evasion strategies, disease etiology, and host responses. Both *in vitro* and *in silico* techniques can be used for examining the intricacies of the virus, especially at the molecular level. The immune responses playing key roles in the viral infection can be studied only in live models[5]. To reduce the risk to humans, animal models are used for the evaluation of vaccination and antiviral agents. The development of animal models should focus on

two key purposes: (1) To evaluate antiviral agents and vaccines; and (2) To characterize viral etiology[6]. The ideal animal models would reflect the pathology, clinical signs, and viral replication observed in humans[7]. A single model cannot reflect every feature of the virus infection; hence, different species are needed to study the various aspects of etiology. Before selecting an animal model for a virus infection, careful consideration is required since each species has its advantages and disadvantages based on the virus being studied. Therefore, researchers should select animals carefully[5]. This review provides a detailed comparison of the available animal models for the two human coronaviruses, SARS-CoV-1 and SARS-CoV-2. The lack of suitable small-animal models for studying the pathogenesis and development of vaccines and antivirals is one of the most serious obstacles to research progress. Several animal models have been used to study coronavirus infections and test the efficacy of vaccines and candidate therapeutic compounds. Reviewing animal models also has an important perspective of selecting rational animal models to evaluate drugs, vaccines and immune responses for tackling COVID-19.

DIFFERENCES AND SIMILARITIES BETWEEN SARS-CoV-1 AND SARS-CoV-2

The family of coronaviruses has been known for the associated risk of respiratory illness after the outbreak of SARS-CoV-1 in 2002 in Guangdong province, China, and the recent outbreak of SARS-CoV-2 in 2019 in Wuhan, China[8]. It is believed that SARS-CoV-2 originated from bats and was transmitted to humans *via* the seafood market in Wuhan. SARS-CoV-1 also originated in bats and was transmitted to humans from market civets[8]. SARS-CoV-1 is a beta coronavirus that belongs to lineages B and C[6]. As indicated by the genome groupings accessible to date, SARS-CoV-2 infection is caused by the strain BatCoVRaTG13, isolated from a bat in China's Yunnan region. Thus, SARS-CoV-2 is not an immediate relative of SARS-CoV-1[9]. Both the viruses are enveloped, nonsegmented, with a positive-strand RNA genome and a spherical shape, characteristic of species of the Coronaviridae family and order Nidovirales[6,10]. SARS-CoV-2 shares a total genome sequence similarity of 79.5% with SARS-CoV-1[11-13], whereas their spike proteins show a nucleotide similarity of 75% to 81%[13]. Both SARS-CoV-1 and SARS-CoV-2 bind to the host cell ACE2 with the help of the spike glycoprotein (S)[14,15]. S is a class I viral fusion protein; a trimeric protein that is proteolytically processed into two subunits S1 and S2[12]. The first difference between these two viruses is that the receptor binding domain (RBD) of SARS-CoV-2 has a higher affinity to ACE2 than that of SARS-CoV-1, making the former more infectious [16]. However, the binding affinity of the entire SARS-CoV-2 S protein to ACE2 is lower when compared to the entire S protein affinity of SARS-CoV-1[16]. Another critical difference is that SARS-CoV-2 RBD always remains in the lying-down position, leading to ineffective receptor binding[15].

In contrast, the SARS-CoV-1 RBD primarily exists in the upright position[17]. Although SARS-CoV-2 RBD is less accessible, it depends on a second strategy called host protease activation to maintain its high infectivity[3]. Another difference between SARS-COV-2 and SARS-CoV-1 is that the former has a furin-like cleavage site in the S protein[18,19]. S protein is cleaved by furin which is essential for cell–cell fusion and entry, whereas preactivation of furin enhances efficient transmission of SARS-CoV-2, allowing entry into host cells with low expression of transmembrane protease serine 2 (TMPRSS2) and cathepsins[19,20]. The SARS-CoV-1 S protein is cleaved at S1/S2 and S2 sites by host cell proteases such as TMPRSS2 and lysosomal cathepsins[17]. The presence of high arginine content at the S1/S2 site of SARS-CoV-2 results in higher cleavability than that observed in SARS-CoV-1[16]. In addition, inhibition of both proteases is required to block SARS-CoV-1 entry into the cells, whereas the blocking of TMPRSS2 is sufficient to inhibit viral replication[17]. Apart from these similarities and differences between SARS-CoV-1 and SARS-CoV-2, they share similarities in their pathogenesis. Both SARS-CoV-1 and SARS-CoV-2 cause host cell apoptosis, activation of immune cells, and an increase in the levels of inflammatory cytokines, leading to a cytokine storm. Finally, diffuse alveolar damage of alveolar epithelial cells has been reported in infections with both viruses, resulting in ARDS[21-23]. Damas evaluated the ACE2 diversity and its correspondence to human ACE2 in 410 vertebrates and developed a scoring system based on the 25 conserved amino acids. This study suggested that nonhuman primates are more susceptible, whereas rodents are less susceptible to the infection[24]. Table 1 list the available animal models for SARS-CoV-2.

Table 1 Comparison of available animal models for SARS-CoV-2 infection

No.	Animal model	Upper respiratory tract	Lower respiratory tract	Feces/Fecal swab	Contact transmission	Airborne transmission	Weight loss	Ref.
1	Cat (6 to 9 mo)	Infectious virus	Nil	Present	Not reported	33%	Not reported	[72]
2	Chicken	Nil	Nil	Not reported	Nil	Not reported	Not reported	[72]
3	Dog	Nil	Nil	Present	Nil	Not reported	Not reported	[72]
4	Duck	Nil	Nil	Not reported	Nil	Not reported	Not reported	[72]
5	Ferret	Infectious virus	Infectious virus	Present	100%	30%	Not reported	[72, 73]
6	hACE2 mouse	Not reported	Infectious titer	Infectious titer	Not reported	Not reported	Present	[57]
7	Hamster	Infectious titer	Infectious titer	Infectious titer	100%	Not reported	Present	[59]
8	Kitten	Infectious titer	Infectious titer	Not reported	Not reported	33%	Not reported	[72]
9	Macaque	Present	Present	Not reported	Not reported	Not reported	Nil	[80]
10	Pig	Nil	Nil	Not reported	Nil	Not reported	Not reported	[72]

MOUSE MODELS

Mouse models are preferred owing to their low cost, convenient husbandry requirements, and ease of availability. However, the drawbacks in using mouse models for human viruses are species tropism, species specificity, immune response factors, *etc.*[25]. Mouse models help us to study the host immune factors by promoting virus infection, making them important for identifying therapeutic targets and developing novel vaccine strategies[26]. Wild-type mouse models, knockout models, transgenic mice, and humanized mice are commonly used in animal studies to study pathogenic diseases, understand the role of specific genes in inhibiting or promoting the disease, and identify therapeutic targets[27].

Wild-type mouse models

BALB/c and C57BL/6 are the most preferred animal models for viral studies so far. However, when infected with SARS-CoV-2, these models showed no clinical signs, mortality, and weight reduction, and there was an absence of viremia. Viral RNA was detected in both types of mice in the lungs only on the first day, while the other organs did not show the presence of the viral RNA. These models tested negative for the anti-SARS-CoV-2 IgG antibodies[28]. These results suggest that BALB/c and C57BL/6 mice models remain uninfected when inoculated with SARS-CoV-2 due to the difference in the ACE2 receptor. Gu *et al*[29] used the mouse-adapted SARS-CoV-2 strain to infect BALB/c mice to overcome these difficulties, and once infected, the BALB/c mice showed inflammation and injury in both young and old mice[29]. Antibody blockade of interferon-α/β receptor alpha chain (IFNAR) in these mice resulted in weight loss and lung inflammation[30]. This study showed that old BALB/c mice were more prone to the disease than the younger ones and can be used to develop candidate vaccines. This was confirmed by the appearance of bronchiolitis in histopathological examination[29]. Likewise, Dinnon *et al*[31] remodeled the spike and RBD of SARS-CoV-2 (SARS-CoV-2 MA) to enable it to bind to the mouse ACE2 receptor[31]; thus, improving the virulence. Several passages were performed, and a virulent strain was generated at P10 (SARS-CoV-2 MA10). When young BALB/c mice were infected with a mouse adapted SARS-CoV-2 MA10 strain, it resulted in weight loss, diffuse alveolar damage, hyaline membrane formation, alveolar septal thickening, and neutrophil presence in alveolar space; whereas 100% mortality was observed in old mice after infecting them with 10^4 and 10^5 plaque-forming units (PFU) of SARS-CoV-2 MA10. However, when infected at 10^3 PFU, the old mice showed weight loss similar to that observed in the young mice, although only rare survival[32]. The infected mice showed inflammatory responses identical to those seen in humans[33]. For the vaccine

study, the Venezuelan equine encephalitis viral vector vaccine was developed to express SARS-CoV-2 S, nucleocapsid, and GFP reporter and primed in BALB/c mice. An initial dose and a booster dose were administered, and the mice were challenged with the SARS-CoV-2 MA10 strain, with the mice vaccinated with S showing neutralizing activity. However, the polyclonal sera had neutralization titers for both SARS-CoV-2 MA10 and SARS-CoV-2, which showed that SARS-CoV-2 MA10 could be used to test vaccine efficacy[32]. Similarly, C57BL/6J young and adult mice were infected with the SARS-CoV-2 MA10 strain.

In comparison to BALB/c mice, significant weight loss was observed with no mortality. Histological changes were observed to be similar in young BALB/c and C57BL/6J mice, but the acute lung injury scores were reduced in C57BL/6J mice[32], which may have been due to its dominant Th1 response, whereas BALB/c mice expressed a Th2 response dominantly[34]. Both BALB/c and C57BL/6J mice, upon infection with SARS-CoV-2 MA10, showed cellular tropism similar to humans, but instead of secretory cell infection, ciliated cells were infected in these mice[32]. Apart from all the other reported mouse models, this model showed limited use for studying alveolar disease pathogenesis. The SARS-CoV-2 MA10 model exhibited several COVID-19 symptoms, such as morbidity and mortality difference with age and host genetics, defects in lung function, and other etiologies[32]. These results show that both BALB/c and C57Bl/6J mice can be used to study mild SARS-CoV-2 MA10 strain, its etiology, and the efficiency of vaccines. Wild-type mouse models remain unaffected by SARS-CoV-2 due to their ACE2 receptor, so mouse-derived viral strains are required for further studies.

SARS-CoV-1, which is similar to SARS-CoV-2, has also been tested in these mouse models. In a study, 4–6-week-old female BALB/c mice were inoculated intranasally with 50 μL of diluted SARS-CoV-1 (Urbani strain). The microscopic examination showed mild and focal bronchiolitis[1]. Tseng *et al*[35] suggested that the viral doses of 103 and 105 median tissue culture infectious dose (TCID50) of the Urbani strain of SARS-CoV-1 were required for initiation of infection[35]. Upon infection, the mice did not develop pulmonary pathology, had no signs of clinical disease, and did not lose weight. Besides, the virus showed high levels of replication in the lower and upper respiratory tract without any symptoms[36]. Upon infection in BALB/c, 129WT and C57BL6 mice, SARS-CoV-1 did not show lethality, but it could replicate in the lungs 2 d post-inoculation (dpi)[2]. The BALB/c mice were also used for vaccine study by Du *et al*[37], where the RBD of SARS-CoV-1 S protein was fused with human IgG1 Fc (RBD-Fc), then injected into mice twice at 3-wk intervals and boosted once again after 1 year. In this study, neutralizing antibodies were found in the mice vaccinated with RBD-Fc, assuring protection from SARS-CoV-1 without any immunopathological damage[37]. However, SARS-CoV-1 replication was not efficient in wild-type mice due to a lack of efficient interaction between the spike protein (S) and murine ACE2[38].

Infection of immunocompetent mouse strain 129SvEv with SARS-CoV-1 showed infection in the conducting airway epithelial cells followed by clearance of the virus from the lungs, which later led to the development of self-limited bronchiolitis[1]. During clinical trials, the infection in young mice showed rapid virus clearance; however, weight loss was followed by several complications in older mice[7]. The 129S mouse strain was more susceptible than the BALB/c strain[1,6]. In addition, the 129S mouse strain showed pneumonitis and mild weight loss after SARS-CoV-1 infection [39]. In the case of weight loss in 129WT, Urbani SARS-CoV-1 virus infection led to morbidity[2]. Upon vaccination of 129S6/SvEv mice with the whole killed virus vaccine (adenovirus-based vaccine), viral replication was inhibited in the murine respiratory tract[40]. However, SARS-CoV-1 IgA antibody was detected in the sera of vaccinated mice, with the vaccine expressing both S protein and nucleocapsid protein (N)[40]. Thus, these studies explain that SARS-CoV-2 and SARS-CoV-1 cannot affect the inbred mouse models due to the difference in ACE2. However, these mice can be used for studying mouse-adapted strains of both viruses for the development of vaccines and antiviral drugs. Young models can be used to study the immune responses to infection, whereas old models can be used to study age-related diseases.

Knockout mouse models

The knockout models are devoid of certain specific genes to study the immune response involved in viral infections and are widely used to study the function of specific genes in inhibiting the disease[24]. Knockout models such as TMPRSS2$^{-/-}$ C57BL/6, IFNAR1$^{-/-}$hCD46, and STAT1 have been used so far to study SARS-CoV-2. The TMPRSS2$^{-/-}$C57BL/6 mice infected with SARS-CoV-2 showed reduced body weight loss and viral replication in the lungs. The absence of TMPRSS2 in the mice might have affected the priming of viral S protein and its subsequent fusion and thus

contained the virus spread within the mice, emphasizing the involvement of TMPRSS2 for the successful establishment of SARS-CoV-2 infection[41]. Knockout mice lacking *IFNAR1* gene but expressing human CD46 (IFNAR1$^{-/-}$hCD46), upon immunization with recombinant measles virus vaccine that expressed stabilized prefusion S protein (rMeV-preS), showed good antibody response[42]. The IFNAR$^{-/-}$mice, upon immunization with the same vaccine, showed an antibody response higher than that detected in human sera from convalescent COVID-19 patients[42]. Thus, the TMPRSS2 knockout model can be used to study pathogenesis, whereas STAT1 knockout mice can be used for study of both pathogenesis and antiviral drugs, but the IFNAR knockout model cannot be used for vaccine study due to its immunodeficiency.

In the case of SARS-CoV-1, the strains used were CD1 (Swiss outbred) and RAG1 (non-leaky SCID mice), which did not develop clinical disease[2]. However, STAT1$^{-/-}$ mice showed bronchiolitis and progressive weight loss[2]. These symptoms progressed to mediastinitis and interstitial pneumonia[2]. In these mice, the development of type 1 interferon (IFN) was indicative of control of SARS-CoV-1 infection, which showed viral replication on day 3. Rag1$^{-/-}$, CD1$^{-/-}$ and STAT1$^{-/-}$mice, which are in the 129S background, were tested against the immunological effectors of the disease. STAT1$^{-/-}$mice supported prolonged viral replication and histopathology similar to that observed in humans[2,6,36]. However, CD1$^{-/-}$mice (lacking natural killer cells) from B6 background, when infected with SARS-CoV-1, showed replication as observed in the lungs of B6 mice[1]. STAT1 knockout mouse models can be used to study the functions of cytokines in immune responses and IFN-mediated responses and analyze inflammation mechanisms[2]. When STAT1$^{-/-}$mice were infected with the same Urbani SARS-CoV-1 strain or with a recombinant isogenic mouse-adapted virus (rMA15), the infection could not be cleared even at 22 dpi[2]. After infection, STAT$^{-/-}$ mice initially lost 15% of their weight, followed by a 30% loss in weight, and the mice were moribund and paved the way for lethal infections[2]. Frieman *et al*[2] reported that epithelial cells of noncartilaginous conducting airways were the primary site of infection in STAT$^{-/-}$mice infected with SARS-CoV-1 of the Toronto-2 strain *via* intranasal inhalation (6×10^6 PFU/30 μL). The conducting airways of epithelial cells had focal intracellular aggregates[2], whereas 129 mice with type I IFN receptor knockout mice (IFNAR1$^{-/-}$) and type I/II double IFN receptor knockout mice (IFNAR$^{-/-}$) showed weight loss followed by morbidity after infection with the Urbani SARS-CoV-1 strain[2]. In ACE2 knockout mice, the copy numbers of S protein RNA were greatly reduced, and only a low number of infectious SARS-CoV-1 could be recovered from the lungs, showing that ACE2 is required for the effective replication of SARS-CoV-1[43]. Thus, STAT1 knockout mice can be used to study pathogenesis, whereas ACE2 knockout models can be used to study SARS-CoV-1-related ARDS. They are not suitable for vaccine and antiviral drug studies due to the immunodeficiency nature of knockout models.

Transgenic mice/genetically engineered models

Several transgenic models have been used widely for investigating the mechanisms related to viral pathogenesis[25]. The limitations of knockout mice in studying SARS-CoV-1 were overcome by developing transgenic mice that expressed human (h)ACE2 [34]. hACE2 transgenic mice may serve as a potential research model. To develop the model for SARS-CoV-1 and SARS-CoV-2 infection, an animal model of transgenic mice that expressed hACE2 had to be developed[44] as the severity of disease development in the transgenic mice model was correlated with the expression of hACE2[45]. The human *ACE2* gene was cloned and inserted into a plasmid, and the mouse ACE2 promoter was also retrieved and inserted upstream of hACE2 coding sequences. The fragments having *hACE2* gene driven by mouse promoter were microinjected into the pronuclei of fertilized mouse ova[44]. Increased expression of hACE2 indicated 100% mortality with severe lung and brain infection, while low levels of hACE2 caused illness without associated mortality[45]. The other requirement in developing the hACE2 mice was controlling the mice's ACE2 receptor that expressed hACE2, which would result in limited tissue distribution of hACE2, making the mice lethargic but surviving the infection. Even after survival, the mice showed interstitial pneumonia with extrapulmonary organ damage, which is indicative of the human model for coronavirus infection[45]. Likewise, using human cytokeratin (CK)18 as a promoter, transgenic mice expressing hACE2 were developed. The CK18 promoter helps efficiently express hACE2 in airway epithelial cells and other organs but not alveolar epithelia. K18-hACE2 mice showed alveolar dysfunction upon infection with SARS-CoV-1[46]. Infected mice showed evidence of perivascular and peribronchial inflammation and lung injury. An increase in the level of chemokines and cytokines was detected in the lungs of K18-hACE2 mice[46]. Extensive studies on this model showed

neuroinvasion by the virus, which started from an olfactory bulb and progressively spread to subcortical and cortical regions of the brain. However, this route of transmission could not be applied to the other infected regions that were not connected to olfactory bulbs[47]. These mouse models have been used for the study of vaccine development, etiology and therapeutics. The studies on SARS-CoV-1 and SARS-CoV-2 have shown that these viruses can infect mice expressing hACE2[44]. Inoculation of SARS-CoV-2 into the transgenic mice showed a reduction in weight, superficial and histological evidence of antibody responses, and lung inflammation, although lung injury was limited[48,49]. The reports on SARS-CoV-2 infection state a lower mortality rate compared to that of SARS-CoV-1[50]. Using hACE2 for further studies encountered whether the expression of hACE2 level and tissue distribution in mice could fully reflect the level and distribution in humans. The murine models usually have ACE2 expression in the bronchial epithelium, whereas humans generally have its distribution in the lungs[47,51,52]. The distribution of hACE2 also depends on the species. A better model for severe SARS-CoV-2 infection can be developed by targeted positioning of hACE2 into the endogenous mouse locus[50]. Using CRISPR/Cas9, hACE2 was inserted into the endogenous mouse ACE2 locus, and these mice were susceptible to SARS-CoV-2 infection and showed greater lung neutrophil infiltration with increasing age. Infection in these mice also occurred *via* the intragastric route[53]. Transgenic mice expressing hACE2 under the CK18 promoter showed an increased viral titer in the brain when infected intranasally by SARS-CoV-2 [54]. Remarkably, García-Arriaza *et al*[55] developed COVID-19 vaccines using modified vaccinia virus Ankara (MVA) as vectors, which expressed the entire SARS-CoV-2 spike protein (MVA-CoV2-S). Upon administration of one dose of this vaccine to k18-hACE2 models, the mice were protected from a lethal dose of SARS-CoV-2. After two doses of vaccine, the viral replication in the lungs was fully inhibited[55]. The same results were observed when the researchers used recombinant MVAs as vectors for delivering SARS-CoV-2 S protein in k18-hACE2 mice[56]. In a comparative study between SARS-CoV-1 and SARS-CoV-2 pathogenicity, SARS-CoV-2 was found to be milder than SARS-CoV-1 in the hACE2-expressing mice. In the case of SARS-CoV-1, extrapulmonary organ damage, cerebral vasculitis, and hemorrhage were observed. In the case of SARS-CoV-2, only interstitial pneumonia was observed. Viral replication was seen in both the upper and lower respiratory tracts. More studies are required in this knock-in hACE2 mouse model for a better understanding of the pathogenesis of the infection[57]. Following all the results available, it is inferred that the transgenic mice expressing hACE2 had a more severe infection when compared with wild-type mice. These mice are a better choice for testing the vaccine potential and antiviral drug efficiency when compared to all other available mice models. In addition, the use of mouse-adapted SARS-CoV-2 strains can be replaced with the use of hACE2-expressing mice.

HAMSTERS

Hamster ACE2 shows a large degree of genome sequence similarity to human ACE2 [58]. When golden Syrian hamsters were inoculated with SARS-CoV-2 *via* the nasal route, viral replication was observed in the lungs, along with the development of inflammation, massive leukocyte infiltration, marked lesions of lung congestion, necrotizing bronchiolitis, and necrosis[59]. Infected hamsters also infected the cohoused hamsters along with causing weight reduction in mice and an increased respiration rate[50]. Quantitative polymerase chain reaction (PCR) was used to measure inflammation in the lungs, which revealed a quick response of IFNs and an increase in interleukin (IL)-16 levels. However, lung pathology and the other symptoms were resolved at 14 dpi[50]. STAT2 knockout hamsters, when infected with SARS-CoV-2, displayed high viremia, lung titers, and systemic spread when compared to the wild-type models. This showed that STAT2 knockout mice exhibited limited systemic spread of the infection, whereas the knockout hamsters showed limited leukocyte infiltration, no pneumonia, and attenuated lung pathology. Transgenic strains of hamsters can be used to restrict systemic viral dissemination by studying the molecular pathways[59]. Monchatre-Leroy *et al*[60] conducted a comparative study between hamsters and ferrets using a single strain of SARS-CoV-2 for infection, which suggested that the hamster model was more relevant than the ferret model because of its systemic lung infection, less maintenance, and ease of supply[60]. When vaccinated for SARS-CoV-2 with the patient isolates of early passages, the Syrian hamster exhibited protection in a harsh challenge setup[61]. In another study, hamsters

immunized for SARS-CoV-2 with recombinant measles virus that expressed the perfusion S protein of SARS-CoV-2 (rMeV-preS) exhibited high levels of Th1-based immunity, proving that the recombinant attenuated vaccine could act as an efficacious bivalent vaccine[42]. The Th1-based antibody response can reduce the risk of antibody-dependent enhancement, which is a challenge in vaccine development. Hamsters have also been used in a study evaluating the protective efficacy and immunogenicity of the whole-virion inactivated vaccine candidates, namely BBV152A, BBV152B and BBV152C. These vaccine candidates, along with Algel adjuvant, either alone or chemisorbed with imidazoquinoline, were found to be safe in the preclinical tests on mice, rats and rabbits[62]. BBV152, when injected into hamsters, produced SARS-CoV-2-specific IgG and neutralizing antibodies 3 wk post-inoculation. In the other two candidates of this vaccine, neutralizing antibodies increased until 7 wk after SARS-CoV-2 challenge. However, this study had some limitations, including the cell-mediated immune response elicited by the vaccine candidates, which need to be explored further, along with the period of antibody response and the cross-neutralizing potential of the neutralizing antibody with other coronaviruses[63]. These results suggest that hamsters can be used as a model for vaccine studies. Similarly, a drug study was conducted in the golden Syrian hamster for SARS-CoV-2. When treated with a combination dose of methylprednisolone and remdesivir, the infected hamsters were relieved of the tissue inflammation, and viral replication was reduced in the early stages of infection[64]. In contrast, treatment with methylprednisolone alone prevented weight loss, reduced anti-RBD antibody development, and improved tissue damage and inflammation[65,66], but the tissue viral RNA loads and viral titers were observed to increase. Similarly, for the treatment of severe COVID-19, either the humanized monoclonal antibody tocilizumab (anti-IL-6 receptor) could be used against the IL-6 receptor[67], or anakinra (antagonist) could be used against the IL-1 receptor[68]. Thus, hamsters can be used to study the SARS-CoV-2 vaccine and antiviral drug efficiency, transmission, and immune response of the host.

For SARS-CoV-1, the golden Syrian hamster is preferred as a model as it exhibits viral loads and mild and transient pneumonia followed by pulmonary histopathology similar to those observed in humans[69]. Hamsters, when infected with SARS-CoV-1, showed high levels of viral replication in pulmonary tissues, severe interstitial inflammation, and pulmonary consolidation. The initial infection of SARS-CoV-1 can elicit strong neutralizing antibody responses, which protects the animals from subsequent infection[69]. In a study evaluating the immunogenicity and preventive efficiency in hamsters, the respiratory virus BHPIV3 was used as a vector to express SARS-CoV-1, and it was found that the S glycoprotein acted as a protective antigen and neutralizer against SARS-CoV-1. Thus, the preventive and high immune response against SARS-CoV-1 can be obtained by a single intranasal administration of recombinant vectors that express the S protein[70]. For SARS-CoV-1, recombinant measles virus vaccine conferred protection to immunized Syrian hamsters at viral titers of more than 100-fold; this vaccine encodes the unmodified SARS-CoV-1 S protein, which can induce high titers of neutralizing antibodies and IFN-γ T cell responses[61]. Together, these results suggest that golden Syrian hamsters can be used to study the transmission, drug efficiency, vaccine efficiency, and modeling mechanism for both SARS-CoV-1 and SARS-CoV-2, along with the study of host defense against severe infection. However, it is not used widely because of the lack of research tools, but it can act as a better alternative for transgenic mice models because the ACE2 of hamsters has a remarkable similarity to hACE2.

FERRETS

Ferrets are commonly used animal models for viruses causing respiratory illness in humans. Ferrets can be used for both viral transmission and pharmacological studies. They are also used to study mucoviscidosis[71]. Ferrets are more susceptible to SARS-CoV-2 infection compared to dogs[72]. Ferrets also show the same symptoms as humans after inoculation with SARS-CoV-2, like elevated temperature suggestive of pyresis, coughing between 2 and 12 dpi, reduced activity, and loss of appetite[72,73]. In ferrets, replication occurred in the soft palate, nasal turbinates, tonsils, and digestive tract, while the virus was absent in the lung lobes, even when inoculation was intratracheal[74]. Severe pulmonary lymphoplasmacytic perivasculitis and vasculitis were detected in the lungs of infected ferrets when observed histologically[72]. The viral shedding profile of ferrets resembled that of asymptomatic human patients who efficiently transmit SARS-CoV-2[75]. Ferrets were infected with SARS-CoV-2 and

treated with certain FDA-approved antiviral drugs, which revealed that emtricitabine–tenofovir showed antiviral efficacy in the respiratory and gastrointestinal tract[76]. Thus, the ferret is a suitable animal model for studying mild and asymptomatic SARS-CoV-2 infection, transmission, and pathogenesis.

When ferrets were inoculated with SARS-CoV-1, a subset showed clinical illness, while the remaining animals did not show infection[77]. The ferret models were characterized by higher cytotoxicity in the upper respiratory tract with fever and sneezing associated with histological changes in the lungs, including lymphohistiocytic bronchopneumonia[69,78]. Viral replication was not detected in the lower respiratory tract in the ferrets, making it a candidate model for antiviral and vaccine testing[79]. Naïve ferrets were used for studying viral transmission by placing them in direct and indirect contact with infected ferrets. Ferrets left in direct contact showed symptoms of infections at 2–6 dpi, whereas those left in indirect contact remained asymptomatic, with only some ferrets showing viral RNA indicating transmission *via* air. Ferrets can also be used to study the immune responses against infection[50,73]. Thus, ferrets can be used to study transmission, immune response against infection, and effect of antivirals and vaccines for both SARS-CoV-1 and SARS-CoV-2.

NONHUMAN PRIMATES

Among the various nonhuman primate models for SARS-CoV-2, cynomolgus macaques and rhesus macaques are used the most, and the common marmoset has shown resistance to infection[48,80,81]. For SARS-CoV-2, the most convincing model that has been suggested by Yu *et al*[81] is the rhesus macaque, which, when inoculated intratracheally, orally, intranasally, and in both eyes, showed asymmetrical breathing patterns and tachypnea in a few animals, suggesting a certain degree of ARDS development[81]. Since age is said to be the major threat factor for COVID-19, mature rhesus macaques (15 years old) were compared with younger macaques (3–5 years old), and an increase in viral load at 7 dpi was seen in the older animals[81]. Thus, aged rhesus macaques can be used as a model for acute disease. Another study was conducted with rhesus macaques on the development of protective immunity after the initial infection. Two animals were inoculated intratracheally and then again after 28 d. Bao *et al*[48] observed the development of protective immunity in macaques with the lack of viral shedding[48]. Rhesus macaques were used for studying the BBV152 vaccine (Covaxin). The animals were given two doses of vaccine at an interval of 14 d and then challenged with SARS-CoV-2. SARS-CoV-2-specific IgG and neutralizing antibodies were produced, showing the protective efficacy of the vaccine. Virus clearance was observed at 7 dpi in the macaques, and this vaccine is now in phase III of its trial[82]. A comparative study on the etiology of SARS-CoV-2 and SARS-CoV-1 was conducted in nonhuman primates, and it was found that cynomolgus macaques remained uninfected after inoculation with SARS-CoV-2. This model shed the virus for an extended period, and the virus was capable of replicating efficiently in both the upper and lower respiratory tract of the model. This model can be used for studying the etiology of SARS-CoV-2 and the analysis of therapeutic approaches to the disease [80]. SARS-CoV-2 was inoculated in both young and mature cynomolgus macaques. The lesions showed pulmonary alveolar edema, formation of hyaline membrane, and other signs of acute lung injury[80]. Koo and workers observed acute interstitial pneumonia with endotheliitis in both rhesus and cynomolgus macaques infected with SARS-CoV-2[83]. These observations showed that cynomolgus macaques could be used as a model for studying the mechanism of severe SARS-CoV-2 infection, and rhesus macaques can be used to study the etiology, immune response, and vaccine efficiency.

Based on previously published studies, SARS-CoV-1 was reported to infect old and new world monkeys, including common marmosets, squirrel monkeys, rhesus macaques, mustached tamarins, cynomolgus macaques, and African green monkeys [69]. SARS-CoV-1 infections in these nonhuman primates showed symptoms such as diarrhea, fever and pneumonitis[69]. The pneumonitis, which was observed in each species, varied with the inoculum dose and route[7]. The highest viral replication was seen in the cynomolgus monkeys followed by African green monkeys, with the findings affected by many factors, including dose, age, route of infection, animal source, inoculation of the virus, and history of the environment[38]. The SARS-CoV-1 Urbani strain showed mild symptoms followed by infection in cynomolgus macaques, rhesus macaques and green monkeys[69]. Replication of SARS-CoV-1 did not occur in mustached tamarins and squirrel monkeys[6]. African green monkeys, when

immunized with recombinant attenuated parainfluenza virus (BHPIV3) that expressed the SARS-CoV S protein, showed the production of SARS-CoV neutralizing serum antibodies, indicating the effectiveness of mucosal immunization[84]. Thus, nonhuman primates can be used to study age-related effectiveness, pathogenesis, and vaccines for both SARS-CoV-1 and SARS-CoV-2. However, they are not used largely because their maintenance and handling are difficult and not available easily.

CATS

Domestic cats were found to test positive for both SARS-CoV-1 and SARS-CoV-2, which were presumed to be infected by their owners[85]. Cats can be infected experimentally with SARS-CoV-1 and SARS-CoV-2, and they show pulmonary changes, viral shedding, and infection similar to humans[86]. The cats inoculated with SARS-CoV-1 *via* the intranasal route showed viral replication in the lungs followed by pneumonitis[38]. Rudd *et al*[87] found that when cats were intratracheally infected with SARS-CoV-1, they showed pulmonary disease with diffuse alveolar damage[87]. They also observed predominant clinical signs, including fever, cough, lethargy, and increased respiratory effort in the cats inoculated intratracheally with SARS-CoV-2. They also found pulmonary lesions such as diffuse alveolar damage and evidence of vascular injury[85]. In another study, cats infected with SARS-CoV-1 developed pulmonary lesions, and active infection and shedding were also observed, which were similar to those occurring in humans. However, they also developed tracheo-bronchoadenitis, which has not been reported in humans[77]. The infected cats were also capable of transmitting the virus to other cats[86]. In the case of SARS-CoV-2, Zhang *et al*[79] infected 8-month-old cats intranasally and found infectious virus in the upper respiratory tract, small intestine, and feces. The same symptoms were observed in 14-week-old kittens, and they also showed histopathological changes suggesting that infection is more severe in younger cats. The mode of transmission of SARS-CoV-2 from infected cats to adjacent uninfected cats could be through feces or respiratory droplets[72]. Likewise, another study on transmission was done on three cats that were inoculated with SARS-CoV-2 and cohoused in pairs with uninfected cats after 1 d of inoculation. After 1 dpi, the shedding of viral particles was confirmed from the inoculated cats that infected the cohoused cats as the shedding of virus from the inmates was recorded after 3–5 d, ensuring the transmission of SARS-CoV-2. However, none of the cats showed clinical signs and no virus detection in the rectal swabs, although all cats developed antibodies[88]. In the United States, zoo-housed tigers and domestic cats belonging to the Felidae family were also positive for SARS-CoV-2[38]. Finally, all these studies prove that cats are susceptible to SARS-CoV-2 and SARS-CoV-1 infection and its capability to develop neutralizing antibodies, which protected them from reinfection[86]. More studies on cats are required to develop medicines for veterinary animals[50]. Further studies must be done on domestic cats to study transmission crossing the species barrier, and the studies should be focused on specific antibody production in cats.

ANIMALS INFECTED MINIMALLY: DOGS, CHICKENS, PIGS AND TREE SHREWS

Few results are available for infection in tree shrews, pigs, chickens and dogs, none of which have shown signs of COVID-19, except for dogs displaying shedding of virus in feces[72]. No respiratory disease was seen in domestic dogs with positive PCR results. Live virus isolation and viral RNA detection were reported for one dog, although there was no transmission to other dogs in the same household[89]. Also, no infection has been observed in pigs or their cell lines[90]. Similarly, chickens are found to be resistant to SARS-CoV-1 and SARS-CoV-2. Chickens inoculated with the virus showed viral RNA, but it was not possible to isolate the replicating virus from them[91]. Chickens also did not transmit the infection to cohoused chickens[74]. When embryonated eggs were injected with these viruses, no replication was observed[72, 92]. The same results were reported for tree shrews, with no clinical signs except for an increase in temperature that was observed only in females[93]. Based on the evidence mentioned above, these animals are not preferred for SARS-CoV-1 and SARS-CoV-2 related studies.

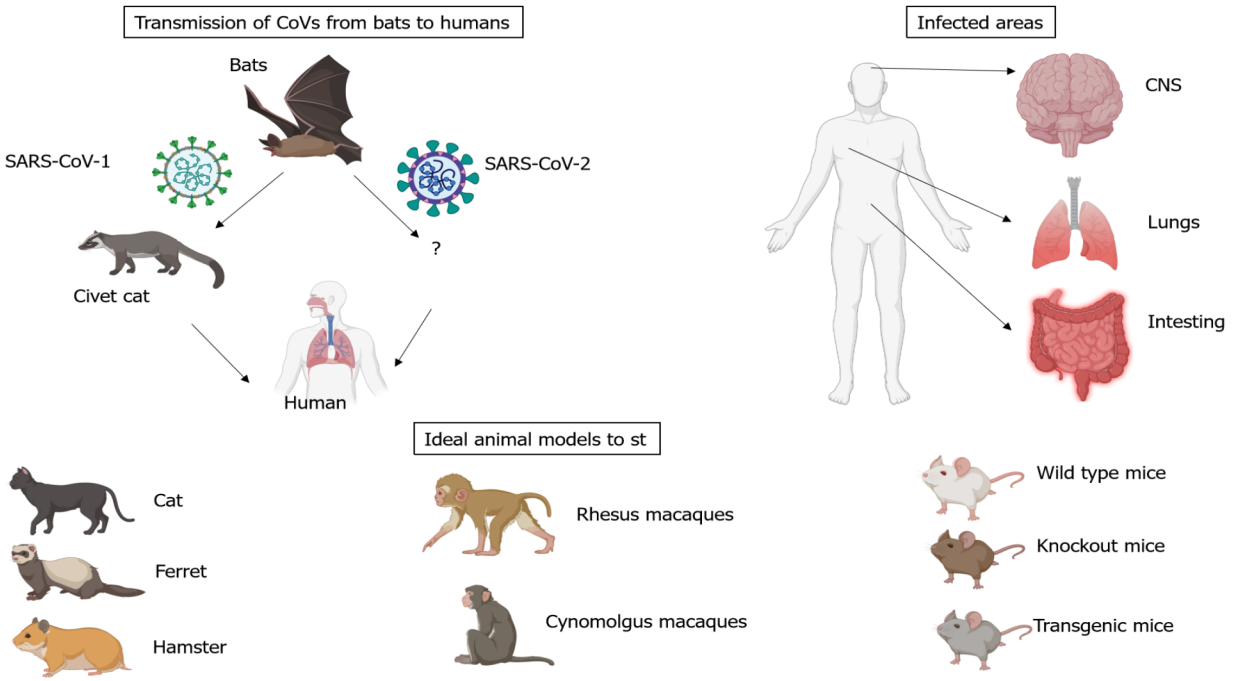


Figure 1 Searching for an ideal animal model to study COVID-19 transmission and pathogenesis. CNS: Central nervous system.

WILDLY CAUGHT POSITIVE ANIMALS

During the disease outbreak, a few wild animals were found to be positive for SARS-CoV-2, including the *Rhinolophus* and *Hipposideros* species of pangolins, bats, palm civets, bamboo rats, raccoon dogs, hog badgers, and hedgehogs[94]. In the Netherlands, some studies on farms revealed that the strain passed from humans to mink, spreading to other humans and the mink population. Viral RNA was detected in air–dust particles in mink farms[95]. Respiratory diseases were detected in infected mink, with interstitial pneumonia, lung inflammation, and little mortality. This shows that minks can serve as a more nuanced model than ferrets, but controlled studies would be needed. Infected lions and tigers showed loss of appetite and respiratory symptoms, but they recovered[96]. From these observations, it is clear that more measures should be taken to stop the transmission of SARS-CoV-2 to other species and to protect the wild animals.

CONCLUSION

Animal models for SARS-CoV-2 and another human coronavirus are used extensively. Animal models that accurately reproduce the severe COVID-19 symptoms exhibited by humans are required to design novel therapeutic approaches. The existing animal models are currently preferred (Figure 1), but efforts must be made to assess them with proper *in vitro* experiments and generate reliable scientific data before being put into use. It is impossible to study the etiology, transmission, therapeutic approaches, drug treatment, and vaccine development in a single animal model due to their inborn differences. Furthermore, there are many differences in biology, behavior, genetics, adaptability, and receptor expression level; all of which influence the infection rate. Thus, various animal models are required to develop a good understanding of the disease and obtain better results. The preferred animal model for each study would depend on reproducibility, efficacy, etiology, *etc.* Laboratory mice and hamsters are preferred due to their ease of availability, easy handling, low cost, small size, and possibility of manipulation at the genetic level. In SARS-CoV-2, cynomolgus macaques and rhesus macaques are better models than all other models discussed. Based on available studies, Lakdawala and Menachery[72] suggested that hamsters, ferrets and cats can serve as alternatives for nonhuman primates and transgenic mouse models [72]. Cats and ferrets can be used as models for studying the transmission and effectiveness of antivirals to limit viral spread. The nonhuman primates that showed reduced viral loads and hamsters that produced neutralizing antibodies and specific

immune responses can be used as models for evaluating the effectiveness of vaccines and antivirals before deployment to humans[72]. For SARS-CoV-1, all nonhuman primate models are suggested to be the best, and among them, ferrets and hamsters are the preferred ones. Various studies have been done on the neuroinvasive capacity of SARS-CoV-2, revealing that SARS-CoV-2 can directly infect neural cells and cause neurological symptoms. These have also given the strategy of using human brain organoids to study SARS-CoV-2 effects on the central nervous system[54,97-99]. Nonetheless, more studies must be conducted in animal models to study the neuroinvasive mechanisms. The recent pandemic is a major threat to global human health, and to overcome this situation, RNA virus-inactivating drugs, and broad-range vaccines are needed. Hydroxychloroquine, remdesivir, and lopinavir/ritonavir are under evaluation for COVID-19 treatment as multiple-target direct antivirals[100]. Developing more antivirals and vaccines against various viruses requires complete information on virus replication and etiology, which requires a detailed study on animal models before testing on humans.

REFERENCES

1 **Glass WG**, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J Immunol* 2004; **173**: 4030-4039 [PMID: 15356152 DOI: 10.4049/jimmunol.173.6.4030]

2 **Frieman MB**, Chen J, Morrison TE, Whitmore A, Funkhouser W, Ward JM, Lamirande EW, Roberts A, Heise M, Subbarao K, Baric RS. SARS-CoV pathogenesis is regulated by a STAT1 dependent but a type I, II and III interferon receptor independent mechanism. *PLoS Pathog* 2010; **6**: e1000849 [PMID: 20386712 DOI: 10.1371/journal.ppat.1000849]

3 **Rossi GA**, Sacco O, Mancino E, Cristiani L, Midulla F. Differences and similarities between SARS-CoV and SARS-CoV-2: spike receptor-binding domain recognition and host cell infection with support of cellular serine proteases. *Infection* 2020; **48**: 665-669 [PMID: 32737833 DOI: 10.1007/s15010-020-01486-5]

4 **Yuki K**, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol* 2020; **215**: 108427 [PMID: 32325252 DOI: 10.1016/j.clim.2020.108427]

5 **Baxter VK**, Griffin DE. Animal Models: No model is perfect, but many are useful. *Viral Patho* 2016; **10**: 125-138 [DOI: 10.1016/b978-0-12-800964-2.00010-0]

6 **Sutton TC**, Subbarao K. Development of animal models against emerging coronaviruses: From SARS to MERS coronavirus. *Virology* 2015; **479-480**: 247-258 [PMID: 25791336 DOI: 10.1016/j.virol.2015.02.030]

7 **Gretebeck LM**, Subbarao K. Animal models for SARS and MERS coronaviruses. *Curr Opin Virol* 2015; **13**: 123-129 [PMID: 26184451 DOI: 10.1016/j.coviro.2015.06.009]

8 **Cui J**, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 2019; **17**: 181-192 [PMID: 30531947 DOI: 10.1038/s41579-018-0118-9]

9 **Decaro N**, Lorusso A. Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. *Vet Microbiol* 2020; **244**: 108693 [PMID: 32402329 DOI: 10.1016/j.vetmic.2020.108693]

10 **Corman VM**, Muth D, Niemeyer D, Drosten C. Hosts and Sources of Endemic Human Coronaviruses. *Adv Virus Res* 2018; **100**: 163-188 [PMID: 29551135 DOI: 10.1016/bs.aivir.2018.01.001]

11 **Neuman BW**, Buchmeier MJ. Supramolecular Architecture of the Coronavirus Particle. *Adv Virus Res* 2016; **96**: 1-27 [PMID: 27712621 DOI: 10.1016/bs.aivir.2016.08.005]

12 **Tortorici MA**, Veesler D. Structural insights into coronavirus entry. *Adv Virus Res* 2019; **105**: 93-116 [PMID: 31522710 DOI: 10.1016/bs.aivir.2019.08.002]

13 **Chen Y**, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol* 2020; **92**: 418-423 [PMID: 31967327 DOI: 10.1002/jmv.25681]

14 **Robson B**. Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus. *Comput Biol Med* 2020; **119**: 103670 [PMID: 32209231 DOI: 10.1016/j.compbiomed.2020.103670]

15 **Letko M**, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B beta coronaviruses. *Nat Microbiol* 2020; **5**: 562-569 [DOI: 10.1038/s41564-020-0688-y]

16 **Yan R**, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 2020; **367**: 1444-1448 [PMID: 32132184 DOI: 10.1126/science.abb2762]

17 **Ou X**, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun* 2020; **11**: 1620 [PMID: 32221306 DOI: 10.1038/s41467-020-15562-9]

18 **Follis KE**, York J, Nunberg JH. Furin cleavage of the SARS coronavirus spike glycoprotein

enhances cell-cell fusion but does not affect virion entry. *Virology* 2006; **350**: 358-69 [DOI: 10.1016/j.virol.2006.02.003]

19 **Hoffmann M**, Kleine-Weber H, Pöhlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. *Mol Cell* 2020; **78**: 779-784.e5 [DOI: 10.1016/j.molcel.2020.04.022]

20 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

21 **Fani M**, Teimoori A, Ghafari S. Comparison of the COVID-2019 (SARS-CoV-2) pathogenesis with SARS-CoV and MERS-CoV infections. *Future Virol* 2020; **15**: 317-323 [DOI: 10.2217/fvl-2020-0050]

22 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

23 **Parasher A**. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. *Postgrad Med J* 2021; **97**: 312-320 [PMID: 32978337 DOI: 10.1136/postgradmedj-2020-138577]

24 **Damas J**, Hughes GM, Keough KC, Painter CA, Persky NS, Corbo M, Hiller M, Koepfli KP, Pfenning AR, Zhao H, Genereux DP, Swofford R, Pollard KS, Ryder OA, Nweeia MT, Lindblad-Toh K, Teeling EC, Karlsson EK, Lewin HA. Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates. *Proc Natl Acad Sci U S A* 2020; **117**: 22311-22322 [PMID: 32826334 DOI: 10.1073/pnas.2010146117]

25 **Krishnakumar V**, Durairajan SSK, Alagarasu K, Li M, Dash AP. Recent Updates on Mouse Models for Human Immunodeficiency, Influenza, and Dengue Viral Infections. *Viruses* 2019; **11** [PMID: 30871179 DOI: 10.3390/v11030252]

26 **Empey KM**, Peebles RS Jr, Janssen WJ. Mouse Models of Viral Infection. *Methods Mol Biol* 2018; **1809**: 395-414 [PMID: 29987803 DOI: 10.1007/978-1-4939-8570-8_26]

27 **Sarkar S**, Heise MT. Mouse Models as Resources for Studying Infectious Diseases. *Clin Ther* 2019; **41**: 1912-1922 [PMID: 31540729 DOI: 10.1016/j.clinthera.2019.08.010]

28 **Mohandas S**, Jain R, Yadav PD, Shete-Aich A, Sarkale P, Kadam M, Kumar A, Deshpande G, Baradkar S, Patil S, Sapkal G, Mali D, Salve M, Patil D, Majumdar T, Suryawanshi A, Kaushal H, Lakra R, Dighe H, Gupta N, Abraham P, Gangakhedkar RR. Evaluation of the susceptibility of mice & hamsters to SARS-CoV-2 infection. *Indian J Med Res* 2020; **151**: 479-482 [PMID: 32611917 DOI: 10.4103/ijmr.IJMR_2235_20]

29 **Gu H**, Chen Q, Yang G, He L, Fan H, Deng YQ, Wang Y, Teng Y, Zhao Z, Cui Y, Li Y, Li XF, Li J, Zhang NN, Yang X, Chen S, Guo Y, Zhao G, Wang X, Luo DY, Wang H, Han G, He Y, Zhou X, Geng S, Sheng X, Jiang S, Sun S, Qin CF, Zhou Y. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science* 2020; **369**: 1603-1607 [PMID: 32732280 DOI: 10.1126/science.abc4730]

30 **Hassan AO**, Case JB, Winkler ES, Thackray LB, Kafai NM, Bailey AL, McCune BT, Fox JM, Chen RE, Alsoussi WB, Turner JS, Schmitz AJ, Lei T, Shrihari S, Keeler SP, Fremont DH, Greco S, McCray PB Jr, Perlman S, Holtzman MJ, Ellebedy AH, Diamond MS. A SARS-CoV-2 Infection Model in Mice Demonstrates Protection by Neutralizing Antibodies. *Cell* 2020; **182**: 744-753.e4 [PMID: 32553273 DOI: 10.1016/j.cell.2020.06.011]

31 **Dinnon KH 3rd**, Leist SR, Schäfer A, Edwards CE, Martinez DR, Montgomery SA, West A, Yount BL Jr, Hou YJ, Adams LE, Gully KL, Brown AJ, Huang E, Bryant MD, Choong IC, Glenn JS, Gralinski LE, Sheahan TP, Baric RS. A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. *Nature* 2020; **586**: 560-566 [PMID: 32854108 DOI: 10.1038/s41586-020-2708-8]

32 **Leist SR**, Dinnon KH 3rd, Schäfer A, Tse LV, Okuda K, Hou YJ, West A, Edwards CE, Sanders W, Fritch EJ, Gully KL, Scobey T, Brown AJ, Sheahan TP, Moorman NJ, Boucher RC, Gralinski LE, Montgomery SA, Baric RS. A Mouse-Adapted SARS-CoV-2 Induces Acute Lung Injury and Mortality in Standard Laboratory Mice. *Cell* 2020; **183**: 1070-1085.e12 [PMID: 33031744 DOI: 10.1016/j.cell.2020.09.050]

33 **Sinha P**, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? *JAMA Intern Med* 2020; **180**: 1152-1154 [PMID: 32602883 DOI: 10.1001/jamainternmed.2020.3313]

34 **Fukushima A**, Yamaguchi T, Ishida W, Fukata K, Taniguchi T, Liu FT, Ueno H. Genetic background determines susceptibility to experimental immune-mediated blepharoconjunctivitis: comparison of Balb/c and C57BL/6 mice. *Exp Eye Res* 2006; **82**: 210-218 [PMID: 16102751 DOI: 10.1016/j.exer.2005.06.010]

35 **Tseng CT**, Huang C, Newman P, Wang N, Narayanan K, Watts DM, Makino S, Packard MM, Zaki SR, Chan TS, Peters CJ. Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human Angiotensin-converting enzyme 2 virus receptor. *J Virol* 2007; **81**: 1162-1173 [PMID: 17108019 DOI: 10.1128/JVI.01702-06]

36 **Subbarao K**, Roberts A. Is there an ideal animal model for SARS? *Trends Microbiol* 2006; **14**: 299-303 [PMID: 16759866 DOI: 10.1016/j.tim.2006.05.007]

37 **Du L**, Zhao G, He Y, Guo Y, Zheng BJ, Jiang S, Zhou Y. Receptor-binding domain of SARS-CoV spike protein induces long-term protective immunity in an animal model. *Vaccine* 2007; **25**: 2832-

2838 [DOI: 10.1016/j.vaccine.2006.10.031]
38 **Rosa RB**, Dantas WM, do Nascimento JCF, da Silva MV, de Oliveira RN, Pena LJ. In Vitro and In Vivo Models for Studying SARS-CoV-2, the Etiological Agent Responsible for COVID-19 Pandemic. *Viruses* 2021; **13** [PMID: 33673614 DOI: 10.3390/v13030379]
39 **Singh A**, Singh RS, Sarma P, Batra G, Joshi R, Kaur H, Sharma AR, Prakash A, Medhi B. A Comprehensive Review of Animal Models for Coronaviruses: SARS-CoV-2, SARS-CoV, and MERS-CoV. *Virol Sin* 2020; **35**: 290-304 [PMID: 32607866 DOI: 10.1007/s12250-020-00252-z]
40 **See RH**, Zakhartchouk AN, Petric M, Lawrence DJ, Mok CPY, Hogan RJ, Rowe T, Zitzow LA, Karunakaran KP, Hitt MM, Graham FL, Prevec L, Mahony JB, Sharon C, Auperin TC, Rini JM, Tingle AJ, Scheifele DW, Skowronski DM, Patrick DM, Voss TG, Babiuk LA, Gauldie J, Roper RL, Brunham RC, Finlay BB. Comparative evaluation of two severe acute respiratory syndrome (SARS) vaccine candidates in mice challenged with SARS coronavirus. *J Gen Virol* 2006; **87**: 641-650 [PMID: 16476986 DOI: 10.1099/vir.0.81579-0]
41 **Iwata-Yoshikawa N**, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 Contributes to Virus Spread and Immunopathology in the Airways of Murine Models after Coronavirus Infection. *J Virol* 2019; **93** [PMID: 30626688 DOI: 10.1128/JVI.01815-18]
42 **Lu M**, Dravid P, Zhang Y, Trivedi S, Li A, Harder O, Kc M, Chaiwatpongsakorn S, Zani A, Kenney A, Zeng C, Cai C, Ye C, Liang X, Shimamura M, Liu SL, Mejias A, Ramilo O, Boyaka PN, Qiu J, Martinez-Sobrido L, Yount JS, Peeples ME, Kapoor A, Niewiesk S, Li J. A safe and highly efficacious measles virus-based vaccine expressing SARS-CoV-2 stabilized prefusion spike. *Proc Natl Acad Sci USA* 2021; **118**: e2026153118 [DOI: 10.1073/pnas.2026153118]
43 **Kuba K**, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; **11**: 875-879 [PMID: 16007097 DOI: 10.1038/nm1267]
44 **Yang XH**, Deng W, Tong Z, Liu YX, Zhang LF, Zhu H, Gao H, Huang L, Liu YL, Ma CM, Xu YF, Ding MX, Deng HK, Qin C. Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. *Comp Med* 2007; **57**: 450-459 [DOI: 10.1101/2020.04.06.20055475]
45 **Lutz C**, Maher L, Lee C, Kang W. COVID-19 preclinical models: human angiotensin-converting enzyme 2 transgenic mice. *Hum Genomics* 2020; **14**: 20 [PMID: 32498696 DOI: 10.1186/s40246-020-00272-6]
46 **McCray PB Jr**, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, Netland J, Jia HP, Halabi C, Sigmund CD, Meyerholz DK, Kirby P, Look DC, Perlman S. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J Virol* 2007; **81**: 813-821 [PMID: 17079315 DOI: 10.1128/JVI.02012-06]
47 **Natoli S**, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? *Eur J Neurol* 2020; **27**: 1764-1773 [PMID: 32333487 DOI: 10.1111/ene.14277]
48 **Bao L**, Wei Deng, Hong Gao, Chong Xiao, Jiayi Liu, Jing Xue, Qi Lv, Jiangning Liu, Pin Yu, Yanfeng Xu, Feifei Qi, Yajin Qu, Fengdi Li, Zhiguang Xiang, Haisheng Yu, Shuran Gong, Mingya Liu, Guanpeng Wang, Shunyi Wang, Zhiqi Song, Wenjie Zhao, Yunlin Han, Linna Zhao, Xing Liu, Qiang Wei, Chuan Qin. Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2. 2020 Preprint; Available from: Bio-Rxiv:2020.03.13.990226
49 **Winkler ES**, Bailey AL, Kafai NM, Nair S, McCune BT, Yu J, Fox JM, Chen RE, Earnest JT, Keeler SP, Ritter JH, Kang LI, Dort S, Robichaud A, Head R, Holtzman MJ, Diamond MS. SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. *Nat Immunol* 2020; **21**: 1327-1335 [PMID: 32839612 DOI: 10.1038/s41590-020-0778-2]
50 **Cleary SJ**, Pitchford SC, Amison RT, Carrington R, Robaina Cabrera CL, Magnen M, Looney MR, Gray E, Page CP. Animal models of mechanisms of SARS-CoV-2 infection and COVID-19 pathology. *Br J Pharmacol* 2020; **177**: 4851-4865 [PMID: 32462701 DOI: 10.1111/bph.15143]
51 **Sodhi CP**, Nguyen J, Yamaguchi Y, Werts AD, Lu P, Ladd MR, Fulton WB, Kovler ML, Wang S, Prindle T Jr, Zhang Y, Lazartigues ED, Holtzman MJ, Alcorn JF, Hackam DJ, Jia H. A Dynamic Variation of Pulmonary ACE2 Is Required to Modulate Neutrophilic Inflammation in Response to *Pseudomonas aeruginosa* Lung Infection in Mice. *J Immunol* 2019; **203**: 3000-3012 [PMID: 31645418 DOI: 10.4049/jimmunol.1900579]
52 **Sun K**, Gu L, Ma L, Duan Y. Atlas of ACE2 gene expression reveals novel insights into transmission of SARS-CoV-2. *Heliyon* 2021; **7**: e05850 [PMID: 33392409 DOI: 10.1016/j.heliyon.2020.e05850]
53 **Sun SH**, Chen Q, Gu HJ, Yang G, Wang YX, Huang XY, Liu SS, Zhang NN, Li XF, Xiong R, Guo Y, Deng YQ, Huang WJ, Liu Q, Liu QM, Shen YL, Zhou Y, Yang X, Zhao TY, Fan CF, Zhou YS, Qin CF, Wang YC. A Mouse Model of SARS-CoV-2 Infection and Pathogenesis. *Cell Host Microbe* 2020; **28**: 124-133.e4 [PMID: 32485164 DOI: 10.1016/j.chom.2020.05.020]
54 **Song E**, Zhang C, Israelow B, Lu-Culligan A, Prado AV, Skriabine S, Lu P, Weizman OE, Liu F, Dai Y, Szigeti-Buck K, Yasumoto Y, Wang G, Castaldi C, Heltke J, Ng E, Wheeler J, Alfajaro MM, Levavasseur E, Fontes B, Ravindra NG, Van Dijk D, Mane S, Gunel M, Ring A, Kazmi SAJ, Zhang K, Wilen CB, Horvath TL, Plu I, Haik S, Thomas JL, Louvi A, Farhadian SF, Huttner A, Seilhean D, Renier N, Bilguvar K, Iwasaki A. Neuroinvasion of SARS-CoV-2 in human and mouse brain. *bioRxiv* 2020 [PMID: 32935108 DOI: 10.1101/2020.06.25.169946]

55 **García-Arriaza J**, Esteban M, López D. Modified Vaccinia Virus Ankara as a Viral Vector for Vaccine Candidates against Chikungunya Virus. *Biomedicines* 2021; **9** [PMID: 34572308 DOI: 10.3390/biomedicines9091122]

56 **Liu R**, Americo JL, Cotter CA, Earl PL, Erez N, Peng C, Moss B. MVA Vector Vaccines Inhibit SARS CoV-2 Replication in Upper and Lower Respiratory Tracts of Transgenic Mice and Prevent Lethal Disease. *bioRxiv* 2021 [PMID: 33442693 DOI: 10.1101/2020.12.30.424878]

57 **Bao L**, Deng W, Huang B, Gao H, Liu J, Ren L, Wei Q, Yu P, Xu Y, Qi F, Qu Y, Li F, Lv Q, Wang W, Xue J, Gong S, Liu M, Wang G, Wang S, Song Z, Zhao L, Liu P, Ye F, Wang H, Zhou W, Zhu N, Zhen W, Yu H, Zhang X, Guo L, Chen L, Wang C, Wang Y, Wang X, Xiao Y, Sun Q, Liu H, Zhu F, Ma C, Yan L, Yang M, Han J, Xu W, Tan W, Peng X, Jin Q, Wu G, Qin C. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature* 2020; **583**: 830-833 [PMID: 32380511 DOI: 10.1038/s41586-020-2312-y]

58 **Chan JF**, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, Chan WM, Fan Z, Tsoi HW, Wen L, Liang R, Cao J, Chen Y, Tang K, Luo C, Cai JP, Kok KH, Chu H, Chan KH, Sridhar S, Chen Z, Chen H, To KK, Yuen KY. Simulation of the Clinical and Pathological Manifestations of Coronavirus Disease 2019 (COVID-19) in a Golden Syrian Hamster Model: Implications for Disease Pathogenesis and Transmissibility. *Clin Infect Dis* 2020; **71**: 2428-2446 [DOI: 10.1093/cid/ciaa325]

59 **Boudewijns R**, Thibaut HJ, Kaptein SJF, Li R, Vergote V, Seldeslachts L, Van Weyenbergh J, De Keyzer C, Bervoets L, Sharma S, Liesenborghs L, Ma J, Jansen S, Van Looveren D, Vercruysse T, Wang X, Jochmans D, Martens E, Roose K, De Vlieger D, Schepens B, Van Buyten T, Jacobs S, Liu Y, Martí-Carreras J, Vanmechelen B, Wawina-Bokalanga T, Delang L, Rocha-Pereira J, Coelmont L, Chiu W, Leyssen P, Heylen E, Schols D, Wang L, Close L, Matthijnssens J, Van Ranst M, Compernolle V, Schramm G, Van Laere K, Saelens X, Callewaert N, Opdenakker G, Maes P, Weynand B, Cawthorne C, Vande Velde G, Wang Z, Neyts J, Dallmeier K. STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters. *Nat Commun* 2020; **11**: 5838 [PMID: 33203860 DOI: 10.1038/s41467-020-19684-y]

60 **Monchatre-Leroy E**, Lesellier S, Wasniewski M, Picard-Meyer E, Richomme C, Boué F, Lacôte S, Murri S, Pulido C, Vulin J, Salguero FJ, Gouilh MA, Servat A, Marianneau P. Hamster and ferret experimental infection with intranasal low dose of a single strain of SARS-CoV-2. *J Gen Virol* 2021; **102** [PMID: 33612147 DOI: 10.1099/jgv.0.001567]

61 **Vandeputte J**, Van Damme P, Neyts J, Audonnet JC, Baay M, Neels P. Animal experiments show impact of vaccination on reduction of SARS-CoV-2 virus circulation: A model for vaccine development? *Biologicals* 2021; **73**: 1-7 [PMID: 34489162 DOI: 10.1016/j.biologicals.2021.08.001]

62 **Ganneru B**, Jogdand H, Dharam VK, Molugu NR, Prasad SD, Vellimudu S, Ella KM, Ravikrishnan R, Awasthi A, Jose J, Rao P. Evaluation of Safety and Immunogenicity of an Adjuvanted, TH-1 Skewed, Whole Virion Inactivated SARS-CoV-2 Vaccine-Bbv152. 2020 Preprint; Available from: bioRxiv:2020.09.09.285445

63 **Mohandas S**, Yadav PD, Shete-Aich A, Abraham P, Vadrevu KM, Sapkal G, Mote C, Nyayanit D, Gupta N, Srinivas VK, Kadam M, Kumar A, Majumdar T, Jain R, Deshpande G, Patil S, Sarkale P, Patil D, Ella R, Prasad SD, Sharma S, Ella KM, Panda S, Bhargava B. Immunogenicity and protective efficacy of BBV152, whole virion inactivated SARS-CoV-2 vaccine candidates in the Syrian hamster model. *iScience* 2021; **24**: 102054 [PMID: 33521604 DOI: 10.1016/j.isci.2021.102054]

64 **Ye ZW**, Yuan S, Chan JF, Zhang AJ, Yu CY, Ong CP, Yang D, Chan CC, Tang K, Cao J, Poon VK, Cai JP, Chu H, Yuen KY, Jin DY. Beneficial effect of combinational methylprednisolone and remdesivir in hamster model of SARS-CoV-2 infection. *Emerg Microbes Infect* 2021; **10**: 291-304 [PMID: 33538646 DOI: 10.1080/22221751.2021.1885998]

65 **Huo J**, Le Bas A, Ruza RR, Duyvesteyn HME, Mikolajek H, Malinauskas T, Tan TK, Rijal P, Dumoux M, Ward PN, Ren J, Zhou D, Harrison PJ, Weckener M, Clare DK, Vogirala VK, Radecke J, Moynié L, Zhao Y, Gilbert-Jaramillo J, Knight ML, Tree JA, Buttigieg KR, Coombes N, Elmore MJ, Carroll MW, Carrique L, Shah PNM, James W, Townsend AR, Stuart DI, Owens RJ, Naismith JH. Neutralizing nanobodies bind SARS-CoV-2 spike RBD and block interaction with ACE2. *Nat Struct Mol Biol* 2020; **27**: 846-854 [PMID: 32661423 DOI: 10.1038/s41594-020-0469-6]

66 **Liu Z**, Xu W, Xia S, Gu C, Wang X, Wang Q, Zhou J, Wu Y, Cai X, Qu D, Ying T, Xie Y, Lu L, Yuan Z, Jiang S. RBD-Fc-based COVID-19 vaccine candidate induces highly potent SARS-CoV-2 neutralizing antibody response. *Signal Transduct Target Ther* 2020; **5**: 282 [PMID: 33247109 DOI: 10.1038/s41392-020-00402-5]

67 **Castelnovo L**, Tamburello A, Lurati A, Zaccara E, Marrazza MG, Olivetti M, Mumoli N, Mastroiacovo D, Colombo D, Ricchiuti E, Vigano' P, Paola F, Mazzone A. Anti-IL6 treatment of serious COVID-19 disease: A monocentric retrospective experience. *Medicine (Baltimore)* 2021; **100**: e23582 [PMID: 33429732 DOI: 10.1097/MD.0000000000023582]

68 **Dimopoulos G**, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, Netea MG, Spyridopoulos T, Verheggen RJ, Hoogerwerf J, Lachana A, van de Veerdonk FL, Giamarellos-Bourboulis EJ. Favorable Anakinra Responses in Severe Covid-19 Patients with Secondary Hemophagocytic Lymphohistiocytosis. *Cell Host Microbe* 2020; **28**: 117-123.e1 [PMID: 32411313 DOI: 10.1016/j.chom.2020.05.007]

69 **Yuan L**, Tang Q, Cheng T, Xia N. Animal models for emerging coronavirus: progress and new insights. *Emerg Microbes Infect* 2020; **9**: 949-961 [PMID: 32378471 DOI:

10.1080/22221751.2020.1764871]

70 **Buchholz UJ**, Bukreyev A, Yang L, Lamirande EW, Murphy BR, Subbarao K, Collins PL. Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity. *Proc Natl Acad Sci U S A* 2004; **101**: 9804-9809 [PMID: 15210961 DOI: 10.1073/pnas.0403492101]

71 **Sun X**, Sui H, Fisher JT, Yan Z, Liu X, Cho HJ, Joo NS, Zhang Y, Zhou W, Yi Y, Kinyon JM, Lei-Butters DC, Griffin MA, Naumann P, Luo M, Ascher J, Wang K, Frana T, Wine JJ, Meyerholz DK, Engelhardt JF. Disease phenotype of a ferret CFTR-knockout model of cystic fibrosis. *J Clin Invest* 2010; **120**: 3149-3160 [PMID: 20739752 DOI: 10.1172/JCI43052]

72 **Lakdawala SS**, Menachery VD. The search for a COVID-19 animal model. *Science* 2020; **368**: 942-943 [PMID: 32467379 DOI: 10.1126/science.abc6141]

73 **Kim YI**, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, Chang JH, Kim EJ, Lee S, Casel MAB, Um J, Song MS, Jeong HW, Lai VD, Kim Y, Chin BS, Park JS, Chung KH, Foo SS, Poo H, Mo IP, Lee OJ, Webby RJ, Jung JU, Choi YK. Infection and Rapid Transmission of SARS-CoV-2 in Ferrets. *Cell Host Microbe* 2020; **27**: 704-709.e2 [PMID: 32259477 DOI: 10.1016/j.chom.2020.03.023]

74 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

75 **Dhakal S**, Ruiz-Bedoya CA, Zhou R, Creisher PS, Villano JS, Littlefield K, Ruelas Castillo J, Marinho P, Jedlicka AE, Ordonez AA, Bahr M, Majewska N, Betenbaugh MJ, Flavahan K, Mueller ARL, Looney MM, Quijada D, Mota F, Beck SE, Brockhurst J, Braxton AM, Castell N, Stover M, D'Alessio FR, Metcalf Pate KA, Karakousis PC, Mankowski JL, Pekosz A, Jain SK, Klein SL; Johns Hopkins COVID-19 Hamster Study Group. Sex Differences in Lung Imaging and SARS-CoV-2 Antibody Responses in a COVID-19 Golden Syrian Hamster Model. *mBio* 2021; **12**: e0097421 [PMID: 34253053 DOI: 10.1128/mBio.00974-21]

76 **Park SJ**, Yu KM, Kim YI, Kim SM, Kim EH, Kim SG, Kim EJ, Casel MAB, Rollon R, Jang SG, Lee MH, Chang JH, Song MS, Jeong HW, Choi Y, Chen W, Shin WJ, Jung JU, Choi YK. Antiviral Efficacies of FDA-Approved Drugs against SARS-CoV-2 Infection in Ferrets. *mBio* 2020; **11**: e01114-20 [PMID: 32444382 DOI: 10.1128/mBio.01114-20]

77 **van den Brand JM**, Haagmans BL, Leijten L, van Riel D, Martina BE, Osterhaus AD, Kuiken T. Pathology of experimental SARS coronavirus infection in cats and ferrets. *Vet Pathol* 2008; **45**: 551-562 [DOI: 10.1354/vp.45-4-551]

78 **Chu YK**, Ali GD, Jia F, Li Q, Kelvin D, Couch RC, Harrod KS, Hutt JA, Cameron C, Weiss SR, Jonsson CB. The SARS-CoV ferret model in an infection-challenge study. *Virology* 2008; **374**: 151-163 [DOI: 10.1016/j.virol.2007.12.032]

79 **Zhang Q**, Zhang H, Gao J, Huang K, Yang Y, Hui X, He X, Li C, Gong W, Zhang Y, Zhao Y, Peng C, Gao X, Chen H, Zou Z, Shi ZL, Jin M. A serological survey of SARS-CoV-2 in cat in Wuhan. *Emerg Microbes Infect* 2020; **9**: 2013-2019 [PMID: 32867625 DOI: 10.1080/22221751.2020.1817796]

80 **Khan AA**, Alahmari AA, Almuzaini Y, Alamri F, Alsofayan YM, Aburas A, Al-Muhsen S, Van Kerkhove M, Yezli S, Ciottone GR, Assiri AM, Jokhdar HA. Potential Cross-Reactive Immunity to COVID-19 Infection in Individuals With Laboratory-Confirmed MERS-CoV Infection: A National Retrospective Cohort Study From Saudi Arabia. *Front Immunol* 2021; **12**: 727989 [PMID: 34603300 DOI: 10.3389/fimmu.2021.727989]

81 **Yu P**, Qi F, Xu Y, Li F, Liu P, Liu J, Bao L, Deng W, Gao H, Xiang Z, Xiao C, Lv Q, Gong S, Song Z, Qu Y, Xue J, Wei Q, Liu M, Wang G, Wang S, Yu H, Liu X, Huang B, Wang W, Zhao L, Wang H, Ye F, Zhou W, Zhen W, Han J, Wu G, Jin Q, Wang J, Tan W, Qin C. Age-related rhesus macaque models of COVID-19. *Animal Model Exp Med* 2020; **3**: 93-97 [PMID: 32318665 DOI: 10.1002/ame2.12108]

82 **Yadav PD**, Ella R, Kumar S, Patil DR, Mohandas S, Shete AM, Vadrevu KM, Bhati G, Sapkal G, Kaushal H, Patil S, Jain R, Deshpande G, Gupta N, Agarwal K, Gokhale M, Mathapati B, Metkari S, Mote C, Nyayanit D, Patil DY, Sai Prasad BS, Suryawanshi A, Kadam M, Kumar A, Daigude S, Gopale S, Majumdar T, Mali D, Sarkale P, Baradkar S, Gawande P, Joshi Y, Fulari S, Dighe H, Sharma S, Gunjikar R, Kalele K, Srinivas VK, Gangakhedkar RR, Ella KM, Abraham P, Panda S, Bhargava B. Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques. *Nat Commun* 2021; **12**: 1386 [PMID: 33654090 DOI: 10.1038/s41467-021-21639-w]

83 **Koo BS**, Oh H, Kim G, Hwang EH, Jung H, Lee Y, Kang P, Park JH, Ryu CM, Hong JJ. Transient Lymphopenia and Interstitial Pneumonia With Endotheliitis in SARS-CoV-2-Infected Macaques. *J Infect Dis* 2020; **222**: 1596-1600 [PMID: 32745172 DOI: 10.1093/infdis/jiaa486]

84 **Bukreyev A**, Lamirande EW, Buchholz UJ, Vogel LN, Elkins WR, St Claire M, Murphy BR, Subbarao K, Collins PL. Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. *Lancet* 2004; **363**: 2122-2127 [PMID: 15220033 DOI: 10.1016/S0140-6736(04)16501-X]

85 **Barrs VR**, Peiris M, Tam KWS, Law PYT, Brackman CJ, To EMW, Yu VYT, Chu DKW, Perera

RAPM, Sit THC. SARS-CoV-2 in Quarantined Domestic Cats from COVID-19 Households or Close Contacts, Hong Kong, China. *Emerg Infect Dis* 2020; **26**: 3071-3074 [PMID: 32938527 DOI: 10.3201/eid2612.202786]

86 **Hosie MJ**, Hofmann-Lehmann R, Hartmann K, Egberink H, Truyen U, Addie DD, Belák S, Boucraut-Baralon C, Frymus T, Lloret A, Lutz H, Marsilio F, Pennisi MG, Tasker S, Thiry E, Möstl K. Anthropogenic Infection of Cats during the 2020 COVID-19 Pandemic. *Viruses* 2021; **13** [PMID: 33530620 DOI: 10.3390/v13020185]

87 **Rudd JM**, Selvan MT, Cowan S, Kao YF, Midkiff CC, Ritchey JW, Miller CA. Clinicopathologic features of a feline SARS-CoV-2 infection model parallel acute COVID-19 in humans. *bioRxiv* 2021 [PMID: 33880467 DOI: 10.1101/2021.04.14.439863]

88 **Halfmann PJ**, Hatta M, Chiba S, Maemura T, Fan S, Takeda M, Kinoshita N, Hattori SI, Sakai-Tagawa Y, Iwatsuki-Horimoto K, Imai M, Kawaoka Y. Transmission of SARS-CoV-2 in Domestic Cats. *N Engl J Med* 2020; **383**: 592-594 [PMID: 32402157 DOI: 10.1056/NEJMc2013400]

89 **Sit THC**, Brackman CJ, Ip SM, Tam KWS, Law PYT, To EMW, Yu VYT, Sims LD, Tsang DNC, Chu DKW, Perera RAPM, Poon LLM, Peiris M. Infection of dogs with SARS-CoV-2. *Nature* 2020; **586**: 776-778 [PMID: 32408337 DOI: 10.1038/s41586-020-2334-5]

90 **Schlottau K**, Rissmann M, Graaf A, Schön J, Sehl J, Wylezich C, Höper D, Mettenleiter TC, Balkema-Buschmann A, Harder T, Grund C, Hoffmann D, Breithaupt A, Beer M. SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study. *Lancet Microbe* 2020; **1**: e218-e225 [PMID: 32838346 DOI: 10.1016/S2666-5247(20)30089-6]

91 **Weingartl HM**, Copps J, Drebot MA, Marszal P, Smith G, Gren J, Andova M, Pasick J, Kitching P, Czub M. Susceptibility of pigs and chickens to SARS coronavirus. *Emerg Infect Dis* 2004; **10**: 179-184 [PMID: 15030680 DOI: 10.3201/eid1002.030677]

92 **Swayne DE**, Suarez DL, Spackman E, Tumpey TM, Beck JR, Erdman D, Rollin PE, Ksiazek TG. Domestic poultry and SARS coronavirus, southern China. *Emerg Infect Dis* 2004; **10**: 914-916 [PMID: 15200830 DOI: 10.3201/eid1005.030827]

93 **Zhao Y**, Wang J, Kuang D, Xu J, Yang M, Ma C, Zhao S, Li J, Long H, Ding K, Gao J, Liu J, Wang H, Li H, Yang Y, Yu W, Yang J, Zheng Y, Wu D, Lu S, Liu H, Peng X. Susceptibility of tree shrew to SARS-CoV-2 infection. *Sci Rep* 2020; **10**: 16007 [PMID: 32994418 DOI: 10.1038/s41598-020-72563-w]

94 **Wong MC**, Javornik Cregeen SJ, Ajami NJ, Petrosino JF. Evidence of recombination in coronaviruses implicating pangolin origins of nCoV-2019. 2020 Preprint; Available from: bioRxiv:2020.02.07.939207

95 **Oreshkova N**, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Hakze-van der Honing RW, Gerhards N, Tolsma P, Bouwstra R, Sikkema RS, Tacken MG, de Rooij MM, Weesendorp E, Engelsma MY, Bruschke CJ, Smit LA, Koopmans M, van der Poel WH, Stegeman A. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. *Euro Surveill* 2020; **25** [PMID: 32553059 DOI: 10.2807/1560-7917.ES.2020.25.23.2001005]

96 **Johansen MD**, Irving A, Montagutelli X. Animal and translational models of SARS-CoV-2 infection and COVID-19. *Mucosal Immunol* 2020; 877-891 [DOI: 10.1038/s41385-020-00340-z]

97 **Bhatia HK**, Singh H, Grewal N, Natt NK. Sofosbuvir: A novel treatment option for chronic hepatitis C infection. *J PharmacolPharmacother* 2014; **5**: 278-284 [PMID: 25422576 DOI: 10.4103/0976-500X.142464]

98 **Mesci P**, Macia A, Saleh A, Martin-Sancho L, Yin Y, Snethlage C, Avansini S, Chanda SK, Muotri A. Sofosbuvir protects human brain organoids against SARS-CoV-2. 2020 Preprint; Available from: bioRxiv:2020.05.30.125856

99 **Sanclemente-Alaman I**, Moreno-Jiménez L, Benito-Martín MS, Canales-Aguirre A, Matías-Guiu JA, Matías-Guiu J, Gómez-Pinedo U. Experimental Models for the Study of Central Nervous System Infection by SARS-CoV-2. *Front Immunol* 2020; **11**: 2163 [PMID: 32983181 DOI: 10.3389/fimmu.2020.02163]

100 **Cortegiani A**, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020; **57**: 279-283 [PMID: 32173110 DOI: 10.1016/j.jcrc.2020.03.005]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 57-72

DOI: 10.5501/wjv.v11.i1.57

ISSN 2220-3249 (online)

MINIREVIEWS

Chronic hepatitis B: New potential therapeutic drugs target

Wattana Leowattana, Tawithep Leowattana

ORCID number: Wattana Leowattana 0000-0003-4257-2480; Tawithep Leowattana 0000-0003-2316-3585.

Author contributions: Leowattana W wrote the paper; Leowattana T collected the data.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

Country/Territory of origin: Thailand

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

Wattana Leowattana, Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand

Tawithep Leowattana, Department of Medicine, Faculty of Medicine, Srinakharinwirot University, Bangkok 10110, Thailand

Corresponding author: Wattana Leowattana, MD, MSc, PhD, Professor, Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, No. 420/6 rajavithi road, rachatawee, Bangkok 10400, Thailand. wattana.leo@mahidol.ac.th

Abstract

Chronic hepatitis B (CHB) infection remains the most causative agent of liver-related morbidity and mortality worldwide. It impacts nearly 300 million people. The current treatment for chronic infection with the hepatitis B virus (HBV) is complex and lacks a durable treatment response, especially hepatitis B surface antigen (HBsAg) loss, necessitating indefinite treatment in most CHB patients due to the persistence of HBV covalently closed circular DNA (cccDNA). New drugs that target distinct steps of the HBV life cycle have been investigated, which comprise inhibiting the entry of HBV into hepatocytes, disrupting or silencing HBV cccDNA, modulating nucleocapsid assembly, interfering HBV transcription, and inhibiting HBsAg release. The achievement of a functional cure or sustained HBsAg loss in CHB patients represents the following approach towards HBV eradication. This review will explore the up-to-date advances in the development of new direct-acting anti-HBV drugs. Hopefully, with the combination of the current antiviral drugs and the newly developed direct-acting antiviral drugs targeting the different steps of the HBV life cycle, the ultimate eradication of CHB infection will soon be achieved.

Key Words: Chronic hepatitis B; Hepatitis B surface antigen; Hepatitis B surface antibody; Covalently closed circular DNA; Direct acting antiviral drugs; Functional cure; Entry block; Nucleocapsid assembly modulator; Interfering hepatitis B virus transcription; Inhibiting hepatitis B surface antigen release

Core Tip: Current treatment of chronic hepatitis B infection with nucleos(t)ide analogs causes long-term suppression of hepatitis B virus (HBV) DNA levels, significantly

Received: May 31, 2021
Peer-review started: May 31, 2021
First decision: July 31, 2021
Revised: August 13, 2021
Accepted: January 5, 2022
Article in press: January 5, 2022
Published online: January 25, 2022

P-Reviewer: Yin GQ
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

improving hepatocellular injury and extrahepatic complications. However, the risk of hepatocellular carcinoma remains increased. New direct antiviral drugs that target the HBV life cycle, including entry blockers, assembly modulators, covalently closed circular DNA (cccDNA) disruptors, and hepatitis B surface antigen release inhibitors, would lead to hepatitis B surface antigen loss and a functional cure. Moreover, a combination of antiviral drugs with an immune-modulator could enhance the elimination of cccDNA and provide a definitive cure.

Citation: Leowattana W, Leowattana T. Chronic hepatitis B: New potential therapeutic drugs target. *World J Virol* 2022; 11(1): 57-72
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/57.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.57

INTRODUCTION

Chronic hepatitis B (CHB) virus infection is a significant public health problem and causes substantial morbidity and mortality. It affects more than 257 million people worldwide, and the first-ever global hepatitis report published in 2017 indicated that in 2015, 887000 persons died from cirrhosis and hepatocellular carcinoma (HCC)[1,2]. The cumulative incidence of CHB infection in children less than 5-years-old fell from 4.7% in the pre-vaccine era to 1.3% in 2015. This reduction in incidence is attributable to progress in immunization coverage. Although we have effective vaccines and potential antiviral drugs to treat CHB patients, the mortality rate of CHB infection still increased over the last 10 years.

Antiviral drugs, such as pegylated-interferon (Peg-INF)-α-2a, Peg-INF-α-2b, Peg-INF-α-1b, and nucleoside or nucleotide analogs (NAs), have been used to treat CHB patients. They strongly suppress HBV replication and slow progression to cirrhosis and HCC. A limitation of the current treatments is the low rate of serological responses because covalently closed circular DNA (cccDNA) persists in the hepatocyte nucleus[3,4]. Hepatitis B surface antigen (HBsAg) loss is uncommon with current therapies, causing the majority of CHB patients to need indefinite therapy. The IFN treatment produces a higher rate of HBsAg loss, but most patients cannot tolerate the adverse events caused by it.

The combination of Peg-IFN and NAs may synergize the treatment effect to enable more CHB patients to achieve HBsAg loss[5,6]. However, a recent randomized controlled, open-label trial did not support the advantage of a combination of Peg-IFN and NAs in CHB patients[7]. Moreover, the patients also need frequent clinical and laboratory monitoring. Numerous clinical trials of drugs that interrupt the HBV life cycle in hepatocytes have been conducted. The novel agents for HBsAg loss include the direct-acting antiviral drugs targeting the different steps of the HBV life cycle and the indirect antiviral drugs modulating host immune response to eradicate HBV[8,9].

This review will address the newly investigated therapeutic drugs, and the results of clinical trials that aim to cure HBV.

HBV GENOME AND LIFE CYCLE

HBV is a small virus of the *Hepadnaviridae* family which infects hepatocytes, replicates, and persists in the nucleus. HBV particles include the HBV genome, nucleocapsid, and envelope proteins. The HBV genome is partially double-stranded DNA, with approximately 3200 base pairs that form a relaxed circular DNA (rcDNA) genome. The minus (-) strand is the longer-strand DNA which complements pre-genomic RNA (pgRNA). The plus (+) strand is the shorter-strand DNA. The minus (-) strand has four overlapping open reading frames (ORFs), consisting of PreC/C, P, PreS/S, and X. The PreC/C ORF encodes the hepatitis B e antigen (HBeAg) and hepatitis B core antigen (HBcAg). The P ORF encodes the HBV DNA polymerase. The PreS/S ORF encodes the large (L), the middle (M), and the small (S) envelope proteins. The X ORF encodes the X protein (HBx)[10].

The large envelope protein contains the receptor-binding domain and is involved in viral entry into the cytoplasm by receptor-mediated endocytosis. This process involves the sodium taurocholate co-transporting polypeptide (NTCP) receptor in the hepatocyte membrane. After attachment, two pathways for cell entry include endocytosis and fusion of the HBV envelope with the plasma membrane[11]. Then, individual rcDNAs are modified into cccDNAs, packaged into chromatin by histone and non-histone proteins[12]. The cccDNAs are responsible for viral persistence in the nuclei of infected cells. These cccDNAs also use pre-C mRNA and all other sub-genomic mRNAs that code for the main viral proteins.

An HBe protein is translated from the pre-C mRNA transcripts, which have a longer reading frame than HBc protein, and is finally secreted into the bloodstream as HBeAg, the immunoactive biomarker for HBV infection[13]. This replication cycle is concomitant with the release of incomplete sub-viral particles and infectious viral particles. The most abundant of these exported sub-viral particles are particulate forms of viral envelopes formed with such HBs proteins as HBs antigen (HBsAg), a primary immunoactive biomarker for HBV infection in conjunction with HBeAg.

The encapsulated mRNAs are known as HBcAg, which can be detected in serum, even when HBV DNA cannot.

CURRENT ANTIVIRAL DRUGS AGAINST HBV

Currently, two different therapeutic strategies have been approved to treat CHB patients. These included IFN-α or Peg-IFN-α and direct-acting antivirals comprised of NAs that include nucleoside analogs, lamivudine (LAM), telbivudine (LdT) and entecavir (ETV), or NAs adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate (TDF)[14,15].

IFNs

IFN-α suppresses viral DNA synthesis by stimulating antiviral enzyme production, which results in the clearance of infected hepatocytes, enabling a proportion of CHB patients to achieve a sustained virologic response (SVR). Several studies have demonstrated that IFN-α exhibits an SVR of up to 37%, with a mean loss rate of 33% in HBeAg and 8% in HBsAg. However, other factors influencing SVRs following IFN-α treatment comprised low serum levels of HBV DNA, early infection, treatment-naïve status, HBV genotypes, pre-core HBV mutation detection, chronicity, and co-infection with human immunodeficiency virus (commonly known as HIV)[16]. Due to its limited efficacy, low SVRs, and frequent injections, IFN-α has been replaced with the long-acting Peg-IFN-α.

Peg-IFN-α could prolong the effective half-life of IFN-α, reduce functional dose levels, increase efficacy, and lower side effects[17]. However, randomized clinical trials suggest that Peg-IFN-α effects are better in CHB patients who are HBeAg-positive than in those who are HBeAg-negative. Long-term treatment with Peg-IFN-α in CHB patients with HBeAg-positive status led to viral suppression in 10%–40%, HBeAg loss in 30%–35%, and normalization of alanine aminotransferase (ALT) levels in 35%–50%. Moreover, an HBsAg loss was established in 5% of patients 6 mo after stopping treatment and 10% of patients 3 years post-treatment[18]. Unfortunately, the benefits of Peg-IFN-α treatment vary with patient geographical distributions and HBV genotype, resulting in it not being effective in all CHB patients[19,20-22].

Nucleosides or NAs

The NAs are the small molecule drugs that directly inhibit the HBV DNA polymerase reverse transcriptase activity, resulting in reduced virion production[23]. Moreover, they also compete with natural nucleotide substrates for the elongating DNA chain, interrupting HBV DNA synthesis[24]. There are six NAs approved for CHB treatment: LAM, ADV, ETV, LdT, TDF, and tenofovir alafenamide (TAF). Long-term treatment with NAs can reduce the cccDNA pool in hepatocytes infected with HBV by inhibiting nucleocapsid recycling. However, they cannot prevent the initial cccDNA formation in newly infected hepatocytes[25].

The first generations of NAs are LAM, ADV, and LdT. The NA approved by the United States Food and Drug Administration in 1998 for the treatment of CHB is LAM, which can compete for cytosine in the synthesis of viral DNA. The CHB patients who were treated with 100 mg LAM for 104 wk achieved 52% virological response. However, after 5 years of treatment, approximately 70% of the patients developed LAM resistance[26,27]. ADV, a phosphonate acyclic NA of adenosine monophosphate,

was approved in 2002. In 2003, Marcellin *et al*[28] reported that after 48 wk of 10 mg ADV treatment in HBeAg-positive CHB patients, 53% had histologic improvement, 21% had undetectable serum levels HBV DNA, and 12% had HBeAg seroconversion. Furthermore, Hadziyannis *et al*[29] demonstrated that after 48 wk of 10 mg ADV treatment in HBeAg-negative CHB patients, 64% had histologic improvement and 51% had undetectable serum levels of HBV DNA. However, long-term treatment with ADV also results in a high drug resistance rate of nearly 30% after 5 years of treatment [30]. LdT, the unmodified β-l enantiomer of thymidine, was approved for CHB treatment in 2007[31]. In 2009, Liaw *et al*[32] reported that LdT was superior to LAM in patients with CHB. They found that the rates of therapeutic response in HBeAg-positive and HBeAg-negative patients treated with 104 wk of LdT compared with LAM were 63% *vs* 48% and 78% *vs* 66%. However, long-term treatment with LdT led to nearly 35% drug resistance after 3 years of therapy[33].

ETV, TDF, and TAF are second-generation NAs with a high genetic barrier to HBV resistance. They are used as the first-line drugs for CHB treatment. In 2005, ETV, a guanosine NA with selective activity against HBV, was launched. The effective concentration (EC_{50}) of ETV is 4 nM. This EC_{50} is 100-fold more potent than ADV or LAM in HBV suppression[34]. In 2016, Ahn *et al*[35] reported that ETV had shown durable and increasing viral suppression in 84.6% of HBeAg-positive patients and 96.2% of HBeAg-negative patients over 5 years of treatment. However, the cumulative probability of HBsAg loss at year 5 was 5.2% in HBeAg-positive patients and 4.6% in HBeAg-negative patients. TDF, an acyclic NA with activity against retroviruses, was approved for CHB treatment in 2008. Buti and colleagues[36] reported that 437 patients remained on the study at year 7; among them, 54.5% and 11.8% achieved HBeAg and HBsAg loss in HBeAg-positive patients but only 0.3% of the HBeAg-negative patients achieved HBsAg loss. Although TDF resistance is relatively low, it has been associated with dose-dependent renal toxicity and induced Fanconi syndrome[37,38]. Recently, TAF was approved to be an alternative to TDF because it caused fewer side effects and was suitable for the treatment of CHB patients at risk of renal dysfunction[39]. Moreover, TAF has been demonstrated to be more effective than TDF with continued improved renal and bone safety[40].

Combination of NA plus Peg-IFN-a

Although the current monotherapy of anti-HBV drugs can suppress viral replication, prevent the progression of CHB to cirrhosis, and decrease the rates of HBV-related HCC in most CHB patients, long-term anti-HBV monotherapy rarely achieves the higher rate of HBsAg loss. Hence, to accomplish the goal of a functional cure in more CHB patients, the combination of NA with Peg-IFN-α has been evaluated. The reason for this is that the two classes of anti-HBV drugs have different mechanisms of action. Thus, their combination would result in a synergistic anti-HBV effect. Several studies have demonstrated that the combination of NA with Peg-IFN-α can substantially enhance the rates of HBsAg loss, but the benefits are mainly limited to a small proportion of patients and depend on HBV genotype and patient geographical distributions[41-44]. Moreover, NAs and Peg-IFN-α treatment have no direct impact on viral transcription or cccDNA. Thus, there is a very high risk of reactivation of HBV and the emergence of downstream disease symptoms after stopping treatment. Therefore, new therapeutic drugs that target different HBV life cycle steps or modulate the host immune system are needed.

NEW DRUGS TARGETING HBV LIFE CYCLE

HBV entry inhibitors

Bulevirtide (Myrcludex B): NTCP has been demonstrated as a functional receptor for HBV entry into hepatocytes[11]. Therefore, the new drugs targeting viral entry receptors have been proposed as potential agents for preventing uninfected hepatocytes. Bulevirtide (Myrcludex B) is a synthetic lipopeptide of 47 amino acids obtained from the HBV preS1 domain. When bulevirtide binds to NTCP, it will effectively prevent HBV spread among intrahepatic cells and hinder the amplification of intrahepatic cccDNA pool in infected hepatocytes[45,46].

In 2016, Blank *et al*[47] conducted a prospective, open-label, first-in-human, phase 1 clinical trial in 36 healthy volunteers. They found that bulevirtide was well tolerated, with no serious side effects and no immunogenic effects up to the highest dose of 20 mg intravenously. Moreover, the pharmacokinetic model showed that 10 mg and above of bulevirtide subcutaneous injection could reach a target saturation of over 80%

for at least 15 h. Furthermore, Blank *et al*[48] conducted a study to investigate the effects of bulevirtide on plasma bile acid disposition, TDF pharmacokinetics, and perpetrator characteristics on cytochrome (CYP) P450 3A in 12 healthy volunteers. All of the volunteers received 300 mg TDF orally and 10 mg of subcutaneous bulevirtide. They found that bulevirtide increased total plasma bile acid by 19.2-fold without signs of cholestasis, and co-administration of TDF with bulevirtide revealed no relevant changes in TDF pharmacokinetics.

Recently, Wedemeyer *et al*[49] conducted a phase 2b clinical trial in 60 patients with chronic HBV/hepatitis D virus (HDV) co-infection. They randomized 1:1:1:1 into the following four groups: Peg-IFN-α once-weekly (qw) (n = 15, Arm A); bulevirtide 2 mg once daily (QD) subcutaneous (sc) injection + Peg-IFN-α qw (n = 15, Arm B); bulevirtide 5 mg QD sc + Peg-IFN-α qw (n = 15, Arm C); or bulevirtide 2 mg QD (n = 15, Arm D) for 48 wk. They found that HBsAg levels declined by more than 1 Log_{10} in 6/15 (40%) and 2/15 (13.33%) patients from Arm B and Arm C, respectively. Notably, 4/15 (27%) patients from Arm B had undetectable HBsAg levels, and 3/4 (75%) patients established HBsAg seroconversion. Bulevirtide is moving along to phase 3 studies, whereby monotherapy extended or in combination with Peg-IFN-α will be investigated in CHB patients (Table 1).

cccDNA disruptors

The cccDNA plays a crucial role in the viral life cycle, where it acts as the template for viral transcription, while pgRNA is the template for viral replication. It interacts with histone and non-histone proteins, resembling cellular chromatin within the nucleus [50]. Disruption of cccDNA is considered an optimal target of HBV treatment because its persistence in the nucleus of infected hepatocytes is the crucial reason why HBsAg loss is currently not possible. The blocking of cccDNA formation, enhancing its destruction, and silencing its transcription, are currently under exploration.

Gene editing: The four ORFs of the HBV genome (surface, core, polymerase, and X protein) are translated into seven essential proteins for viral replication. The blocking of any one of the seven proteins would likely be essential to inhibit viral gene expression. Several small molecules have been developed as sequence-specific RNA-guided (gRNA) nucleases and proteins which can block the formation, enhance the destruction, and silence the transcription of cccDNA, while stimulating cell division [51]. These comprise cleaving sequence-specific DNA targets using the transcription activator-like effector nucleases (TALENs), zinc-finger nucleases (ZFNs), and clustered regularly interspaced short palindromic repeats-associated 9 (CRISPR/Cas9) systems that could demonstrate antiviral efficacy[52-54].

In 2014, Lin *et al*[55] demonstrated that the CRISPR/Cas9 system could disrupt the HBV genome both *in vitro* and *in vivo*. They showed that the HBV-specific gRNAs significantly decreased the production of HBV core and HBsAg in Huh-7 cells transfected with an HBV-expression vector. They also reported that the CRISPR/Cas9 system could cleave the intrahepatic HBV genome-containing plasmid and facilitate its clearance *in vivo*, causing a reduction in serum HBsAg levels. In 2015, Kennedy *et al* [56] reported the effective inhibition of HBV DNA production in *in vitro* models of both chronic and *de novo* HBV infection using lentiviral transduction of a bacterial Cas9 gene and single-guide RNAs (sgRNAs) specific for HBV. They showed that Cas9/sgRNA combinations specific for HBV reduced HBV DNA levels by up to 1000-fold and HBV cccDNA levels by up to 10-fold. Moreover, this method could inactivate the mutation of residual viral DNA. They concluded that CRISPR/Cas9 systems could serve as effective tools for disrupting the cccDNA pool in chronically-infected HBV patients.

Furthermore, Liu *et al*[57] showed that HBV-specific gRNA/Cas9 could inhibit the HBV replication of different genotypes *in vitro* and *in vivo* due to error-prone repair of viral DNA templates. Dong *et al*[58] reported that the CRISPR/Cas9 system could be used for disrupting intracellular cccDNA and viral replication in pre-cccDNA-transfected Huh7 cells and a new mouse model carrying HBV cccDNA. Zhen *et al*[59] studied the effects of the CRISPR/Cas9 system targeted to the HBsAg-encoding region of HBV in a cell culture system and *in vivo*. They found that the concentration of HBsAg secreted in the cell culture and mouse serum was decreased by CRISPR/Cas9 treatment. They concluded that a CRISPR/Cas9 system inhibited HBV replication and expression *in vitro* and *in vivo*, and may constitute a new therapeutic strategy for HBV infection. Seeger and Sohn[60] reported that HBV infections could be inhibited up to 8-fold by HBV-specific guide RNAs in NTCP-expressing HepG2 cells. Ramanan *et al*[61] demonstrated that the CRISPR/Cas9 system could specifically target and cleave conserved regions in the HBV genome, causing robust suppression of viral gene

Table 1 Developing new therapeutic drug targets for chronic hepatitis B

Drugs	Mechanism of action	Therapeutic class	Route of administration	Clinical trial	Results
HBV entry inhibitors					
Bulevirtide (Myrcludex B)[49]	Competition with NTCP	Peptide	Subcutaneous injection	IIb	HBsAg loss in 27% of HBV/HDV co-infected patients after 48 wk of treatment with Bulevirtide + pegIFN-α and 24 wk treatment-free follow-up
cccDNA disruptors					
CRISPR/Cas9[67]	Disruption of cccDNA	Gene editing	*In vivo*	Pre-clinical	Significantly improved survival of human hepatocytes in liver-humanized FRG mice and demonstrated a decreasing of total liver HBV-DNA and cccDNA
ZFNs[69]	Disruption of cccDNA	Gene editing	*In vitro*	Pre-clinical	Efficiently suppress the cellular template for HBV persistence and inhibit active HBV replication
Nucleocapsid assembly modulators					
JNJ-632 and BAY41-4109[73]	Misdirecting the formation of capsid-like structures	Capsid assembly modulators	*In vitro*	Pre-clinical	Induce the formation of morphologically intact viral capsids and prevented formation of cccDNA
NVR3-778[78]	Misdirecting the formation of capsid-like structures	Capsid assembly modulator	*In vivo*	I/II	The largest mean reduction in serum HBV DNA levels was achieved from the combination treatment of 600 mg NVR3-778 BD + pegIFN 180 mg subcutaneous weekly (1.97 log10 IU/mL)
JNJ-6379[76]	Misdirecting the formation of capsid-like structures	Capsid assembly modulators	Oral	II	No clinically significant changes in levels of HBsAg were observed
ABI-H0731[77]	Misdirecting the formation of capsid-like structures	Capsid assembly modulators	Oral	I/II	Dose-dependent reduces in HBV DNA and HBV RNA not HBsAg was seen in both HBeAg-positive and HBeAg-negative patients
HBV transcription inhibitors					
ARC-520[84]	Interference viral mRNA	Transcription inhibitor	Intravenous injection	II	CHB patients with high dose significantly reduced HBsAg and persisted for $\geq$85 d after the last dose
GSK3389404[85]	Interference viral mRNA	Transcription inhibitor	Subcutaneous injection	I	Dose 120 mg for 4 wk was safe and well tolerate
RG7834[87]	Interference viral mRNA	Gene expression inhibitor	*In vivo*	Pre-clinical	Reduced WHsAg by a mean of 2.57 $\log_{10}$ and WHV DNA by a mean of 1.71 $\log_{10}$ from baseline. However, WHsAg and WHV DNA rebounded to baseline after stopped treatment and WHsAb was not observed.
HBsAg release inhibitors					
REP 2055 and REP 2139-Ca[88]	HBsAg release inhibitors	NAPs	Intravenous injection	II	Substantially reduction of HBsAg levels, HBV DNA levels and increasing of serum HBsAb
REP 2139-Mg and REP 2165-Mg[90]	HBsAg release inhibitors	NAPs	Intravenous injection	II	Addition of NAPs to TDF + pegINFα-2a significantly increased rates of HBsAg loss during therapy and functional cure after therapy

cccDNA: Covalently closed circular DNA; CHB: Chronic hepatitis B; CRISPR/Cas9: Clustered regularly interspaced short palindromic repeats/CRISPR-associated 9; HBsAb: Hepatitis B surface antibody; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HDV: Hepatitis D virus; NAPs: Nucleic acid polymers; NTCP: Sodium taurocholate co-transporting polypeptide; pegIFN-α: Pegylated interferon-alpha; TDF: Tenofovir disoproxil fumarate; WHsAb: Woodchuck hepatitis surface antibody; WHsAg: Woodchuck hepatitis surface antigen; WHV: Woodchuck hepatitis virus.

expression and replication both *in vitro* and *in vivo*, and extended this antiviral activity to a virus isolated from patients. They also reported that upon continuous Cas9/sgRNA, a sharp decline of cccDNA and HBV proteins resulted in a *de novo* infection model.

Wang *et al*[62] evaluated the efficiency of each gRNA and 11 dual-gRNAs on the suppression of HBV (genotypes A-D) replication using the measurement of HBsAg or HBeAg in the culture supernatant. They found that all dual gRNAs could efficiently suppress HBsAg and HBeAg production for HBV of genotypes A-D, and the efficacy of dual gRNAs was significantly increased compared to the single gRNA used alone. Karimova *et al*[63] identified cross-genotype conserved HBV sequences in the S and X region of the HBV genome targeted for specific and effective cleavage by a Cas9 nickase. This technique could disrupt episomal cccDNA, and chromosomally integrated HBV target sites in reporter cell lines and HBV replication in chronically and *de novo* infected hepatoma cell lines.

In 2019, Kostyushev *et al*[64] evaluated CRISPR/Cas9 systems from four different species using co-expressed cell lines with gRNAs targeting conserved regions of the HBV genome. They found that the CRISPR/Cas9 systems from *Streptococcus pyogenes* (Sp) and *Streptococcus thermophilus* (St) targeting conserved regions of the HBV genome could block HBV replication and degrade over 90% HBV cccDNA by 6 d post-transfection. They concluded that the St CRISPR/Cas9 system represented the safest system with high anti-HBV activity.

In 2020, Yang *et al*[65] investigated the utility of CRISPR/Cas-mediated "base editors" (BES) in inactivating HBV gene expression without cleavage of DNA. They found that Cas9-mediated base editing is a potential strategy to cure CHB by permanently inactivating integrated HBV DNA and cccDNA without double-strand breaks of the host genome. Recently, Kayesh *et al*[66] evaluated the effects of adeno-associated virus 2 (AAV2) vector-mediated delivery of 3 selected from 16 gRNAs. These gRNAs/Cas9 significantly suppressed HBV replication in cells, with WJ11/Cas9 demonstrating the highest efficacy. Furthermore, AAV2/WJ11-Cas9 also substantially inhibited HBV replication and significantly reduced cccDNA in the tested cells. It also enhanced ETV actions when used in combination due to different modes of action. They concluded that AAV2/WJ11-Cas9 significantly suppressed HBcAg, HBsAg, and HBV DNA along with cccDNA in the liver tissues without significant cytotoxicity in humanized chimeric mice. A pre-clinical study was reported by Stone *et al*[67], in which HBV-specific AAV-*Staphylococcus aureus* (Sa)-Cas9 therapy significantly improved survival of human hepatocytes in liver-humanized FRG mice and demonstrated a decrease in total liver HBV DNA and cccDNA; in addition, a good tolerance profile was found. The investigators concluded that this approach was safe and feasible for *in vivo* gene editing therapy in CHB infections, and it may be a plausible method to cure CHB patients.

In 2010, Cradick *et al*[68] demonstrated the effective cleavage of viral DNA targets by HBV-specific ZFNs within cultured cells. Moreover, the cleaved fragments were mis-repaired, which could potentially inactivate HBV. The authors suggested that AAVs can transfect 100% of mouse hepatocytes and could be used to deliver ZFNs to the human livers. In 2014, Weber *et al*[69] evaluated three ZFNs that target sequences within the HBV polymerase, core, and X genes. They demonstrated that HBV-targeted ZFNs could efficiently suppress the cellular template for HBV persistence and inhibit active HBV replication, causing them to be potential candidates for cccDNA disruptors (Table 1).

Overall, gene editing techniques have demonstrated the usefulness of destroying HBV cccDNA *in vitro* and *in vivo* and shown the therapeutic potential in acute and chronic HBV infection. Gene editing is at an exciting stage, and the future of curative anti-HBV regimens for chronic HBV infection may well entail the use of it combined with other drugs.

Nucleocapsid assembly modulators

HBV capsid has numerous functions in the HBV life cycle, including reverse transcription, genome packaging, and intracellular trafficking. It is an excellent target for the development of new antiviral drugs[70]. The capsid assembly modulators (CAMs) can disturb pgRNA encapsidation and HBV DNA replication by misdirecting the formation of capsid-like structures[71]. There are two categories of CAM: type I represented by heteroaryl-dihydro pyrimidine, which misdirects the formation of aberrant structures; and type II represented by phenylpropenamides and sulfamoyl-benzamides, which accelerate the formation of morphologically intact empty capsids [72].

In 2017, Berke *et al*[73] conducted the study to evaluate the CAM JNJ-632 and CAM BAY41-4109, novel and potent inhibitors of HBV replication, *in vitro* across genotypes A to D. They found that it can induce the formation of morphologically intact viral capsids. They prevented the formation of cccDNA in a dose-dependent fashion when added with the viral inoculum. Moreover, it also reduced intracellular HBV RNA, HBeAg, HBcAg, and HBsAg concentrations in the cell culture supernatant. They concluded that CAMs have a dual mechanism of action that inhibits early and late steps of the viral life cycle, whereas NAs did not. In 2018, Lam *et al*[74] conducted a pre-clinical characterization of CAM NVR3-778 in HepG2.2.15 cells, mice, and dogs. They found that CAM NVR3-778 suppressed HBsAg, HBeAg, and intracellular HBV RNA production in primary human hepatocytes. Furthermore, it can block cccDNA formation during *de novo* infection and the subsequent transcription and viral protein translation steps. Furthermore, Klumpp *et al*[75] performed a comparative study of NVR3-778 to determine the *in vivo* antiviral efficacy and effects on innate and endoplasmic reticulum stress responses alone or in combination with Peg-IFN-α and compared with entecavir in 61 uPA/SCID mice with humanized livers. Mice were infected with an HBV genotype C preparation and then waited for 8 wk. They were randomly assigned to six groups (control, NVR3-778, entecavir, Peg-IFN-α, NVR3-778 + entecavir, or NVR3-778 + Peg-IFN-α) for 6 wk. Ultimately, the mice given NVR3-778 or entecavir alone for 6 wk showed reduced serum levels of HBV DNA compared with controls or mice given Peg-IFN-α. Moreover, the most considerable HBV DNA serum level reduction was demonstrated in mice given NVR3-778 + Peg-IFN-α. Serum levels of HBsAg and HBeAg were reduced in the groups that received Peg-IFN-α.

In 2020, Zoulim *et al*[76] performed a double-blind study of 57 treatment-naïve patients with HBeAg-positive or -negative CHB infection without cirrhosis. They were randomly assigned to five groups to receive either 25 mg (100 mg loading dose), 75 mg, 150 mg, or 250 mg JNJ-6379 or placebo daily for 4 wk, with an 8-wk follow-up period. They found that all doses of JNJ-6379 tested were well tolerated, demonstrated dose-dependent pharmacokinetics, and had potent antiviral activity in patients with CHB. However, no clinically significant changes in levels of HBsAg were observed. Recently, Yuen *et al*[77] conducted a phase 1/2, randomized, placebo-controlled study to explore the safety, pharmacokinetics, and pharmacodynamics of ABI-H0731 in healthy subjects and patients with CHB in two parts. In part 1, healthy adults were randomly assigned to receive single oral doses of ABI-H0731 (100, 300, 600, or 1000 mg) or matching placebo, or once-daily or twice-daily doses ABI-H0731 800 mg or matching placebo for 7 d. In part 2, HBeAg-positive or HBeAg-negative CHB adults were randomly assigned to receive ABI-H0731 (100, 200, 300, or 400 mg) or matching placebo once daily for 28 d. Overall, ABI-H0731 was safe and well-tolerated. There were no serious adverse events, nor clinically significant drug-related, dose-dependent, or treatment-emergent laboratory findings. ABI-H0731 showed dose-related activity with once-daily dosing. The mean maximal HBV DNA reductions from baseline of 1.7 Log_{10} IU/mL at 100 mg to 2.8 Log_{10} IU/mL at 300 mg after 28 d for the HBeAg-positive and HBeAg-negative patients. The authors concluded that dose-dependent reduction in HBV DNA and HBV RNA with ABI-H0731 occurred in both HBeAg-positive and HBeAg-negative patients. There were no serious adverse events related to the 1600 mg daily doses in healthy subjects or patients with CHB infection receiving doses up to 300 mg once daily.

Furthermore, Yuen *et al*[78] also performed a phase 1/2 study to examine the safety, pharmacokinetics, and antiviral activity of NVR3-778 in 73 patients with HBeAg-positive CHB infection without cirrhosis. The study had eight cohorts comprised of one placebo cohort and seven treatment cohorts. The four dose-escalation cohorts received NVR3-778 of 100 mg (10 cases), 200 mg (10 cases), or 400 mg once daily (QD) (8 cases), or 600 mg twice daily (BD) (8 cases). The fifth cohort was treated with 600 mg NVR3-778 BD + Peg-IFN 180 mg subcutaneous weekly (10 cases). The sixth cohort was treated with Peg-IFN 180 mg subcutaneous weekly + placebo (10 cases). The seventh cohort was treated with 1000 mg NVR 3-778 BD (7 cases). The eighth cohort was treated with a placebo. The investigators found that mean HBV DNA decline was minimal with low once-daily doses of NVR3-778, but when daily dosing was increased to 1200 mg/d, HBV DNA reductions became substantial. The fourth cohort (600 mg NVR3-778 BD) showed a mean HBV DNA reduction of 1.72 Log_{10} IU/mL. The most significant mean reduction in serum HBV DNA levels was achieved from the combination treatment of 600 mg NVR3-778 BD + Peg-IFN 180 mg subcutaneous weekly (1.97 Log_{10} IU/mL). They concluded that NVR3-778 treatment for 28 d up to a dose of 1000 mg BD was well tolerated. Substantial and correlated decreases in serum HBV DNA and HBV RNA concentrations were demonstrated with the higher-dose cohorts and were notably most excellent for combination treatment with NVR3-778

and Peg-IFN. They do not evaluate serum HBsAg, HBeAg, immunomodulatory effects, and effects on cccDNA persistence. These encouraging data suggested that CAMs can result in a substantial reduction in HBV DNA and HBV RNA levels. Longer-term treatments alone or combined with other antiviral agents will be needed to investigate whether CAMs will result in HBeAg, HBsAg, and cccDNA loss (Table 1).

HBV transcription inhibitors

After HBV enters the infected hepatocytes, partially double-stranded DNA (pdsDNA) moves to the nucleus and is converted to cccDNA. Furthermore, it is wrapped by histones to form a mini-chromosome. RNA interference (RNAi) and antisense oligonucleotides are mechanisms in which a double-stranded RNA (dsRNA) inhibits gene expression by degrading mRNA or blocking a specific gene's translation pathway. RNAi can directly target HBV transcripts and induce their degradation, causing gene silencing. Antisense oligonucleotides are small nucleic acids complementary to the target transcript, that induce degradation after binding. Hence, targeting the viral mRNA using RNAi and antisense oligonucleotides may be an effective method to control HBV infection. Many studies of RNAi and antisense oligonucleotides are in progress[79-81].

In 2017, Schluep *et al*[82] conducted a phase 1 randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of ARC-520 injection in 54 healthy volunteers (36 ARC-520 *vs* 18 placeboes). They found that ARC-520 was safe and well-tolerated. In the same year, Wooddell *et al*[83] conducted a phase 2 randomized, double-blind, placebo-controlled study to determine the safety, tolerability, and pharmacological effect of ARC-520 in 40 CHB patients with or without preceding nucleos(t)ide viral replication inhibitors (NUC) treatment. They found that ARC-520 resulted in a rapid and potent decrease in serum HBV DNA. However, the reduction of HBsAg was only demonstrated in HBeAg-positive patients. Follow-up studies in chimpanzees showed that the HBsAg being produced in the HBeAg-negative patients was predominantly derived from an integrated virus, which ARC-520 did not target.

In 2020, Yuen *et al*[84] conducted 2 randomized, multicenter studies to evaluate in-depth HBsAg decline using 1 mg/kg or 2 mg/kg ARC-520 compared with placebo at four monthly doses in 58 HBeAg-negative and 32 HBeAg-positive CHB patients concomitantly with NUC. They found that both HBeAg-negative and HBeAg-positive high-dose groups had significantly reduced HBsAg compared with placebo, with mean reductions of 0.38 and 0.54 Log IU/mL, respectively. Moreover, HBsAg reductions persisted for 85 d in HBeAg-negative patients and > 85 d in HBeAg-positive patients after the last dose of ARC-520. They concluded that ARC-520 was active in both HBeAg-negative and HBeAg-positive CHB patients treated by NUC. However, absolute HBsAg reductions were moderate, which may occur due to HBsAg expression from integrated HBV DNA.

In 2019, GSK3389404, an antisense oligonucleotide, was studied by Han *et al*[85]. The investigators conducted a randomized, double-blind, phase 1 study to assess the safety and pharmacokinetics of GSK3389404 in healthy subjects. Four single ascending-dose cohorts (10 mg, 30 mg, 60 mg, and 120 mg subcutaneously) and three multiple ascending-dose cohorts (30 mg, 60 mg, and 120 mg once weekly for 4 wk) each comprised 6 subjects randomized to GSK3389404 and 2 subjects randomized to placebo. They reported that there were no serious adverse events (SAEs) or withdrawals due to SAEs. GSK3389404 dosing has been tested up to 120 mg for 4 wk with an acceptable safety and pharmacokinetic profile and suitable for further clinical evaluation in CHB patients.

In 2018, Mueller *et al*[86] reported that RG7834, a novel oral HBV gene expression inhibitor, could reduce the levels of viral proteins and lower viremia. RG7834 is a small-molecule compound belonging to the dihydroquinolizinones chemical class similar to RNAi but through a different mechanism. They found that oral treatment of HBV-infected humanized mice with RG7834 Led to a mean HBsAg reduction of 1.09 Log_{10} compared to entecavir, which had no significant reduction on HBsAg levels. In 2020, Menne *et al*[87] conducted a study to evaluate the potency of RG7834 alone and in combination with ETV or woodchuck interferon-α (wIFN-α) in the woodchuck model of chronic HBV infection. RG7834 could reduce woodchuck hepatitis virus (WHV) surface antigen (WHsAg) by a mean of 2.57 Log_{10} from baseline and WHV DNA by a mean of 1.71 Log_{10}. ETV + wIFN-α reduced WHsAg and WHV DNA by 2.40 Log_{10} and 6.70 Log_{10}, respectively. RG7834 combined with ETV and wIFN-α significantly decreased WHsAg and WHV DNA concentrations by 5.0 Log_{10} and 7.46 Log_{10}, respectively. However, WHsAg and WHV DNA rebounded to baseline after stopping treatment, and WHsAb was not observed. Notably, both RNAi and antisense

oligonucleotides do not eliminate cccDNA, and rebound of HBsAg levels to pretreatment points after stopping treatment has been reported. Therefore, it is likely to be used in combination with other drugs (Table 1).

HBsAg release inhibitors

HBsAg release inhibitors function under the same exact mechanism as the RNAi and antisense oligonucleotides that block the release of subviral HBsAg particles. Circulating HBsAg is an immunoinhibitory factor that blocks the innate immune response. Clearance of circulating HBsAg is a crucial step in the functional control of HBV infection and permits anti-HBs seroconversion. In 2016, Al-Mahtab *et al*[88] conducted two studies to evaluate REP 2055 and REP 2139-Ca, nucleic acid polymers (NAPs), in 8 and 12 CHB patients, respectively. The results from both studies showed that NAP monotherapy was accompanied by 2-7 Log_{10} reductions of HBsAg levels, 3-9 Log_{10} reductions in HBV DNA levels, and the appearance of serum hepatitis B surface antibody (HBsAb) (10-1712 mIU/mL). Eight of the nine patients treated with the combination of NAP and immunotherapy experienced HBsAg loss, and all nine patients experienced substantial increases in serum HBsAb antibody titers before treatment was stopped. Moreover, 1 year after the REP 2055 therapy was stopped, a rebound of serum HBV DNA > 1000 copies/mL or HBsAg > 1 IU/mL was not observed in 3/8 CHB patients. Suppression of serum HBV DNA > 1000 copies/mL or HBsAg > 1 IU/mL was further maintained for 290 and 231 wk in 2 of these patients. For REP 2139-Ca treatment, 8 patients achieved HBV DNA < 116 copies/mL after treatment withdrawal. The rebound of serum HBV DNA > 1000 copies/mL or HBsAg > 1 IU/mL occurred over 12 to 123 wk in 7 patients but was still absent in 2 patients at 135 and 137 wk of follow-up. The authors concluded that NAP could elicit significant antiviral responses during treatment which may improve the effect of immunotherapy. NAPs may be a potentially useful component of future combination therapies for the treatment of CHB.

In 2017, Bazinet *et al*[89] conducted an open-label, non-randomized, phase 2 trial to assess the safety and efficacy of REP 2139 and Peg-INF-α-2a in 12 patients with CHB HDV co-infection. The results showed that 6 patients had HBsAg concentrations < 50 IU/mL by the end of treatment. Five patients maintained the level of suppression at the end of 1-year follow-up. Six patients had HBsAb titers > 10 mIU/mL at the end of treatment (five had maximum HBsAb levels of 7681-86532 mIU/mL during treatment), which were maintained at the end of 1-year follow-up. By the end of 1-year follow-up, normalization of serum aspartate aminotransferase (AST) and ALT occurred in 9 of 12 patients. They concluded that combined REP 2139 and Peg-INF-α-2a therapy is well-tolerated, safe, and establishes functional control of HBV and HDV co-infection and normalization of serum AST and ALT in a high proportion of patients 1 year after therapy. In 2020, Bazinet *et al*[90] performed an open-label, phase 2 study of the safety and efficacy of REP 2139 or REP 2165 combined with TDF and Peg-INF-α-2a in 40 HBeAg-negative CHB patients. Forty patients were randomly assigned to groups that received 48 wk of experimental therapy (TDF + Peg-INF-α-2a + REP 2139-Mg or REP 2165-Mg) or 24 wk of control therapy (TDF + Peg-INF-α-2a) followed by 48 wk of experimental therapy. At 48 wk, when patients completed the TDF + Peg-INF-α-2a + NAPs regimen, HBsAg concentrations were ≤ 0.05 IU/mL in 24 of 40 (60%) patients, while all of the patient's achieved seroconversion with HBsAb up to 233055 mIU/mL. During 48 wk of treatment-free follow-up, virologic control persisted in 13 of 40 (32.5%) patients, whereas functional cure persisted in 14 of 40 (35%) patients with persistent HBsAg loss. They concluded that the addition of NAPs to TDF + Peg-INF-α-2a significantly increased rates of HBsAg loss during therapy and functional cure after therapy. However, these results should be carefully applied for Asian race because Van Hees *et al*[91] found that Caucasian patients had more than 6-fold increased chance of HBsAg loss compared to other ethnicities. Further studies regarding ethnicity and HBsAg loss are needed. Thus, NAPs alone or combined with TDF or Peg-INF-α-2a may allow better functional control of HBV infection (Table 1). A longer duration of NAPs treatment would be needed to identify their sustained virological effects and potential risk for adverse events.

CONCLUSION

Tremendous progress has been explored in understanding the pathophysiology and treatment of CHB over the past 20 years. The CHB current treatment with a potent and a high genetic barrier NA (ETV, TDF, and TAF) can suppress the viral replication to an

undetectable level in most CHB patients. They also prevent the progression of CHB to cirrhosis and markedly reducing the rates of HBV-related HCC. Regardless of viral suppression by NAs, there are many obstacles to achieve a functional cure or HBsAg loss in CHB patients. HBV could persist in the hepatocyte nucleus by continuously replenishing the cccDNA with a long half-life and the integrated forms of viral DNA. Moreover, the defective immune response and the ine□cient innate immune response prevent HBV-infected hepatocytes from being cleared by host immunity.

HBsAg loss with or without HBsAb seroconversion is one of the most desired endpoints of new drug development. Targeting HBsAg by inhibiting the entry of HBV into hepatocytes, disrupting or silencing HBV cccDNA, modulating nucleocapsid assembly, interfering HBV transcription, and inhibiting HBsAg release are the primary targets for functional cure in CHB patients. However, newly developed drugs still have limitations in being used alone without IFN and NAs to induce HBsAg loss. Interestingly, a new strategic therapy in treating chronic HBV infection is to use a combination of multiple drugs, including a backbone of a NA, one or more new direct-acting antiviral drugs, and at least one immunomodulator. With the collaborative efforts of basic research scientists and clinical experts, the ultimate elimination of CHB infection is likely to be achieved soon.

REFERENCES

1 **Polaris Observatory Collaborators**. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; **3**: 383-403 [PMID: 29599078 DOI: 10.1016/S2468-1253(18)30056-6]

2 **World Health Organization**. Global hepatitis report, 2017. [cited 30 April 2021]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

3 **Nassal M**. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]

4 **Lythgoe KA**, Lumley SF, Pellis L, McKeating JA, Matthews PC. Estimating hepatitis B virus cccDNA persistence in chronic infection. *Virus Evol* 2021; **7**: veaa063 [PMID: 33732502 DOI: 10.1093/ve/veaa063]

5 **Stelma F**, van der Ree MH, Jansen L, Peters MW, Janssen HLA, Zaaijer HL, Takkenberg RB, Reesink HW. HBsAg loss after peginterferon-nucleotide combination treatment in chronic hepatitis B patients: 5 years of follow-up. *J Viral Hepat* 2017; **24**: 1107-1113 [PMID: 28632898 DOI: 10.1111/jvh.12738]

6 **Marcellin P**, Ahn SH, Ma X, Caruntu FA, Tak WY, Elkashab M, Chuang WL, Lim SG, Tabak F, Mehta R, Petersen J, Foster GR, Lou L, Martins EB, Dinh P, Lin L, Corsa A, Charuworn P, Subramanian GM, Reiser H, Reesink HW, Fung S, Strasser SI, Trinh H, Buti M, Gaeta GB, Hui AJ, Papatheodoridis G, Flisiak R, Chan HL. Study 149 Investigators. Combination of Tenofovir Disoproxil Fumarate and Peginterferon α-2a Increases Loss of Hepatitis B Surface Antigen in Patients With Chronic Hepatitis B. *Gastroenterology* 2016; **150**: 134-144.e10 [PMID: 26453773 DOI: 10.1053/j.gastro.2015.09.043]

7 **de Niet A**, Jansen L, Stelma F, Willemse SB, Kuiken SD, Weijer S, van Nieuwkerk CMJ, Zaaijer HL, Molenkamp R, Takkenberg RB, Koot M, Verheij J, Beuers U, Reesink HW. Peg-interferon plus nucleotide analogue treatment *versus* no treatment in patients with chronic hepatitis B with a low viral load: a randomised controlled, open-label trial. *Lancet Gastroenterol Hepatol* 2017; **2**: 576-584 [PMID: 28522204 DOI: 10.1016/S2468-1253(17)30083-3]

8 **Lee HW**, Lee JS, Ahn SH. Hepatitis B Virus Cure: Targets and Future Therapies. *Int J Mol Sci* 2020; **22**: 213 [PMID: 33379331 DOI: 10.3390/ijms22010213]

9 **Naggie S**, Lok AS. New Therapeutics for Hepatitis B: The Road to Cure. *Annu Rev Med* 2021; **72**: 93-105 [PMID: 33085923 DOI: 10.1146/annurev-med-080119-103356]

10 **Seeger C**, Mason WS. Molecular biology of hepatitis B virus infection. *Virology* 2015; **479**: 672-686 [PMID: 25759099 DOI: 10.1016/j.virol.2015.02.031]

11 **Yan H**, Zhong G, Xu G, He W, Jing Z, Gao Z, Huang Y, Qi Y, Peng B, Wang H, Fu L, Song M, Chen P, Gao W, Ren B, Sun Y, Cai T, Feng X, Sui J, Li W. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *Elife* 2012; **1**: e00049 [PMID: 23150796 DOI: 10.7554/eLife.00049]

12 **Bock CT**, Schranz P, Schröder CH, Zentgraf H. Hepatitis B virus genome is organized into nucleosomes in the nucleus of the infected cell. *Virus Genes* 1994; **8**: 215-229 [PMID: 7975268 DOI: 10.1007/BF01703079]

13 **Seeger C**, Summers J, Mason WS. Viral DNA synthesis. *Curr Top Microbiol Immunol* 1991; **168**: 41-60 [PMID: 1893778 DOI: 10.1007/978-3-642-76015-0_3]

14 **Fanning GC**, Zoulim F, Hou J, Bertoletti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. *Nat Rev Drug Discov* 2019; **18**: 827-844 [PMID: 31455905 DOI: 10.1038/s41573-019-0037-0]

15 **Vittal A**, Ghany MG. WHO Guidelines for Prevention, Care and Treatment of Individuals Infected

with HBV: A US Perspective. *Clin Liver Dis* 2019; **23**: 417-432 [PMID: 31266617 DOI: 10.1016/j.cld.2019.04.008]

16 **European Association for the Study of The Liver**. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]

17 **Brunetto MR**, Bonino F. Interferon therapy of chronic hepatitis B. *Intervirology* 2014; **57**: 163-170 [PMID: 25034484 DOI: 10.1159/000360941]

18 **Koumbi L**. Current and future antiviral drug therapies of hepatitis B chronic infection. *World J Hepatol* 2015; **7**: 1030-1040 [PMID: 26052392 DOI: 10.4254/wjh.v7.i8.1030]

19 **Yeh ML**, Huang JF, Yu ML, Chuang WL. Hepatitis b infection: progress in identifying patients most likely to respond to peginterferon alfa. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 427-435 [PMID: 33338385 DOI: 10.1080/17474124.2021.1866985]

20 **Zhang Y**, Wu Y, Ye S, Wang T, Zhao R, Chen F, Abe K, Jin X. The response to interferon is influenced by hepatitis B virus genotype *in vitro* and in vivo. *Virus Res* 2013; **171**: 65-70 [PMID: 23123214 DOI: 10.1016/j.virusres.2012.10.027]

21 **Nishio A**, Bolte FJ, Takeda K, Park N, Yu ZX, Park H, Valdez K, Ghany MG, Rehermann B. Clearance of pegylated interferon by Kupffer cells limits NK cell activation and therapy response of patients with HBV infection. *Sci Transl Med* 2021; **13** [PMID: 33790025 DOI: 10.1126/scitranslmed.aba6322]

22 **Duraisamy GS**, Bhosale D, Lipenská I, Huvarova I, Růžek D, Windisch MP, Miller AD. Advanced Therapeutics, Vaccinations, and Precision Medicine in the Treatment and Management of Chronic Hepatitis B Viral Infections; Where Are We and Where Are We Going? *Viruses* 2020; **12**: 998 [PMID: 32906840 DOI: 10.3390/v12090998]

23 **Hongthanakorn C**, Lok AS. New pharmacologic therapies in chronic hepatitis B. *Gastroenterol Clin North Am* 2010; **39**: 659-680 [PMID: 20951923 DOI: 10.1016/j.gtc.2010.08.012]

24 **Menéndez-Arias L**, Álvarez M, Pacheco B. Nucleoside/nucleotide analog inhibitors of hepatitis B virus polymerase: mechanism of action and resistance. *Curr Opin Virol* 2014; **8**: 1-9 [PMID: 24814823 DOI: 10.1016/j.coviro.2014.04.005]

25 **Tang L**, Sheraz M, McGrane M, Chang J, Guo JT. DNA Polymerase alpha is essential for intracellular amplification of hepatitis B virus covalently closed circular DNA. *PLoS Pathog* 2019; **15**: e1007742 [PMID: 31026293 DOI: 10.1371/journal.ppat.1007742]

26 **Liaw YF**, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Chien RN, Dent J, Roman L, Edmundson S, Lai CL. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *Gastroenterology* 2000; **119**: 172-180 [PMID: 10889166 DOI: 10.1053/gast.2000.8559]

27 **Jarvis B**, Faulds D. Lamivudine. A review of its therapeutic potential in chronic hepatitis B. *Drugs* 1999; **58**: 101-141 [PMID: 10439933 DOI: 10.2165/00003495-199958010-00015]

28 **Marcellin P**, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 437 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348**: 808-816 [PMID: 12606735 DOI: 10.1056/NEJMoa020681]

29 **Hadziyannis SJ**, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 438 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348**: 800-807 [PMID: 12606734 DOI: 10.1056/NEJMoa021812]

30 **Salpini R**, Alteri C, Cento V, Pollicita M, Micheli V, Gubertini G, De Sanctis GM, Visca M, Romano S, Sarrecchia C, Andreoni M, Angelico M, Parruti G, Svicher V, Perno CF. Snapshot on drug-resistance rate and profiles in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. *J Med Virol* 2013; **85**: 996-1004 [PMID: 23588725 DOI: 10.1002/jmv.23567]

31 **Amarapurkar DN**. Telbivudine: a new treatment for chronic hepatitis B. *World J Gastroenterol* 2007; **13**: 6150-6155 [PMID: 18069753 DOI: 10.3748/wjg.v13.i46.6150]

32 **Liaw YF**, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV; GLOBE Study Group. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486-495 [PMID: 19027013 DOI: 10.1053/j.gastro.2008.10.026]

33 **Seto WK**, Lai CL, Fung J, Wong DK, Yuen JC, Hung IF, Yuen MF. Significance of HBV DNA levels at 12 weeks of telbivudine treatment and the 3 years treatment outcome. *J Hepatol* 2011; **55**: 522-528 [PMID: 21147187 DOI: 10.1016/j.jhep.2010.11.018]

34 **Shepherd J**, Gospodarevskaya E, Frampton G, Cooper K. Entecavir for the treatment of chronic hepatitis B infection. *Health Technol Assess* 2009; **13** Suppl 3: 31-36 [PMID: 19846026 DOI: 10.3310/hta13suppl3/05]

35 **Ahn J**, Lee HM, Lim JK, Pan CQ, Nguyen MH, Ray Kim W, Mannalithara A, Trinh H, Chu D, Tran T, Min A, Do S, Te H, Reddy KR, Lok AS. Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. *Aliment Pharmacol Ther* 2016; **43**: 134-144 [PMID: 26510638 DOI: 10.1111/apt.13440]

36 **Buti M**, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, Aguilar Schall R, Flaherty JF, Martins EB, Charuworn P, Kitrinos KM, Subramanian GM, Gane E, Marcellin P. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci*

2015; **60**: 1457-1464 [PMID: 25532501 DOI: 10.1007/s10620-014-3486-7]

37 **Van Rompay KK**, Durand-Gasselin L, Brignolo LL, Ray AS, Abel K, Cihlar T, Spinner A, Jerome C, Moore J, Kearney BP, Marthas ML, Reiser H, Bischofberger N. Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy: summary of pharmacokinetics and biological and virological effects. *Antimicrob Agents Chemother* 2008; **52**: 3144-3160 [PMID: 18573931 DOI: 10.1128/AAC.00350-08]

38 **Magalhães-Costa P**, Matos L, Barreiro P, Chagas C. Fanconi syndrome and chronic renal failure in a chronic hepatitis B monoinfected patient treated with tenofovir. *Rev Esp Enferm Dig* 2015; **107**: 512-514 [PMID: 26228957]

39 **Childs-Kean LM**, Egelund EF, Jourjy J. Tenofovir Alafenamide for the Treatment of Chronic Hepatitis B Monoinfection. *Pharmacotherapy* 2018; **38**: 1051-1057 [PMID: 30120841 DOI: 10.1002/phar.2174]

40 **Agarwal K**, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, Ahn SH, Izumi N, Chuang WL, Bae H, Sharma M, Janssen HLA, Pan CQ, Çelen MK, Furusyo N, Shalimar D, Yoon KT, Trinh H, Flaherty JF, Gaggar A, Lau AH, Cathcart AL, Lin L, Bhardwaj N, Suri V, Mani Subramanian G, Gane EJ, Buti M, Chan HLY; GS-US-320-0110; GS-US-320-0108 Investigators. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol* 2018; **68**: 672-681 [PMID: 29756595 DOI: 10.1016/j.jhep.2017.11.039]

41 **Ren H**, Huang Y. Effects of pegylated interferon-α based therapies on functional cure and the risk of hepatocellular carcinoma development in patients with chronic hepatitis B. *J Viral Hepat* 2019; **26** Suppl 1: 5-31 [PMID: 31380584 DOI: 10.1111/jvh.13150]

42 **Bourlière M**, Rabiega P, Ganne-Carrie N, Serfaty L, Marcellin P, Barthe Y, Thabut D, Guyader D, Hezode C, Picon M, Causse X, Leroy V, Bronowicki JP, Carrieri P, Riachi G, Rosa I, Attali P, Molina JM, Bacq Y, Tran A, Grangé JD, Zoulim F, Fontaine H, Alric L, Bertucci I, Bouvier-Alias M, Carrat F; ANRS HB06 PEGAN Study Group. Effect on HBs antigen clearance of addition of pegylated interferon alfa-2a to nucleos(t)ide analogue therapy *versus* nucleos(t)ide analogue therapy alone in patients with HBe antigen-negative chronic hepatitis B and sustained undetectable plasma hepatitis B virus DNA: a randomised, controlled, open-label trial. *Lancet Gastroenterol Hepatol* 2017; **2**: 177-188 [PMID: 28404133 DOI: 10.1016/S2468-1253(16)30189-3]

43 **van Campenhout MJH**, Brouwer WP, Xie Q, Guo S, Chi H, Qi X, Tabak F, Streinu-Cercel A, Wang JY, Zhang NP, Idilman R, Reesink HW, Diculescu M, Simon K, Akdogan M, Mazur W, de Knegt RJ, Verhey E, Hansen BE, Janssen HLA; ARES Study Group. Long-term follow-up of patients treated with entecavir and peginterferon add-on therapy for HBeAg-positive chronic hepatitis B infection: ARES long-term follow-up. *J Viral Hepat* 2019; **26**: 109-117 [PMID: 30187612 DOI: 10.1111/jvh.12997]

44 **Hu P**, Shang J, Zhang W, Gong G, Li Y, Chen X, Jiang J, Xie Q, Dou X, Sun Y, Liu Y, Liu G, Mao D, Chi X, Tang H, Li X, Xie Y, Zhao P, Hou J, Gao Z, Fan H, Ding J, Zhang D, Ren H. HBsAg Loss with Peg-interferon Alfa-2a in Hepatitis B Patients with Partial Response to Nucleos(t)ide Analog: New Switch Study. *J Clin Transl Hepatol* 2018; **6**: 25-34 [PMID: 29577029 DOI: 10.14218/JCTH.2017.00072]

45 **Volz T**, Allweiss L, Ben MBarek M, Warlich M, Lohse AW, Pollok JM, Alexandrov A, Urban S, Petersen J, Lütgehetmann M, Dandri M. The entry inhibitor Myrcludex-B efficiently blocks intrahepatic virus spreading in humanized mice previously infected with hepatitis B virus. *J Hepatol* 2013; **58**: 861-867 [PMID: 23246506 DOI: 10.1016/j.jhep.2012.12.008]

46 **Zhao K**, Liu S, Chen Y, Yao Y, Zhou M, Yuan Y, Wang Y, Pei R, Chen J, Hu X, Zhou Y, Zhao H, Lu M, Wu C, Chen X. Upregulation of HBV transcription by sodium taurocholate cotransporting polypeptide at the postentry step is inhibited by the entry inhibitor Myrcludex B. *Emerg Microbes Infect* 2018; **7**: 186 [PMID: 30459339 DOI: 10.1038/s41426-018-0189-8]

47 **Blank A**, Markert C, Hohmann N, Carls A, Mikus G, Lehr T, Alexandrov A, Haag M, Schwab M, Urban S, Haefeli WE. First-in-human application of the novel hepatitis B and hepatitis D virus entry inhibitor myrcludex B. *J Hepatol* 2016; **65**: 483-489 [PMID: 27132172 DOI: 10.1016/j.jhep.2016.04.013]

48 **Blank A**, Eidam A, Haag M, Hohmann N, Burhenne J, Schwab M, van de Graaf S, Meyer MR, Maurer HH, Meier K, Weiss J, Bruckner T, Alexandrov A, Urban S, Mikus G, Haefeli WE. The NTCP-inhibitor Myrcludex B: Effects on Bile Acid Disposition and Tenofovir Pharmacokinetics. *Clin Pharmacol Ther* 2018; **103**: 341-348 [PMID: 28543042 DOI: 10.1002/cpt.744]

49 **Wedemeyer H**, Bogomolov P, Blank A, Allweiss L, Dandri-Petersen M, Bremer B, Voronkova N, Schöneweis K, Pathil A, Burhenne J, Haag M, Schwab M, Haefeli WE, Wiesch JSZ, Alexandrov A, Urban S. Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection. *J Hepatol* 2018; **68**: S3 [DOI: 10.1016/s0168-8278(18)30224-1]

50 **Allweiss L**, Dandri M. The Role of cccDNA in HBV Maintenance. *Viruses* 2017; **9**: 156 [PMID: 28635668 DOI: 10.3390/v9060156]

51 **Ruiz de Galarreta M**, Lujambio A. Therapeutic editing of hepatocyte genome in vivo. *J Hepatol* 2017; **67**: 818-828 [PMID: 28527665 DOI: 10.1016/j.jhep.2017.05.012]

52 **Ely A**, Moyo B, Arbuthnot P. Progress With Developing Use of Gene Editing To Cure Chronic Infection With Hepatitis B Virus. *Mol Ther* 2016; **24**: 671-677 [PMID: 26916283 DOI: 10.1038/mt.2016.43]

53 **Brezgin S**, Kostyusheva A, Bayurova E, Gordeychuk I, Isaguliants M, Goptar I, Nikiforova A,

Smirnov V, Volchkova E, Glebe D, Kostyushev D, Chulanov V. Replenishment of Hepatitis B Virus cccDNA Pool Is Restricted by Baseline Expression of Host Restriction Factors In Vitro. *Microorganisms* 2019; **7**: 533 [PMID: 31698767 DOI: 10.3390/microorganisms7110533]

54 **Gaj T**, Gersbach CA, Barbas 3rd CF. ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. *Trends Biotechnol* 2013; **31**: 397-405 [PMID: 23664777 DOI: 10.1016/j.tibtech.2013.04.004]

55 **Lin SR**, Yang HC, Kuo YT, Liu CJ, Yang TY, Sung KC, Lin YY, Wang HY, Wang CC, Shen YC, Wu FY, Kao JH, Chen DS, Chen PJ. The CRISPR/Cas9 System Facilitates Clearance of the Intrahepatic HBV Templates In Vivo. *Mol Ther Nucleic Acids* 2014; **3**: e186 [PMID: 25137139 DOI: 10.1038/mtna.2014.38]

56 **Kennedy EM**, Bassit LC, Mueller H, Kornepati AVR, Bogerd HP, Nie T, Chatterjee P, Javanbakht H, Schinazi RF, Cullen BR. Suppression of hepatitis B virus DNA accumulation in chronically infected cells using a bacterial CRISPR/Cas RNA-guided DNA endonuclease. *Virology* 2015; **476**: 196-205 [PMID: 25553515 DOI: 10.1016/j.virol.2014.12.001]

57 **Liu X**, Hao R, Chen S, Guo D, Chen Y. Inhibition of hepatitis B virus by the CRISPR/Cas9 system *via* targeting the conserved regions of the viral genome. *J Gen Virol* 2015; **96**: 2252-2261 [PMID: 25904148 DOI: 10.1099/vir.0.000159]

58 **Dong C**, Qu L, Wang H, Wei L, Dong Y, Xiong S. Targeting hepatitis B virus cccDNA by CRISPR/Cas9 nuclease efficiently inhibits viral replication. *Antiviral Res* 2015; **118**: 110-117 [PMID: 25843425 DOI: 10.1016/j.antiviral.2015.03.015]

59 **Zhen S**, Hua L, Liu YH, Gao LC, Fu J, Wan DY, Dong LH, Song HF, Gao X. Harnessing the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated Cas9 system to disrupt the hepatitis B virus. *Gene Ther* 2015; **22**: 404-412 [PMID: 25652100 DOI: 10.1038/gt.2015.2]

60 **Seeger C**, Sohn JA. Targeting Hepatitis B Virus With CRISPR/Cas9. *Mol Ther Nucleic Acids* 2014; **3**: e216 [PMID: 25514649 DOI: 10.1038/mtna.2014.68]

61 **Ramanan V**, Shlomai A, Cox DB, Schwartz RE, Michailidis E, Bhatta A, Scott DA, Zhang F, Rice CM, Bhatia SN. CRISPR/Cas9 cleavage of viral DNA efficiently suppresses hepatitis B virus. *Sci Rep* 2015; **5**: 10833 [PMID: 26035283 DOI: 10.1038/srep10833]

62 **Wang J**, Xu ZW, Liu S, Zhang RY, Ding SL, Xie XM, Long L, Chen XM, Zhuang H, Lu FM. Dual gRNAs guided CRISPR/Cas9 system inhibits hepatitis B virus replication. *World J Gastroenterol* 2015; **21**: 9554-9565 [PMID: 26327763 DOI: 10.3748/wjg.v21.i32.9554]

63 **Karimova M**, Beschorner N, Dammermann W, Chemnitz J, Indenbirken D, Bockmann JH, Grundhoff A, Lüth S, Buchholz F, Schulze zur Wiesch J, Hauber J. CRISPR/Cas9 nickase-mediated disruption of hepatitis B virus open reading frame S and X. *Sci Rep* 2015; **5**: 13734 [PMID: 26334116 DOI: 10.1038/srep13734]

64 **Kostyushev D**, Brezgin S, Kostyusheva A, Zarifyan D, Goptar I, Chulanov V. Orthologous CRISPR/Cas9 systems for specific and efficient degradation of covalently closed circular DNA of hepatitis B virus. *Cell Mol Life Sci* 2019; **76**: 1779-1794 [PMID: 30673820 DOI: 10.1007/s00018-019-03021-8]

65 **Yang YC**, Chen YH, Kao JH, Ching C, Liu IJ, Wang CC, Tsai CH, Wu FY, Liu CJ, Chen PJ, Chen DS, Yang HC. Permanent Inactivation of HBV Genomes by CRISPR/Cas9-Mediated Non-cleavage Base Editing. *Mol Ther Nucleic Acids* 2020; **20**: 480-490 [PMID: 32278307 DOI: 10.1016/j.omtn.2020.03.005]

66 **Kayesh MEH**, Amako Y, Hashem MA, Murakami S, Ogawa S, Yamamoto N, Hifumi T, Miyoshi N, Sugiyama M, Tanaka Y, Mizokami M, Kohara M, Tsukiyama-Kohara K. Development of an *in vivo* delivery system for CRISPR/Cas9-mediated targeting of hepatitis B virus cccDNA. *Virus Res* 2020; **290**: 198191 [PMID: 33049308 DOI: 10.1016/j.virusres.2020.198191]

67 **Stone D**, Long KR, Loprieno MA, De Silva Feelixge HS, Kenkel EJ, Liley RM, Rapp S, Roychoudhury P, Nguyen T, Stensland L, Colón-Thillet R, Klouser LM, Weber ND, Le C, Wagoner J, Goecker EA, Li AZ, Eichholz K, Corey L, Tyrrell DL, Greninger AL, Huang ML, Polyak SJ, Aubert M, Sagartz JE, Jerome KR. CRISPR-Cas9 gene editing of hepatitis B virus in chronically infected humanized mice. *Mol Ther Methods Clin Dev* 2021; **20**: 258-275 [PMID: 33473359 DOI: 10.1016/j.omtm.2020.11.014]

68 **Cradick TJ**, Keck K, Bradshaw S, Jamieson AC, McCaffrey AP. Zinc-finger nucleases as a novel therapeutic strategy for targeting hepatitis B virus DNAs. *Mol Ther* 2010; **18**: 947-954 [PMID: 20160705 DOI: 10.1038/mt.2010.20]

69 **Weber ND**, Stone D, Sedlak RH, De Silva Feelixge HS, Roychoudhury P, Schiffer JT, Aubert M, Jerome KR. AAV-mediated delivery of zinc finger nucleases targeting hepatitis B virus inhibits active replication. *PLoS One* 2014; **9**: e97579 [PMID: 24827459 DOI: 10.1371/journal.pone.0097579]

70 **Peters MG**, Locarnini S. New Direct-Acting Antiviral Agents and Immunomodulators for Hepatitis B Virus Infection. *Gastroenterol Hepatol (N Y)* 2017; **13**: 348-356 [PMID: 28690451]

71 **Zhang X**, Cheng J, Ma J, Hu Z, Wu S, Hwang N, Kulp J, Du Y, Guo JT, Chang J. Discovery of Novel Hepatitis B Virus Nucleocapsid Assembly Inhibitors. *ACS Infect Dis* 2019; **5**: 759-768 [PMID: 30525438 DOI: 10.1021/acsinfecdis.8b00269]

72 **Lahlali T**, Berke JM, Vergauwen K, Foca A, Vandyck K, Pauwels F, Zoulim F, Durantel D. Novel Potent Capsid Assembly Modulators Regulate Multiple Steps of the Hepatitis B Virus Life Cycle. *Antimicrob Agents Chemother* 2018; **62**: e00835-18 [PMID: 30012770 DOI: 10.1128/AAC.00835-18]

73 **Berke JM**, Dehertogh P, Vergauwen K, Van Damme E, Mostmans W, Vandyck K, Pauwels F. Capsid Assembly Modulators Have a Dual Mechanism of Action in Primary Human Hepatocytes Infected with Hepatitis B Virus. *Antimicrob Agents Chemother* 2017; **61**: e00560-17 [PMID: 28584155 DOI: 10.1128/AAC.00560-17]

74 **Lam AM**, Espiritu C, Vogel R, Ren S, Lau V, Kelly M, Kuduk SD, Hartman GD, Flores OA, Klumpp K. Preclinical Characterization of NVR 3-778, a First-in-Class Capsid Assembly Modulator against Hepatitis B Virus. *Antimicrob Agents Chemother* 2019; **63**: e01734-18 [PMID: 30373799 DOI: 10.1128/AAC.01734-18]

75 **Klumpp K**, Shimada T, Allweiss L, Volz T, Lütgehetmann M, Hartman G, Flores OA, Lam AM, Dandri M. Efficacy of NVR 3-778, Alone and In Combination With Pegylated Interferon, *vs* Entecavir In uPA/SCID Mice With Humanized Livers and HBV Infection. *Gastroenterology* 2018; **154**: 652-662 [PMID: 29079518 DOI: 10.1053/j.gastro.2017.10.017]

76 **Zoulim F**, Lenz O, Vandenbossche JJ, Talloen W, Verbinnen T, Moscalu I, Streinu-Cercel A, Bourgeois S, Buti M, Crespo J, Manuel Pascasio J, Sarrazin C, Vanwolleghem T, Shukla U, Fry J, Yogaratnam JZ. JNJ-56136379, an HBV Capsid Assembly Modulator, Is Well-Tolerated and Has Antiviral Activity in a Phase 1 Study of Patients With Chronic Infection. *Gastroenterology* 2020; **159**: 521-533 [PMID: 32343960 DOI: 10.1053/j.gastro.2020.04.036]

77 **Yuen MF**, Agarwal K, Gane EJ, Schwabe C, Ahn SH, Kim DJ, Lim YS, Cheng W, Sievert W, Visvanathan K, Ruby E, Liaw S, Yan R, Huang Q, Colonno R, Lopatin U. Safety, pharmacokinetics, and antiviral effects of ABI-H0731, a hepatitis B virus core inhibitor: a randomised, placebo-controlled phase 1 trial. *Lancet Gastroenterol Hepatol* 2020; **5**: 152-166 [PMID: 31711752 DOI: 10.1016/S2468-1253(19)30346-2]

78 **Yuen MF**, Gane EJ, Kim DJ, Weilert F, Yuen Chan HL, Lalezari J, Hwang SG, Nguyen T, Flores O, Hartman G, Liaw S, Lenz O, Kakuda TN, Talloen W, Schwabe C, Klumpp K, Brown N. Antiviral Activity, Safety, and Pharmacokinetics of Capsid Assembly Modulator NVR 3-778 in Patients with Chronic HBV Infection. *Gastroenterology* 2019; **156**: 1392-1403 [PMID: 30625297 DOI: 10.1053/j.gastro.2018.12.023]

79 **Gish RG**, Yuen MF, Chan HL, Given BD, Lai CL, Locarnini SA, Lau JY, Wooddell CI, Schluep T, Lewis DL. Synthetic RNAi triggers and their use in chronic hepatitis B therapies with curative intent. *Antiviral Res* 2015; **121**: 97-108 [PMID: 26129970 DOI: 10.1016/j.antiviral.2015.06.019]

80 **van den Berg F**, Limani SW, Mnyandu N, Maepa MB, Ely A, Arbuthnot P. Advances with RNAi-Based Therapy for Hepatitis B Virus Infection. *Viruses* 2020; **12**: 851 [PMID: 32759756 DOI: 10.3390/v12080851]

81 **Billioud G**, Kruse RL, Carrillo M, Whitten-Bauer C, Gao D, Kim A, Chen L, McCaleb ML, Crosby JR, Hamatake R, Hong Z, Garaigorta U, Swayze E, Bissig KD, Wieland S. In vivo reduction of hepatitis B virus antigenemia and viremia by antisense oligonucleotides. *J Hepatol* 2016; **64**: 781-789 [PMID: 26658683 DOI: 10.1016/j.jhep.2015.11.032]

82 **Schluep T**, Lickliter J, Hamilton J, Lewis DL, Lai CL, Lau JY, Locarnini SA, Gish RG, Given BD. Safety, Tolerability, and Pharmacokinetics of ARC-520 Injection, an RNA Interference-Based Therapeutic for the Treatment of Chronic Hepatitis B Virus Infection, in Healthy Volunteers. *Clin Pharmacol Drug Dev* 2017; **6**: 350-362 [PMID: 27739230 DOI: 10.1002/cpdd.318]

83 **Wooddell CI**, Yuen MF, Chan HL, Gish RG, Locarnini SA, Chavez D, Ferrari C, Given BD, Hamilton J, Kanner SB, Lai CL, Lau JYN, Schluep T, Xu Z, Lanford RE, Lewis DL. RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg. *Sci Transl Med* 2017; **9** [PMID: 28954926 DOI: 10.1126/scitranslmed.aan0241]

84 **Yuen MF**, Schiefke I, Yoon JH, Ahn SH, Heo J, Kim JH, Lik Yuen Chan H, Yoon KT, Klinker H, Manns M, Petersen J, Schluep T, Hamilton J, Given BD, Ferrari C, Lai CL, Locarnini SA, Gish RG. RNA Interference Therapy With ARC-520 Results in Prolonged Hepatitis B Surface Antigen Response in Patients With Chronic Hepatitis B Infection. *Hepatology* 2020; **72**: 19-31 [PMID: 31654573 DOI: 10.1002/hep.31008]

85 **Han K**, Cremer J, Elston R, Oliver S, Baptiste-Brown S, Chen S, Gardiner D, Davies M, Saunders J, Hamatake R, Losos J, Leivers M, Hood S, van der Berg F, Paff M, Ritter JM, Theodore D. A Randomized, Double-Blind, Placebo-Controlled, First-Time-in-Human Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of GSK3389404 in Healthy Subjects. *Clin Pharmacol Drug Dev* 2019; **8**: 790-801 [PMID: 30861337 DOI: 10.1002/cpdd.670]

86 **Mueller H**, Wildum S, Luangsay S, Walther J, Lopez A, Tropberger P, Ottaviani G, Lu W, Parrott NJ, Zhang JD, Schmucki R, Racek T, Hoflack JC, Kueng E, Point F, Zhou X, Steiner G, Lütgehetmann M, Rapp G, Volz T, Dandri M, Yang S, Young JAT, Javanbakht H. A novel orally available small molecule that inhibits hepatitis B virus expression. *J Hepatol* 2018; **68**: 412-420 [PMID: 29079285 DOI: 10.1016/j.jhep.2017.10.014]

87 **Menne S**, Wildum S, Steiner G, Suresh M, Korolowicz K, Balarezo M, Yon C, Murreddu M, Hong X, Kallakury BV, Tucker R, Yang S, Young JAT, Javanbakht H. Efficacy of an Inhibitor of Hepatitis B Virus Expression in Combination With Entecavir and Interferon-α in Woodchucks Chronically Infected With Woodchuck Hepatitis Virus. *Hepatol Commun* 2020; **4**: 916-931 [PMID: 32490326 DOI: 10.1002/hep4.1502]

88 **Al-Mahtab M**, Bazinet M, Vaillant A. Safety and Efficacy of Nucleic Acid Polymers in Monotherapy and Combined with Immunotherapy in Treatment-Naive Bangladeshi Patients with HBeAg+ Chronic

Hepatitis B Infection. *PLoS One* 2016; **11**: e0156667 [PMID: 27257978 DOI: 10.1371/journal.pone.0156667]

89 **Bazinet M**, Pântea V, Cebotarescu V, Cojuhari L, Jimbei P, Albrecht J, Schmid P, Le Gal F, Gordien E, Krawczyk A, Mijočević H, Karimzadeh H, Roggendorf M, Vaillant A. Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial. *Lancet Gastroenterol Hepatol* 2017; **2**: 877-889 [PMID: 28964701 DOI: 10.1016/S2468-1253(17)30288-1]

90 **Bazinet M**, Pântea V, Placinta G, Moscalu I, Cebotarescu V, Cojuhari L, Jimbei P, Iarovoi L, Smesnoi V, Musteata T, Jucov A, Dittmer U, Krawczyk A, Vaillant A. Safety and Efficacy of 48 Weeks REP 2139 or REP 2165, Tenofovir Disoproxil, and Pegylated Interferon Alfa-2a in Patients With Chronic HBV Infection Naïve to Nucleos(t)ide Therapy. *Gastroenterology* 2020; **158**: 2180-2194 [PMID: 32147484 DOI: 10.1053/j.gastro.2020.02.058]

91 **Van Hees S**, Chi H, Hansen B, Bourgeois S, Van Vlierberghe H, Sersté T, Francque S, Wong D, Sprengers D, Moreno C, Nevens F, Janssen H, Vanwolleghem T. Caucasian Ethnicity, but Not Treatment Cessation is Associated with HBsAg Loss Following Nucleos(t)ide Analogue-Induced HBeAg Seroconversion. *Viruses* 2019; **11**: 687 [PMID: 31357522 DOI: 10.3390/v11080687]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 73-81

DOI: 10.5501/wjv.v11.i1.73

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Observational Study

Rethinking hospital psychiatry in Italy in light of COVID-19 experience

Marco P Piccinelli, Paola Bortolaso, Greg D Wilkinson

ORCID number: Marco P Piccinelli 0000-0002-6668-1887; Paola Bortolaso 0000-0001-8681-0415; Greg D Wilkinson 0000-0002-9635-7770.

Author contributions: Marco P Piccinelli and Paola Bortolaso designed the study, performed acquisition, analysis and interpretation of the data, and drafted the initial manuscript; Greg Wilkinson revised the article critically for important intellectual content and edited the manuscript.

Institutional review board statement: The paper did not require Institutional Review Board Approval.

Institutional animal care and use committee statement: Not applicable.

Clinical trial registration statement: Not applicable.

Informed consent statement: Data included in the paper were collected as part of routine clinical practice not requiring ethical approval, with patients giving their written informed consent at data collection at the time of hospital admission.

Conflict-of-interest statement: All authors confirm that there are no financial or personal relationships

Marco P Piccinelli, Paola Bortolaso, Psychiatric Unit Verbano, Department of Mental Health and Substance Abuse, Cittiglio 21033, Varese, Italy

Greg D Wilkinson, Liverpool University Hospitals NHS Trust, Liverpool University, Liverpool 2170, United Kingdom

Corresponding author: Marco P Piccinelli, MD, MPhil, PhD, Psychiatric Unit Verbano, Department of Mental Health and Substance Abuse, Via Marconi 40, Cittiglio 21033, Varese, Italy. marcopiero.piccinelli@asst-settelaghi.it

Abstract

BACKGROUND

Italy retains a distinctive organization of mental health services according to a community-based model of care with a multidisciplinary team serving a well-defined catchment area under the coordination of the local department of mental health. The coronavirus disease 2019 (COVID-19) pandemic is forcing Italian mental health services to develop new organizational strategies at all levels of care in order to face the associated challenges.

AIM

To explore factors associated with changes in psychiatric admissions to an inpatient psychiatric unit located in Lombardia Region, Italy.

METHODS

All hospital admissions (n = 44) were recorded to an inpatient psychiatric unit during a three month national lockdown in Italy in 2020 and compared with those occurring over the same time period in 2019 (n = 71). For each admission, a 20-item checklist was completed to identify factors leading to admission. Statistical analyses were performed using Statistical Package for Social Sciences for Windows, release 11.0. Chi-square test (or Fisher's exact test) and Mann-Whitney U-test were applied, where appropriate.

RESULTS

Hospital admissions dropped by 38% during the COVID-19 pandemic. No significant differences were found in demographics, clinical variables associated with hospital admissions and length of stay between 2019 and 2020. Compared with 2019, a significantly greater proportion of hospital admissions in 2020 were related to difficulties in organizing care programs outside the hospital (chi-square

with any people or organizations that could inappropriately influence the actions of any author of this manuscript.

Data sharing statement: No additional data are available.

STROBE statement: All authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Italy

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 11, 2021
Peer-review started: March 11, 2021
First decision: July 15, 2021
Revised: August 13, 2021
Accepted: January 3, 2022
Article in press: January 6, 2022
Published online: January 25, 2022

P-Reviewer: Choudhery MS, Nakaji K
S-Editor: Wang LL
L-Editor: A

= 4.91, df 1, one-way P = 0.035) and in patients' family contexts (chi-square = 3.71, df 1, one-way P = 0.049). On the other hand, logistic and communication difficulties pertaining to residential facilities and programs were significantly more common in 2019 than in 2020 (chi-square = 4.38, df 1, one-way P = 0.032).

CONCLUSION
Admissions to the inpatient psychiatric unit dropped significantly during the COVID-19 pandemic in 2020, with difficulties in organizing care programs outside the hospital and in patients' family contexts occurring more frequently compared with 2019.

Key Words: Mental health services; COVID-19; Italy; Psychiatric; Pandemic

Core Tip: During the coronavirus disease 2019 pandemic mental health services in Italy developed new organizational strategies in order to face the associated challenges. Compared with 2019, hospital admissions dropped significantly and were more frequently related to restrictions posed by the pandemic, like difficulties in organizing care programs outside the hospital and in patients' family context. On the other hand, logistic and communication difficulties pertaining to residential facilities and programs were significantly more common in 2019 than in 2020, due to the reorganization of residential facilities as close communities looking after their own patients with little reliance on hospital during the pandemic.

Citation: Piccinelli MP, Bortolaso P, Wilkinson GD. Rethinking hospital psychiatry in Italy in light of COVID-19 experience. *World J Virol* 2022; 11(1): 73-81
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/73.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.73

INTRODUCTION

The present organization of mental health care in Italy stems from a reform law dating back to 1978. On the assumption that individuals with mental disorder should be offered the same treatment standards as those suffering from other types of illness, a gradual dismantling of old mental hospitals occurred alongside the setting up of new community-based services within the framework of local departments of mental health, each promoting and coordinating mental health prevention, care and rehabilitation in a defined catchment area. Although the Italian experience has attracted international attention and promoted similar changes abroad, it has retained distinctiveness. In comparison with the countries belonging to the Group of 7 (G7) more advanced economies, Italy has lower population rates of mental health professionals and of beds for acute psychiatric care in general hospitals; as opposed to higher rates of beds in residential facilities devoted to rehabilitation and daily support programs[1, 2].

Among the services which are part of departments of mental health, inpatient psychiatric units are located in general hospitals with an emergency department and provide crisis interventions on a short-term basis, with patients being referred back to outpatient care or other types of interventions as soon as possible. Most admissions take place on a voluntary basis and only a minority are compulsory. According to the national mental health information system, mental health service utilization varies considerably across Italian regions[2]. This is due to the substantial autonomy that each region retains in organization of health care within its territory, according to the general principles and recommendations set out by the national government. Moreover, psychiatric admissions were found to be influenced by a wide array of different factors, such as demographics, illness and treatment variables, mental health service organisation and practice, interaction between inpatient psychiatric units and other health services and/or social agencies, and the role of patients' families, leading to significant variation in pathways to care, typologies of admissions, length of

P-Editor: Wang LL

hospital stay and the care process itself[3-6].

The coronavirus disease 2019 (COVID-19) pandemic is posing huge challenges to the health care system in general, as well as mental health services, driving the implementation of novel strategies and interventions. However, accounts of changes in mental health service organization and activities in Italy during the pandemic have been mainly narrative, indicating the need for a quantitative approach to the effects of COVID-19 pandemic[7].

The aim of this study was to explore changes in number of psychiatric admissions to an inpatient psychiatric unit located in the Italian region most severely affected by the first peak of COVID-19 pandemic in 2020, and to identify relevant factors associated with the detected changes in comparison with the same time period of 2019.

MATERIALS AND METHODS

Study design

All admissions were recorded to a locked, inpatient psychiatric unit within a general hospital in Cittiglio, a small town located in Lombardia Region, North-western Italy, between February 24th and May 24th, 2020 and compared with those occurring over the same time period in 2019.

Although relatively short, the study interval was chosen because it corresponded to a strict lockdown imposed on the country, which marked a definite and profound difference compared to the previous period. Indeed, a Legislative Decree signed by the Italian Prime Minister on February 23rd, 2020, ordered that: people were not allowed to leave home except for work, health needs or urgent reasons; remote working was promoted whenever possible; commercial activities were suspended unless they supplied essential goods or basic necessities; all types of schools were shut down and distance learning education was offered to students; access to public places and social settings favoring crowding and close contacts among individuals was forbidden, including, among the others, pubs, restaurants, cinemas, theatres, museums, concert halls, public gardens, cultural places, swimming pools, fitness centers, gyms; public events of any type were cancelled and civil and religious ceremonies were strictly limited; access of patients' relatives and caregivers to health services and residential facilities was discouraged or forbidden. A subsequent Legislative Decree on May 13th, 2020, allowed a gradual lessening of the strict limitations listed above, which became noticeable by May 24th.

From the very beginning, mental health services continued to pursue their activities as part of essential health care and reimbursement of their interventions was left unchanged. However, at the outset of the pandemic inpatient units reduced their usual number of beds to pursue isolation requirements and interpersonal distancing and to devote staff to treatment of individuals suffering from COVID-19 illness and its complications. Moreover, psychiatric contacts with the emergency department and hospital admissions were discouraged and limited to urgent cases which could not receive adequate treatment outside the hospital and whose admission could not be postponed.

Data included in the paper were collected as part of routine clinical practice not requiring ethical approval, with patients giving their written informed consent at data collection at the time of hospital admission.

For patients admitted to the inpatient unit a 20-item checklist was completed to identify relevant factors leading to admission and including: (1) Clinical variables (illness severity; difficulties in instigating treatment; diagnostic difficulties; co-morbid physical illness); (2) Negative factors affecting quality of care during hospital stay (insufficient patient's evaluation; negative doctor-patient relationship; defensive psychiatry); (3) Difficulties in the care process (unclear reason for admission; insufficient communication between the inpatient unit and the outpatient clinic; difficulties in planning care programs outside the hospital); (4) Logistic variables within the hospital (delay in specialist consultations or diagnostic tests; organizational problems); (5) Logistic and communication difficulties between the mental health department and other agencies (social agencies, rehabilitation facilities, elderly care facilities, legal system); (6) Variables related to the patients' family context (objective difficulties in the family; insufficient or negative relationship between the mental health staff and family members); (7) Legal acts; and (8) Exceptional personal, familial or social events.

Up to mid-April, patients were admitted to the inpatient unit provided that they had no temperature or other COVID-related symptoms, but did not perform a COVID test; from mid-April onwards patients were tested on a COVID test at the emergency

department and only those negative were admitted to the inpatient unit.

Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, release 11.0[8].

Chi-square test (or Fisher's exact test) and Mann-Whitney U-test were applied, where appropriate, to investigate differences between admissions in 2019 and those in 2020 according to sex, age, diagnosis (grouping ICD-10 diagnoses into four categories: schizophrenia and related psychoses; affective disorders; personality disorders; other diagnoses, mainly including substance use disorders or organic conditions), type of admission (voluntary *vs* compulsory), occurrence of mechanical restraints, length of stay, and reasons for admission.

RESULTS

Hospital admissions dropped by 38% during the pandemic, being 44 in 2020 as opposed to 71 during the corresponding period of 2019.

In 2020, admissions by males were 28 and accounted for 63.6% of the sample. Median age (and interquartile range) of admitted patients was 38.5 (29.25-54.75) years. Diagnoses of schizophrenia and related psychoses, affective disorder and personality disorder were evenly distributed in the sample and overall accounted for 82% of the total. Ten (22.7%) individuals reported substance abuse and 8 (18.2%) carried suicidal risk. Only one (2.3%) patient underwent compulsory admission and 4 (9.1%) were restrained to bed. No significant differences were found on the demographic and clinical variables mentioned above according to study year.

In 2020, length of stay ranged between one and 34 d, with a median (and interquartile range) of 10 (4.25-17) d, and did not differ significantly compared to 2019. The effect of diagnosis on length of stay was explored among patients residing in the service catchment area, since they completed their hospitalization at the inpatient unit under study, whereas non-resident patients were transferred to their local psychiatric services within a few days after admission. A significant difference in length of stay was found according to diagnosis (Kruskall-Wallis Chi-square = 19.88; d.f. 3, $P < 0.0001$), with shorter admissions for personality disorder compared with other diagnoses. However, diagnoses accounted for only approximately 6% of the variance in length of stay.

In 2020, no non-resident patients were under compulsory admission or restraint; whereas in 2019, 29.6% of non-resident patients as opposed to 6.8% of resident ones were so restrained, and the difference was statistically significant (Chi-square = 6.65; d.f. 1; $P = 0.01$). A higher percentage of non-resident patients in 2019 were under compulsory admission, but the difference was not statistically significant.

The Table 1 shows the factors associated with hospital admission, derived from the 20-item checklist mentioned above and ranked according to frequency in 2020. Illness severity was far more common, being rated in about two-thirds of patients, and was followed by other clinical factors such as difficulties in instigating treatment and presence of organic co-morbidity, each occurring in 20.5% of hospital admissions. Among non-clinical factors, impaired relationship with patients' family members (20.5%) and difficulties in planning care programs outside the hospital (11.4%) were more common. Illness severity was significantly more common among the factors associated with hospital admission in 2019 compared to 2020, whereas difficulties in planning care outside the hospital occurred more frequently in 2020.

Overall, in 2020 sole clinical factors were reported in 28 (63.6%) of hospital admissions, sole non-clinical factors (*i.e.*, logistic, communication and family factors) in 8 (18.2%), with a combination of the two in the remaining 8 admissions (18.2%). No significant difference was found compared to 2019.

For further analyses, reasons associated with hospital admission were grouped into five broad categories. Findings were in the expected direction. No significant differences were found between 2019 and 2020 in clinical factors and in the care process. Compared to 2019, during the pandemic a significantly greater proportion of hospital admissions were related to difficulties in organizing care programs outside the hospital (chi-square = 4.91, df 1, one-way $P = 0.035$) and in patients' family contexts (chi-square = 3.71, df 1, one-way $P = 0.049$). On the other hand, logistic and communication difficulties pertaining to residential facilities and programs were significantly more common in 2019 than in 2020 (chi-square = 4.38, df 1, one-way $P = 0.032$).

Table 1 Factors associated with hospital admission, derived from the 20-item checklist described in the study design and ranked according to frequency in the year 2020, *n* (%)

	2019		2020		
Reasons	**No**	**Yes**	**No**	**Yes**	***P* value**
Illness severity	12 (16.9)	59 (83.1)	16 (36.4)	28 (63.6)	0.02
Difficulties in instigating treatment	64 (90.1)	7 (9.9)	35 (79.5)	9 (20.5)	0.11
Organic co-morbidity	64 (90.1)	7 (9.9)	35 (79.5)	9 (20.5)	0.11
Negative relationship with patients' relatives	64 (90.1)	7 (9.9)	35 (79.5)	9 (20.5)	0.11
Difficulties in planning care outside the hospital	70 (98.6)	1 (1.4)	39 (88.6)	5 (11.4)	0.02
Insufficient relationship with social agencies	70 (98.6)	1 (1.4)	41 (93.2)	3 (6.8)	0.12
Objective difficulties in the family system	70 (98.6)	1 (1.4)	42 (95.5)	2 (4.5)	0.31
Insufficient relationship with elderly care facilities	69 (97.2)	2 (2.8)	43 (97.7)	1 (2.3)	0.86
Unclear reason for admission	69 (97.2)	2 (2.8)	43 (97.7)	1 (2.3)	0.86
Insufficient communication with outpatient clinic	70 (98.6)	1 (1.4)	43 (97.7)	1 (2.3)	0.73
Negative doctor-patient relationship	70 (98.6)	1 (1.4)	43 (97.7)	1 (2.3)	0.73
Legal acts	71 (100.0)	0 (0.0)	43 (97.7)	1 (2.3)	0.20
Insufficient relationship with rehabilitation facilities	66 (93.0)	5 (7.0%)	44 (100.0)	0 (0.0)	0.07
Insufficient relationship with legal system	68 (95.8)	3 (4.2)	44 (100.0)	0 (0.0)	0.17
Diagnostic difficulties	70 (98.6)	1 (1.4)	44 (100.0)	0 (0.0)	0.43
Insufficient patient's evaluation	70 (98.6)	1 (1.4)	44 (100.0)	0 (0.0)	0.43

Four items out of 20 (defensive psychiatry; delay in specialist consultations and diagnostic tests; hospital organizational problems; exceptional personal, familial and social events) were null in both 2019 and 2020. More than one factor might be operating on each admission.

DISCUSSION

During the first peak of COVID-19 pandemic, hospital admissions dropped by 38% compared to the previous year. This was the result of strict selection criteria limiting hospital admissions to urgent cases with no alternative options as well as of new organizational strategies involving all levels of mental health care, that were quickly implemented under the coordination of the local department of mental health. Specifically, the outpatient clinic serving the same area of the inpatient unit under study increased contacts with patients combining face-to-face and domiciliary visits with remote consultations: overall contacts were 2727 in 2020 *vs* 2495 in 2019 (+9.3%), with greater increases in contacts by psychiatric rehabilitation professionals (+267.7%), social workers (+117.7%) and nurses (+44.2%). Increased emotional support was also provided to patients' family members and contacts doubled during the pandemic. At the same time, residential facilities were organized as close communities, looking after their own patients with little reliance on the hospital. Indeed, during the pandemic hospital admissions due to difficulties pertaining to residential facilities and programs were found to be significantly lower compared with the previous year.

In other words, team working acquired special relevance in order both to provide emotional support to patients and to cater to their practical needs. The team also ensured a first-line support to health professionals, allowing them to express fears, uncertainties and emotional discomfort, to receive mutual support and devise new interventions in patients' interest, where psychiatrists and psychologists could rely on the indispensable help by those health providers working closer to patients, like nurses, social workers or psychiatric rehabilitation professionals. Remote consultations offered a sort of presence in the absence, but introduced a radically new way of working, with a change from a physical to a digital kind of space, a variation in the subjective experience of the time spent during consultations and difficulties of

different nature (*e.g.*, distraction on behalf of the patient and/or the therapist; external and disturbing factors; greater tiredness during on-line consultations; dehumanization)[9-11].

A reduction in admission rates was reported by other inpatient services across Italy as a consequence of fear of hospitals, seen as potential sites of contagion, and a heightening in the severity threshold of psychiatric symptoms leading to hospital admission upon request by patients' family members or referral by treating clinicians. In most mental health services, outpatient contacts tended to decline during the pandemic though, in some services, they were preserved and, in the catchment area of the inpatient unit under study, increased, as a consequence of different choices in the application of restriction criteria and in service activity[12-14]. These findings suggest that the distinctive organization of mental health services in Lombardia Region, each established according to a community-based model of care with a multidisciplinary team serving a well-defined catchment area under the coordination of the local department of mental health, had the potential: (1) To face and overcome the limitations imposed by the pandemic by changing allocation of human resources and remodeling interventions in order to meet patients' new and different needs; and (2) To implement a shared recommendation that all patients, and especially so those with severe mental disorder, were not left alone and forgotten during the COVID-19 crisis and received regular assessment, emotional support and treatment (*e.g.*, long-acting antipsychotics) by telephone consultations, face-to-face interviews or, in selected cases, domiciliary visits[15,16].

During the pandemic non-resident patients, who were transferred for hospital admission, were likely to be less severely ill and did not require compulsory interventions or restraint. This was probably due to the fact that the Police members were more involved in other tasks of public order during the pandemic and could not provide routine support to health personnel on patients' transfer. Data on admissions in 2019 under standard care showed that non-resident patients were more likely to be restrained, pointing to a delicate ethical issue. In order to promote an efficient use of health resources, Lombardia Region does not pose any limitation on patients' referral to inpatient units other than the local facility, challenging the longstanding practice of a well-defined catchment area pertaining to each department of mental health. However, the lack of reciprocal enduring knowledge by both patients and the health staff-continuity of care-is likely to affect negatively the quality of care and a consequence may be the increased risk for non-resident patients to be restrained at the outset of their hospital admissions.

Although a strong emphasis was placed on trying to shorten hospital admissions during the pandemic in order to ensure ongoing bed availability, avoid patients' transfer and keep interpersonal distancing during hospital stay, no significant difference was found compared to care under standard conditions in 2019. Length of stay varied widely and meaningful variations occurred within each diagnostic group, though individuals with personality disorders tended to have shorter admissions. About one-third of admissions lasted longer than the threshold of 14 d recommended by local health authorities on the basis of regional standards and reimbursement considerations.

These observations suggest that about one-third of patients need longer time periods to achieve clinical improvement and be discharged from hospital, in keeping with the reported limited clinical effectiveness of short hospital admissions that was suggested in patients with severe mental disorders[17] and undermining claims of systematic early onset of action of psychotropics, namely antidepressants and antipsychotics[18-20]. As a result, prediction of resource use in hospital psychiatry can hardly rely on diagnosis and the derived diagnosis-related groups (DRGs), which are inaccurate and explain a very limited proportion of variance in psychiatric length of stay. For this reason, prognosis, rather than diagnosis, has been suggested to provide a better estimate of prospective reimbursement for psychiatry[21-23]. Indeed, among prognostic factors, illness severity was found to be the main reason for psychiatric admissions lasting longer than two weeks, irrespective of diagnosis, which no longer retained any statistically significant effect[6]. Other factors, like those listed in the present paper and related to the care process, logistic and communication aspects of the institutional network, or the patients' social and familial context, could also prove useful as additional variables alongside illness severity to reach a better prediction of hospital length of stay and associated costs. Indeed, in the present investigation non-clinical factors occurred together with clinical ones in 18% of admissions during pandemic; and, in a further 18% of admissions, were the sole reasons, suggesting their specific relevance, even more because psychiatrists during pandemic were invited to give definite priority to clinical factors in deciding hospital admissions. It follows that

imposing strict limitations in length of stay in order to contain costs contradicts findings from everyday clinical practice and carries the risk of increasing inappropriate discharge of patients and/or exposing to financial risks the inpatient care units treating more severe cases. In order to reach a more accurate prediction of the economic impact of psychiatric admissions it would be useful to move from mere length of stay to consider also severity and complexity of clinical picture as well as other context-related factors.

During the pandemic a significantly greater number of hospital admissions were related to difficulties in organizing care programs outside the hospital and in patients' family contexts. The reduction of community-based interventions, the absence or strong limitations of interpersonal relationship and social experiences and the exacerbation of conflicts within families may be responsible for psychiatric crises and reveal that an effective functioning of the mental health system cannot rely on clinical settings only[24]. In this regard, Pelizza&Pupo[25] brought attention to the crucial role of patients' caring communities, mainly represented by family members and local social agencies, and suggested the actual need of a transition from an institutional context, centered on mental health services, to a so-called post-institutional system, where individuals and communities are connected through a rich and articulated set of social ties and patients' settings are not distant and isolated, but connected to mental health services *via* innovative clinical interventions based on new technologies.

Since the COVID-19 pandemic is not decreasing and continues to provide ever-growing and alarming figures over time, the changes mentioned above are likely to last and might even turn into the usual way of working for mental health professionals to come, with the pandemic marking a definite difference between a before and an after[26]. The essential role assigned to mental health services at the outset of the pandemic according to national guidelines and local protocols and their well-established attitude to deliver comprehensive interventions to individuals with mental disorder, covering subjective well-being, daily living, material needs, and social activities, contributed to support mental health professionals' motivation, energy and creativity in planning and implementing interventions during the pandemic. However, if the current situation is lasting for long, a critical evaluation of mental health service organization and requirements (especially, in terms of personnel and technical equipments for online consultations) is mandatory in order to sustain actual efforts.

Some limitations of this study should be acknowledged. Firstly, data were collected in a single inpatient psychiatric unit and this may reduce generalization of findings. However, gender and diagnostic distributions and age at admission in our sample closely resembled those recorded across other inpatient psychiatric units located in Lombardia Region[27] as well as those detected in a representative national sample of inpatient psychiatric units[28], suggesting that the inpatient unit under study was comparable to similar units operating in Italy.

Moreover, the check-list of factors associated to each hospital admission was filled in by a psychiatrist who was also caring for patients, allowing a detailed recording of all the factors involved, though this might reduce objectivity in the estimate of those factors more related to the care process.

CONCLUSION

In conclusion, the COVID-19 pandemic in 2020 forced a re-organization of mental health service activities at all levels of care. Hospital admissions dropped significantly and were more likely to be related to restrictions posed by the pandemic, like difficulties in organizing care programs outside the hospital and in patients' family contexts.

At the same time, community contacts with both patients and their relatives increased through a combination of face-to-face and domiciliary visits with remote consultations.

Finally, residential facilities turned into close communities looking after their own patients with limited reliance on the hospital.

It follows that an accurate evaluation of the effects of the pandemic on psychiatric admissions (with the associated economic impact) should devote concomitant attention to other treatment settings as well (*i.e.*, outpatient services and residential facilities) and include context-related factors alongside severity and complexity of clinical picture.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic forced a re-organization of mental health services at all levels of care. However, most accounts of changes occurring in Italy during the pandemic have been mainly narrative with little reliance on data.

Research motivation

The present study was based on a quantitative data-driven approach to the effects of COVID-19 pandemic on admissions to an inpatient psychiatric unit in Italy.

Research objectives

To explore changes in number of psychiatric admissions to an inpatient psychiatric unit during the COVID-19 pandemic in 2020 and to identify relevant factors associated with the detected changes in comparison with the same time period of 2019.

Research methods

All admissions were recorded to an inpatient psychiatric unit between February 24 and May 24, 2020 and compared with those occurring over the same time period in 2019. A 20-item checklist was completed to identify relevant factors leading to hospital admission.

Research results

During the COVID-19 pandemic hospital admissions dropped significantly compared to 2019 and were more likely to be related to difficulties in organizing care outside the hospital and in patients' family context. On the other hand, admissions related to logistic and communication difficulties pertaining to residential facilities were more common in 2019, due to the re-organization of these facilities as close communities looking after their own patients during the pandemic.

Research conclusions

Mental health services in general, and hospital psychiatry in particular, were forced to face new and different challenges during the COVID-19 pandemic. The Italian community-based model of care with a multidisciplinary team serving a well-defined catchment area had the potential to ensure a proper and rapid re-organization of mental health service activities.

Research perspectives

Since the COVID-19 pandemic is slowly decreasing and the associated limitations persist, the detected changes are expected to last and turn into the usual way of working. Therefore, an ongoing evaluation of mental health service organization, activities and requirements is mandatory to sustain and improve actual efforts.

REFERENCES

1 **Piccinelli M**, Politi P, Barale F. Focus on psychiatry in Italy. *Br J Psychiatry* 2002; **181**: 538-544 [PMID: 12456535 DOI: 10.1192/bjp.181.6.538]

2 **Barbui C**, Papola D, Saraceno B. Forty years without mental hospitals in Italy. *Int J Ment Health Syst* 2018; **12**: 43 [PMID: 30079100 DOI: 10.1186/s13033-018-0223-1]

3 **de Girolamo G**, Mors O, Rossi G, Grandi L, Ardigo' W, Munk-Jørgensen P. Admission to general hospital psychiatric wards in Italy. 1. A comparison between two catchment areas with differing provision of outpatient care. *Int J Soc Psychiatry* 1988; **34**: 248-257 [PMID: 3266203 DOI: 10.1177/002076408803400402]

4 **de Girolamo G**, Mors O, Grandi L, Ardigo' W, Munk-Jørgensen P. Admission to general hospital psychiatric wards in Italy. 2. Inpatient characteristics. *Int J Soc Psychiatry* 1988; **34**: 258-266 [PMID: 3266204 DOI: 10.1177/002076408803400403]

5 **Volpe U**, Fiorillo A, Luciano M, Del Vecchio V, Palumbo C, Calò S, Piras S, Signorelli M, Filippo D, Piselli M, De Fazio P, Gotelli S, Bardicchia F, Cerveri G, Ferrari S, Mulè A, Ribolsi M, Sampogna G, De Rosa C, Sartorius N. Pathways to mental health care in Italy: results from a multicenter study. *Int J Soc Psychiatry* 2014; **60**: 508-513 [PMID: 24051155 DOI: 10.1177/0020764013501648]

6 **Piccinelli M**, Bortolaso P, Bolla E, Cioffi I. Typologies of psychiatric admissions and length of inpatient stay in Italy. *Int J Psychiatry ClinPract* 2016; **20**: 116-120 [PMID: 27049814 DOI: 10.3109/13651501.2016.1166514]

7 **Pelizza L**, Pupo S. COVID-19 epidemic and public mental health care in Italy: ethical considerations. *Soc Psychiatry PsychiatrEpidemiol* 2020; **55**: 1093-1094 [PMID: 32623481 DOI: 10.1007/s00127-020-01907-8]

8 **Statistical Package for Social Sciences for Windows (SPSS)**. Release 11.0 for Windows 2001; Chicago, IL, USA

9 **Inglese M**. Making group among professionals in the care settings [Far gruppo tra professionisti nei luoghi di cura]. *Animazione Sociale* 2020; **340**: 39-49

10 **Fioravanzo RE**. The words in the physical space and in the digital time [Le parole nello spazio fisico e nel tempo digitale]. Tecniche delle Conversazioni. Il Trauma, l'Oggetto, la Parola, 2020; 2: 69-72 [DOI: 10.4399/978882553664510]

11 **Lai G**. Inventory of advantages or disadvantages of online therapies compared with face-to-face therapies [Inventario dei vantaggi oppure svantaggi delle terapie online rispetto alle terapie in presenza]. Tecniche delle Conversazioni. Il Trauma, l'Oggetto, la Parola, 2020; 2: 73-77 [DOI: 10.4399/978882553664511]

12 **Aragona M**, Barbato A, Cavani A, Costanzo G, Mirisola C. Negative impacts of COVID-19 Lockdown on mental health service access and follow-up adherence for immigrants and individuals in socio-economic difficulties. *Public Health* 2020; **186**: 52-56 [PMID: 32771661 DOI: 10.1016/j.puhe.2020.06.055]

13 **Clerici M**, Durbano F, Spinogatti F, Vita A, de Girolamo G, Micciolo R. Psychiatric hospitalization rates in Italy before and during COVID-19: did they change? *Ir J Psychol Med* 2020; **37**: 283-290 [PMID: 32368994 DOI: 10.1017/ipm.2020.29]

14 **Castelpietra G**, Colli C, Tossut D, Furlan M, Balestrieri M, Starace F, Beghi M, Barbone F, Perulli A, Salvador-Carulla L. The impact of Covid-19 pandemic on community-oriented mental health services: The experience of Friuli Venezia Giulia region, Italy. *Health Policy Technol* 2021; **10**: 143-150 [PMID: 33520636 DOI: 10.1016/j.hlpt.2020.12.002]

15 **Aamir A**, Awan S, de Filippis R, Diwan MN, Ullah I. Effect of COVID-19 on Mental Health Rehabilitation Centers. *J PsychosocRehabilMent Health* 2020; 1-4 [PMID: 33106766 DOI: 10.1007/s40737-020-00203-7]

16 **Chaturvedi SK**. Covid-19, Coronavirus and Mental Health Rehabilitation at Times of Crisis. *JPsychosocRehabilMent Health* 2020; 1-2 [PMID: 32292688 DOI: 10.1007/s40737-020-00162-z]

17 **Barbato A**, Parabiaghi A, Panicali F, Battino N, D'Avanzo B, de Girolamo G, Rucci P, Santone G; Progres-Acute Group. Do patients improve after short psychiatric admission? *Nord J Psychiatry* 2011; **65**: 251-258 [PMID: 21062122 DOI: 10.3109/08039488.2010.533387]

18 **Agid O**, Kapur S, Arenovich T, Zipursky RB. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch Gen Psychiatry* 2003; **60**: 1228-1235 [PMID: 14662555 DOI: 10.1001/archpsyc.60.12.1228]

19 **Agid O**, Seeman P, Kapur S. The "delayed onset" of antipsychotic action--an idea whose time has come and gone. *J Psychiatry Neurosci* 2006; **31**: 93-100 [PMID: 16575424]

20 **Lam RW**. Onset, time course and trajectories of improvement with antidepressants. *EurNeuropsychopharmacol* 2012; **22** Suppl 3: S492-S498 [PMID: 22959114 DOI: 10.1016/j.euroneuro.2012.07.005]

21 **Taube C**, Lee ES, Forthofer RN. DRGs in psychiatry.An empirical evaluation. *Med Care* 1984; **22**: 597-610 [PMID: 6431204 DOI: 10.1097/00005650-198407000-00002]

22 **de Figueiredo JM**, Boerstler H. DRGs and reimbursement for inpatient psychiatry. *Compr Psychiatry* 1985; **26**: 567-572 [PMID: 3933901 DOI: 10.1016/0010-440x(85)90024-0]

23 **English JT**, Sharfstein SS, Scherl DJ, Astrachan B, Muszynski IL. Diagnosis-related groups and general hospital psychiatry: the APA Study. *Am J Psychiatry* 1986; **143**: 131-139 [PMID: 3080906 DOI: 10.1176/ajp.143.2.131]

24 **Mezzina R**, Sashidharan SP, Rosen A, Killaspy H, Saraceno B. Mental health at the age of coronavirus: time for change. *Soc Psychiatry PsychiatrEpidemiol* 2020; **55**: 965-968 [PMID: 32472197 DOI: 10.1007/s00127-020-01886-w]

25 **Pelizza L**, Pupo S. Future psychiatric services in Italy: lesson from the COVID-19 pandemic. *Acta Biomed* 2020; **91**: e2020011 [PMID: 32921709 DOI: 10.23750/abm.v91i3.10170]

26 **Arnone D**. Mental health services in the wake of COVID-19 and opportunities for change. *Br J Psychiatry* 2020; **217**: 726 [PMID: 33250066 DOI: 10.1192/bjp.2020.170]

27 **Lora A (editor) Il sistema di Salute Mentale di Regione Lombardia**. Regione Lombardia Sanità, 2006

28 **Preti A**, Rucci P, Gigantesco A, Santone G, Picardi A, Miglio R, de Girolamo G; PROGRES-Acute Group. Patterns of care in patients discharged from acute psychiatric inpatient facilities: a national survey in Italy. *Soc Psychiatry PsychiatrEpidemiol* 2009; **44**: 767-776 [PMID: 19212696 DOI: 10.1007/s00127-009-0498-2]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 82-84

DOI: 10.5501/wjv.v11.i1.82

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Repurposing the antioxidant and anti-inflammatory agent N-acetyl cysteine for treating COVID-19

Josef Finsterer, Fulvio A Scorza, Carla A Scorza, Ana C Fiorini

ORCID number: Josef Finsterer 0000-0003-2839-7305; Fulvio A Scorza 0000-0002-0694-8674; Carla A Scorza 0000-0001-7810-4748; Ana C Fiorini 0000-0003-2989-2308.

Author contributions: Finsterer J contributed to design, first draft, literature search, discussion, final approval; Scorza FA, Scorza CA, and Fiorini AC contributed to the literature search, discussion, final approval.

Conflict-of-interest statement: None of the authors have any conflict of interest.

Country/Territory of origin: Austria

Specialty type: Neurosciences

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

Josef Finsterer, Neurological Department, Messerli Institute, Vienna 1180, Austria

Fulvio A Scorza, Carla A Scorza, Ana C Fiorini, Department of Neurology, University of Sao Paolo, Sao Paolo 01000-000, Brazil

Corresponding author: Josef Finsterer, MD, Lecturer, Neurological Department, Messerli Institute, Postfach 20, Vienna 1180, Austria. fifigs1@yahoo.de

Abstract

Although several considerations have been raised suggesting a beneficial effect of N-acetyl cysteine (NAC) for the treatment of severe acute respiratory syndrome coronavirus 2 infection, there is currently no clinical evidence that NAC truly prevents coronavirus disease 2019 (COVID-19), reduces the severity of the disease, or improves the outcome. Appropriately designed clinical trials are warranted to prove or disprove a therapeutic effect of NAC for COVID-19 patients.

Key Words: N-acetyl cysteine; SARS-CoV-2; COVID-19; Reactive oxygen species; Cytokines

Core tip: N-acetyl cysteine (NAC) is a well-known antioxidant and anti-inflammatory agent that has been considered beneficial in the treatment for coronavirus disease 2019 (COVID-19). Although previous studies in patients with chronic lung disease, chronic heart disease, immune-mediated disease, viral infections, and malignancy have shown promising results, there is currently no clinical evidence that NAC prevents COVID-19, alleviates the severity of COVID-19, or improves the overall outcome of COVID-19 patients.

Citation: Finsterer J, Scorza FA, Scorza CA, Fiorini AC. Repurposing the antioxidant and anti-inflammatory agent N-acetyl cysteine for treating COVID-19. *World J Virol* 2022; 11(1): 82-84
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/82.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.82

Received: May 24, 2021
Peer-review started: May 24, 2021
First decision: June 17, 2021
Revised: June 23, 2021
Accepted: December 10, 2021
Article in press: December 10, 2021
Published online: January 25, 2022

P-Reviewer: Arumugam VA, Ratajewski M, Tantau AI
S-Editor: Gong ZM
L-Editor: Kerr C
P-Editor: Gong ZM

TO THE EDITOR

With interest, we read the review article by Dominari *et al*[1] about the putative therapeutic effect of N-acetyl cysteine (NAC) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients. The authors raise several arguments in favour of a beneficial effect of NAC for coronavirus disease 2019 (COVID-19), discuss preliminary results about ongoing studies with NAC in COVID-19, and conclude that the results of available trials are not clear. The study is appealing but raises the following comments and concerns.

We do not agree with the notion that NAC is an agent for curing SARS-CoV-2 infections[1]. There are several arguments against the antiviral effect of NAC. First, NAC is primarily an antioxidant and a precursor of reduced glutathione (GSH) that replenishes GSH stores[2]. NAC reduces oxidative stress as it scavenges and neutralises reactive oxidative species, such as OH, HOCl, or RO_2[3]. Thus, NAC is approved as a preventive/therapeutic agent in disorders associated with GSH depletion, as an antidote in paracetamol intoxication, and as a mucolytic agent[2]. Since SARS-CoV-2 infections are associated with oxidative stress, NAC can, at best, reduce oxidative stress and thus reduce secondary effects of the infection[2]. Although NAC additionally has an anti-inflammatory effect by reducing cytokine production *via* blocking of matrix metalloproteinase (MMP)-1, MMP-4, intracellular adhesion molecule 1, nuclear factor B, NF-E2-related factor 2, and tryparedoxin-1b[2], NAC cannot neutralise the virus and cannot reduce the virus load. Thus, NAC may have, at best, a complementary but no curative effect in SARS-CoV-2 infections as all infections are associated with increased oxidative stress and cytokine activation. Second, there are no reports that NAC is capable of reducing viral load, preventing infection, alleviating severity of COVID-19, or reducing mortality. Third, many patients are regularly taking NAC for the treatment of bronchitis, bronchiolitis, pneumonia, asthma, or chronic obstructive pulmonary disease. However, there are no indications that patients regularly taking NAC have a decreased risk of SARS-CoV-2 infection, or that morbidity or mortality of SARS-CoV-2 infection in these patients is lower compared with that in patients not taking NAC. Fourth, NAC did not prevent the presence of SARS-CoV-2 in sputum[4]. Arguments in favour of a promising role of NAC in the management of COVID-19, however, are that it generally enhances immunocompetence[5] and that it inhibits the replication of the influenza virus H5N1 [6]. A potential beneficial effect of NAC for treating COVID-19 may also derive from its capacity to increase glutathione, improve T-cell responses, and modulate inflammation[7-12]. Currently, a protocol for using NAC together with heparin has been developed[13] but no results have yet been published. Since several studies concerning the role of NAC in COVID-19 are under way, final conclusions about its contribution for treating COVID-19 cannot be reliably drawn. Future studies may demonstrate that NAC can reduce replication of SARS-CoV-2. Overall, agents that appear beneficial theoretically need to be thoroughly investigated by appropriately designed clinical trials for their putative beneficial effect. This is particularly the case for anti-COVID-19 agents, as there is strong pressure from healthcare authorities, industry, and the global community to provide a safe and effective cure of this global threat that currently influences all segments of social, economic, scientific, and political life. Effective and safe agents are needed as several drugs that were proposed to be beneficial at the beginning of the pandemic turned out to be harmful or inefficient, such as chloroquine, azithromycin and tocilizumab.

REFERENCES

1 **Dominari A**, Hathaway Iii D, Kapasi A, Paul T, Makkar SS, Castaneda V, Gara S, Singh BM, Agadi K, Butt M, Retnakumar V, Chittajallu S, Taugir R, Sana MK, Kc M, Razzack S, Moallem N, Alvarez A, Talalaev M. Bottom-up analysis of emergent properties of N-acetylcysteine as an adjuvant therapy for COVID-19. *World J Virol* 2021; **10**: 34-52 [PMID: 33816149 DOI: 10.5501/wjv.v10.i2.34]
2 **De Flora S**, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. *FASEB J* 2020; **34**: 13185-13193 [PMID: 32780893 DOI: 10.1096/fj.202001807]
3 **Mohanty RR**, Padhy BM, Das S, Meher BR. Therapeutic potential of N-acetyl cysteine (NAC) in preventing cytokine storm in COVID-19: review of current evidence. *Eur Rev Med Pharmacol Sci* 2021; **25**: 2802-2807 [PMID: 33829465 DOI: 10.26355/eurrev_202103_25442]
4 **Peng J**, Lu Y, Song J, Vallance BA, Jacobson K, Yu HB, Sun Z. Direct Clinical Evidence Recommending the Use of Proteinase K or Dithiothreitol to Pretreat Sputum for Detection of SARS-CoV-2. *Front Med (Lausanne)* 2020; **7**: 549860 [PMID: 33043036 DOI: 10.3389/fmed.2020.549860]

5 **Meletis CD**, Wilkes K. Immune Competence and Minimizing Susceptibility to COVID-19 and Other Immune System Threats. *Altern Ther Health Med* 2020; **26**: 94-99 [PMID: 33245701]

6 **Geiler J**, Michaelis M, Naczk P, Leutz A, Langer K, Doerr HW, Cinatl J Jr. N-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus. *Biochem Pharmacol* 2010; **79**: 413-420 [PMID: 19732754 DOI: 10.1016/j.bcp.2009.08.025]

7 **Radtke KK**, Coles LD, Mishra U, Orchard PJ, Holmay M, Cloyd JC. Interaction of N-acetylcysteine and cysteine in human plasma. *J Pharm Sci* 2012; **101**: 4653-4659 [PMID: 23018672 DOI: 10.1002/jps.23325]

8 **Scheffel MJ**, Scurti G, Wyatt MM, Garrett-Mayer E, Paulos CM, Nishimura MI, Voelkel-Johnson C. N-acetyl cysteine protects anti-melanoma cytotoxic T cells from exhaustion induced by rapid expansion *via* the downmodulation of Foxo1 in an Akt-dependent manner. *Cancer Immunol Immunother* 2018; **67**: 691-702 [PMID: 29396710 DOI: 10.1007/s00262-018-2120-5]

9 **Malorni W**, Rivabene R, Lucia BM, Ferrara R, Mazzone AM, Cauda R, Paganelli R. The role of oxidative imbalance in progression to AIDS: effect of the thiol supplier N-acetylcysteine. *AIDS Res Hum Retroviruses* 1998; **14**: 1589-1596 [PMID: 9840292 DOI: 10.1089/aid.1998.14.1589]

10 **De Rosa SC**, Zaretsky MD, Dubs JG, Roederer M, Anderson M, Green A, Mitra D, Watanabe N, Nakamura H, Tjioe I, Deresinski SC, Moore WA, Ela SW, Parks D, Herzenberg LA. N-acetylcysteine replenishes glutathione in HIV infection. *Eur J Clin Invest* 2000; **30**: 915-929 [PMID: 11029607 DOI: 10.1046/j.1365-2362.2000.00736.x]

11 **Liu Y**, Yao W, Xu J, Qiu Y, Cao F, Li S, Yang S, Yang H, Wu Z, Hou Y. The anti-inflammatory effects of acetaminophen and N-acetylcysteine through suppression of the NLRP3 inflammasome pathway in LPS-challenged piglet mononuclear phagocytes. *Innate Immun* 2015; **21**: 587-597 [PMID: 25575547 DOI: 10.1177/1753425914566205]

12 **Lee SI**, Kang KS. N-acetylcysteine modulates lipopolysaccharide-induced intestinal dysfunction. *Sci Rep* 2019; **9**: 1004 [PMID: 30700808 DOI: 10.1038/s41598-018-37296-x]

13 **Poe FL**, Corn J. N-Acetylcysteine: A potential therapeutic agent for SARS-CoV-2. *Med Hypotheses* 2020; **143**: 109862 [PMID: 32504923 DOI: 10.1016/j.mehy.2020.109862]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 January 25; 11(1): 85-89

DOI: 10.5501/wjv.v11.i1.85

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Role of vitamin D deficiency and comorbidities in COVID-19

Gabriela Gama Freire Alberca, Ricardo Wesley Alberca

ORCID number: Gabriela Gama Freire Alberca 0000-0002-3467-5562; Ricardo Wesley Alberca 0000-0002-3602-3306.

Author contributions: Alberca GGF and Alberca RW contributed equally to this work; Alberca GGF and Alberca RW designed, analyzed the data and wrote the study; all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Supported by RWA holds a fellowship from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), No. 19/02679-7.

Country/Territory of origin: Brazil

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Gabriela Gama Freire Alberca, Department of Microbiology, Institute of Biomedical Sciences-University of São Paulo, São Paulo 04307-100, Brazil

Ricardo Wesley Alberca, Laboratorio de Dermatologia e Imunodeficiencias (LIM-56), Departamento de Dermatologia, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo 04307-100, Brazil

Corresponding author: Ricardo Wesley Alberca, PhD, Academic Research, Research Fellow, Laboratorio de Dermatologia e Imunodeficiencias (LIM-56), Departamento de Dermatologia, Faculdade de Medicina FMUSP, Universidade de São Paulo, 455-Cerqueira César, São Paulo 04307-100, Brazil. ricardowesley@gmail.com

Abstract

Recent manuscripts described the incidence of vitamin D hypovitaminosis in coronavirus disease 2019 (COVID-19) patients. Vitamin D deficiency is also common in patients with comorbidities that are associated with a poor COVID-19 prognosis. In this letter, we review the literature regarding the association of comorbidities, vitamin D deficiency, and COVID-19.

Key Words: COVID-19; SARS-CoV-2; Comorbidities; Vitamin D

Core Tip: Vitamin D deficiency is a worldwide problem, and investigations on the benefits of regulating vitamin D levels and the immune response should be performed. Nevertheless, the association between low levels of vitamin D and coronavirus disease 2019 (COVID-19) needs to be further explored, especially investigations on the immune response to COVID-19 and COVID-19 vaccines in patients with and without comorbidities.

Citation: Alberca GGF, Alberca RW. Role of vitamin D deficiency and comorbidities in COVID-19. *World J Virol* 2022; 11(1): 85-89
URL: https://www.wjgnet.com/2220-3249/full/v11/i1/85.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i1.85

Received: May 26, 2021
Peer-review started: May 26, 2021
First decision: July 31, 2021
Revised: August 1, 2021
Accepted: November 14, 2021
Article in press: November 24, 2021
Published online: January 25, 2022

P-Reviewer: Papadimitriou DT
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

TO THE EDITOR

We read with great interest the article entitled "Association between population vitamin D status and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related serious-critical illness and deaths: An ecological integrative approach" recently published by Papadimitriou *et al*[1] in the *World Journal of Virology*[1]. This manuscript raised important questions and the authors performed an extensive analysis on vitamin D levels and COVID-19 incidence and severity in Europe, and the potential benefits of vitamin D supplementation to enhance the immune response to the SARS-CoV-2[1]. In the light of these results, we humbly want to state a few points for consideration.

Severe coronavirus disease 2019 (COVID-19) patients present a systemic inflammatory response with a coagulation disorder, possibly evolving to death[2]. Several comorbidities have been identified as risk factors for poor disease prognosis, such as old age[3], co-infections[4], obesity and diabetes mellitus[5], severe asthma, alcohol drinking[6], chronic obstructive pulmonary disease[7], chronic liver disease[8], and cancer[9].

Vitamin D deficiency is associated with poor response to respiratory infections[10], and few reports have identified vitamin D deficiency in moderate and severe COVID-19 patients with conflicting results[1,11,12].

Vitamin D receptor is expressed in many immune cells, including monocytes, macrophages, dendritic cells, neutrophils, and lymphocytes[13-15]. Vitamin D increases the antimicrobial activity of monocytes and macrophages[16] and has anti-inflammatory effects due to the induction of T regulatory cells and reduction in the T helper-17 immune response and pro-inflammatory cytokine production[15].

Papadimitriou *et al*[1] performed an important investigation on the association of vitamin D deficiency and COVID-19[1]. Vitamin D levels can be influenced by many factors such as sun exposure, genetics, supplementation, and comorbidities[17-20].

Vitamin D hypovitaminosis is associated with several comorbidities that are also related to poor COVID-19 prognoses such as old age[21], co-infections[18], obesity [22], diabetes mellitus[23], alcohol drinking, and smoking[24-26], uncontrolled asthma, but not controlled asthma, chronic obstructive pulmonary disease[25-28], cancer[29], and solid organ transplant recipient patients[30].

Besides comorbidities, vitamin D hypovitaminosis is associated with poor glycemic control[23], which is also associated with poor COVID-19 outcomes in diabetic and non-diabetic patients[31]. Cancer patients present low circulating levels of vitamin D [29] and experimental models have identified that vitamin D can modulate the disease development by regulating cell cycle and inflammatory response[32].

Vitamin D deficiency is a worldwide problem[33,34], and vitamin D supplementation has the potential to enhance the immune response to microorganisms[1]. Vitamin D supplementation has been investigated for the treatment and prevention of severe COVID-19, indicating a potential reduction in COVID-19 severity[35].

A recent investigation found that prophylactic vitamin D supplementation in elderlies improved the SARS-CoV-2 immune response[36], and another investigation identified that the treatment with vitamin D reduces COVID-19 severity[37]. Nevertheless, another report found no additional benefit in vitamin D supplementation during COVID-19[38].

Low vitamin D levels also modulate the Renin-Angiotensin-System, which could increase the susceptibility to COVID-19[39], since SARS-CoV-2 uses the angiotensin-converting enzyme 2 and Transmembrane Protease Serine 2 (TMPRSS2) to invade the host's cells[40]. In addition, the lack of vitamin D is a risk factor for the development of autoimmune and neuropsychiatric disorders[41].

Lakkireddy *et al*[42] identified that increasing the serum levels of vitamin D to 80–100 ng/mL significantly reduced inflammatory biomarkers such as interleukin-6, C-reactive protein, and neutrophil-to-lymphocyte ratio during COVID-19, without side effects[42].

In addition, Papadimitriou *et al*[1] recommendation for vitamin D supplementation should also be considered in a broader context[1], outside the COVID-19 pandemic situation, due to the high incidence of vitamin D hypovitaminosis worldwide, the vast associations with other diseases, and the proposed doses do not require medical supervision[1].

COVID-19 vaccination is ongoing worldwide[43-45], since vitamin D can modulate the immune response to vaccines[46,47], investigations on the vaccines should consider evaluating vitamin D levels and the effects of supplementation on the immune response to vaccines.

In summary, vitamin D hypovitaminosis is associated with comorbidities that are known to affect COVID-19 severity and outcome. Further investigations should focus on patients with low vitamin D levels with and without comorbidities and supplementation trials to investigate the effects of vitamin D on the immune response to COVID-19 and COVID-19 vaccines.

REFERENCES

1 **Papadimitriou DT**, Vassaras AK, Holick MF. Association between population vitamin D status and SARS-CoV-2 related serious-critical illness and deaths: An ecological integrative approach. *World J Virol* 2021; **10**: 111-129 [PMID: 34079693 DOI: 10.5501/wjv.v10.i3.111]

2 **Temgoua MN**, Endomba FT, Nkeck JR, Kenfack GU, Tochie JN, Essouma M. Coronavirus Disease 2019 (COVID-19) as a Multi-Systemic Disease and its Impact in Low- and Middle-Income Countries (LMICs). *SN Compr Clin Med* 2020; 1-11 [PMID: 32838173 DOI: 10.1007/s42399-020-00417-7]

3 **Perrotta F**, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, Komici K, Mazzarella G, Parrella R, Bianco A. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res* 2020; **32**: 1599-1608 [PMID: 32557332 DOI: 10.1007/s40520-020-01631-y]

4 **Alberca RW**, Yendo TM, Leuzzi Ramos YÁ, Fernandes IG, Oliveira LM, Teixeira FME, Beserra DR, de Oliveira EA, Gozzi-Silva SC, Andrade MMS, Branco ACCC, Pietrobon AJ, Pereira NZ, de Brito CA, Orfali RL, Aoki V, Duarte AJDS, Benard G, Sato MN. Case Report: COVID-19 and Chagas Disease in Two Coinfected Patients. *Am J Trop Med Hyg* 2020; **103**: 2353-2356 [PMID: 33025877 DOI: 10.4269/ajtmh.20-1185]

5 **Holman N**, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8**: 823-833 [PMID: 32798471 DOI: 10.1016/S2213-8587(20)30271-0]

6 **Alberca RW**, Rigato PO, Ramos YÁL, Teixeira FME, Branco ACC, Fernandes IG, Pietrobon AJ, Duarte AJDS, Aoki V, Orfali RL, Sato MN. Clinical Characteristics and Survival Analysis in Frequent Alcohol Consumers With COVID-19. *Front Nutr* 2021; **8**: 689296 [PMID: 34150832 DOI: 10.3389/fnut.2021.689296]

7 **Alberca RW**, Lima JC, de Oliveira EA, Gozzi-Silva SC, Leuzzi YÁ, Mary De Souza Andrade M, Beserra DR, Oliveira LDM, Castelo Branco ACC, Pietrobon AJ, Pereira NZ, Teixeira FME, Fernandes IG, Benard G, Sato MN. COVID-19 disease course in formers smokers, smokers and COPD patients. *Front Physiol* 2020 [DOI: 10.3389/fphys.2020.637627]

8 **Leowattana W**. Angiotensin-converting enzyme 2 receptors, chronic liver diseases, common medications, and clinical outcomes in coronavirus disease 2019 patients. *World J Virol* 2021; **10**: 86-96 [PMID: 34079691 DOI: 10.5501/wjv.v10.i3.86]

9 **Riches JC**. Impact of COVID-19 in patients with lymphoid malignancies. *World J Virol* 2021; **10**: 97-110 [PMID: 34079692 DOI: 10.5501/wjv.v10.i3.97]

10 **Dancer RC**, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, Park D, Bartis DG, Mahida R, Turner AM, Sapey E, Wei W, Naidu B, Stewart PM, Fraser WD, Christopher KB, Cooper MS, Gao F, Sansom DM, Martineau AR, Perkins GD, Thickett DR. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax* 2015; **70**: 617-624 [PMID: 25903964 DOI: 10.1136/thoraxjnl-2014-206680]

11 **Radujkovic A**, Hippchen T, Tiwari-Heckler S, Dreher S, Boxberger M, Merle U. Vitamin D Deficiency and Outcome of COVID-19 Patients. *Nutrients* 2020; **12** [PMID: 32927735 DOI: 10.3390/nu12092757]

12 **Brandão CMÁ**, Chiamolera MI, Biscolla RPM, Lima JV Junior, De Francischi Ferrer CM, Prieto WH, de Sá Tavares Russo P, de Sá J, Dos Santos Lazari C, Granato CFH, Vieira JGH. No association between vitamin D status and COVID-19 infection in São Paulo, Brazil. *Arch Endocrinol Metab* 2021 [DOI: 10.20945/2359-3997000000343]

13 **Takahashi K**, Nakayama Y, Horiuchi H, Ohta T, Komoriya K, Ohmori H, Kamimura T. Human neutrophils express messenger RNA of vitamin D receptor and respond to 1alpha,25-dihydroxyvitamin D3. *Immunopharmacol Immunotoxicol* 2002; **24**: 335-347 [PMID: 12375732 DOI: 10.1081/iph-120014721]

14 **Lin R**. Crosstalk between Vitamin D Metabolism, VDR Signalling, and Innate Immunity. *Biomed Res Int* 2016; **2016**: 1375858 [PMID: 27403416 DOI: 10.1155/2016/1375858]

15 **Sassi F**, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. *Nutrients* 2018; **10** [PMID: 30400332 DOI: 10.3390/nu10111656]

16 **Sly LM**, Lopez M, Nauseef WM, Reiner NE. 1alpha,25-Dihydroxyvitamin D3-induced monocyte antimycobacterial activity is regulated by phosphatidylinositol 3-kinase and mediated by the NADPH-dependent phagocyte oxidase. *J Biol Chem* 2001; **276**: 35482-35493 [PMID: 11461902 DOI: 10.1074/jbc.M102876200]

17 **DeLuca HF**. Evolution of our understanding of vitamin D [Internet]. In: Nutrition Reviews. *Nutr Rev* 2008 [DOI: 10.1111/j.1753-4887.2008.00105.x]

18 **Oliveira Junior LR**, Carvalho TB, Santos RMD, Costa ÉAPND, Pereira PCM, Kurokawa CS.

Association of vitamin D3, VDR gene polymorphisms, and LL-37 with a clinical form of Chagas Disease. *Rev Soc Bras Med Trop* 2019; **52**: e20190133 [PMID: 31508781 DOI: 10.1590/0037-8682-0133-2019]

19 **Wöbke TK**, Sorg BL, Steinhilber D. Vitamin D in inflammatory diseases. *Front Physiol* 2014; **5**: 244 [PMID: 25071589 DOI: 10.3389/fphys.2014.00244]

20 **Papadimitriou DT**. The Big Vitamin D Mistake. *J Prev Med Public Health* 2017; **50**: 278-281 [PMID: 28768407 DOI: 10.3961/jpmph.16.111]

21 **Kweder H**, Eidi H. Vitamin D deficiency in elderly: Risk factors and drugs impact on vitamin D status. *Avicenna J Med* 2018; **8**: 139-146 [PMID: 30319955 DOI: 10.4103/ajm.AJM_20_18]

22 **Macdonald HM**, Mavroeidi A, Aucott LA, Diffey BL, Fraser WD, Ormerod AD, Reid DM. Skin color change in Caucasian postmenopausal women predicts summer-winter change in 25-hydroxyvitamin D: findings from the ANSAViD cohort study. *J Clin Endocrinol Metab* 2011; **96**: 1677-1686 [PMID: 21411556 DOI: 10.1210/jc.2010-2032]

23 **Kostoglou-Athanassiou I**, Athanassiou P, Gkountouvas A, Kaldrymides P. Vitamin D and glycemic control in diabetes mellitus type 2. *Ther Adv Endocrinol Metab* 2013; **4**: 122-128 [PMID: 23997931 DOI: 10.1177/2042018813501189]

24 **Lieber CS**. ALCOHOL: its metabolism and interaction with nutrients. *Annu Rev Nutr* 2000; **20**: 395-430 [PMID: 10940340 DOI: 10.1146/annurev.nutr.20.1.395]

25 **Brot C**, Jorgensen NR, Sorensen OH. The influence of smoking on vitamin D status and calcium metabolism. *Eur J Clin Nutr* 1999; **53**: 920-926 [PMID: 10602348 DOI: 10.1038/sj.ejcn.1600870]

26 **Janssens W**, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, Coolen J, Mathieu C, Decramer M, Lambrechts D. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 2010; **65**: 215-220 [PMID: 19996341 DOI: 10.1136/thx.2009.120659]

27 **Menon B**, Nima G, Dogra V, Mittal A, Kaur C, Mittal U. Evaluation of vitamin D in bronchial asthma and the effect of vitamin D supplementation on asthma severity and control: A randomised control trial. *Eur Respir J* 2014; 44 [DOI: 10.13070/rs.en.1.1088]

28 **Alberca RW**, Yendo T, Aoki V, Sato MN. Asthmatic patients and COVID-19: Different disease course? *Allergy* 2021; **76**: 963-965 [PMID: 33675252 DOI: 10.1111/all.14601]

29 **Kennel KA**, Drake MT. Vitamin D in the cancer patient. *Curr Opin Support Palliat Care* 2013; **7**: 272-277 [PMID: 23912386 DOI: 10.1097/SPC.0b013e3283640f74]

30 **Nacif LS**, Zanini LY, Waisberg DR, Pinheiro RS, Galvão F, Andraus W, D'Albuquerque LC. COVID-19 in solid organ transplantation patients: A systematic review. *Clinics (Sao Paulo)* 2020; **75**: e1983 [PMID: 32520225 DOI: 10.6061/clinics/2020/e1983]

31 **Palaiodimos L**, Chamorro-Pareja N, Karamanis D, Li W, Zavras PD, Chang KM, Mathias P, Kokkinidis DG. Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients. *Hormones (Athens)* 2021; **20**: 305-314 [PMID: 33123973 DOI: 10.1007/s42000-020-00246-2]

32 **Bouillon R**, Eelen G, Verlinden L, Mathieu C, Carmeliet G, Verstuyf A. Vitamin D and cancer. *J Steroid Biochem Mol Biol* 2006; **102**: 156-162 [PMID: 17113979 DOI: 10.1016/j.jsbmb.2006.09.014]

33 **Lips P**, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, Stepan J, El-Hajj Fuleihan G, Bouillon R. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* 2019; **180**: P23-P54 [PMID: 30721133 DOI: 10.1530/EJE-18-0736]

34 **Roth DE**, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, Calvo MS, Cashman KD, Combs G, De-Regil LM, Jefferds ME, Jones KS, Kapner H, Martineau AR, Neufeld LM, Schleicher RL, Thacher TD, Whiting SJ. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Ann N Y Acad Sci* 2018; **1430**: 44-79 [PMID: 30225965 DOI: 10.1111/nyas.13968]

35 **Shah K**, Saxena D, Mavalankar D. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. *QJM* 2021; **114**: 175-181 [PMID: 33486522 DOI: 10.1093/qjmed/hcab009]

36 **Annweiler G**, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, Annweiler C. Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study. *Nutrients* 2020; **12** [PMID: 33147894 DOI: 10.3390/nu12113377]

37 **Entrenas Castillo M**, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, Quesada Gomez JM. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol* 2020; **203**: 105751 [PMID: 32871238 DOI: 10.1016/j.jsbmb.2020.105751]

38 **Cereda E**, Bogliolo L, Lobascio F, Barichella M, Zecchinelli AL, Pezzoli G, Caccialanza R. Vitamin D supplementation and outcomes in coronavirus disease 2019 (COVID-19) patients from the outbreak area of Lombardy, Italy. *Nutrition* 2021; **82**: 111055 [PMID: 33288411 DOI: 10.1016/j.nut.2020.111055]

39 **Biesalski HK**. Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship? *Nfs J* 2020; **20**: 10 [DOI: 10.1016/j.nfs.2020.06.001]

40 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry

Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

41 **Wang H**, Chen W, Li D, Yin X, Zhang X, Olsen N, Zheng SG. Vitamin D and Chronic Diseases. *Aging Dis* 2017; **8**: 346-353 [PMID: 28580189 DOI: 10.14336/AD.2016.1021]

42 **Lakkireddy M**, Gadiga SG, Malathi RD, Karra ML, Raju ISSVPM, Ragini, Chinapaka S, Baba KSSS, Kandakatla M. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. *Sci Reports* 2021; **11**: 1-8 [DOI: 10.1038/s41598-021-90189-4]

43 **Sahin U**, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D, Brachtendorf S, Lörks V, Sikorski J, Hilker R, Becker D, Eller AK, Grützner J, Boesler C, Rosenbaum C, Kühnle MC, Luxemburger U, Kemmer-Brück A, Langer D, Bexon M, Bolte S, Karikó K, Palanche T, Fischer B, Schultz A, Shi PY, Fontes-Garfias C, Perez JL, Swanson KA, Loschko J, Scully IL, Cutler M, Kalina W, Kyratsous CA, Cooper D, Dormitzer PR, Jansen KU, Türeci Ö. COVID-19 vaccine BNT162b1 elicits human antibody and T_H1 T cell responses. *Nature* 2020; **586**: 594-599 [PMID: 32998157 DOI: 10.1038/s41586-020-2814-7]

44 **Sadoff J**, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, Goepfert PA, Truyers C, Fennema H, Spiessens B, Offergeld K, Scheper G, Taylor KL, Robb ML, Treanor J, Barouch DH, Stoddard J, Ryser MF, Marovich MA, Neuzil KM, Corey L, Cauwenberghs N, Tanner T, Hardt K, Ruiz-Guiñazú J, Le Gars M, Schuitemaker H, Van Hoof J, Struyf F, Douoguih M; ENSEMBLE Study Group. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med* 2021; **384**: 2187-2201 [PMID: 33882225 DOI: 10.1056/NEJMoa2101544]

45 **Zhang Y**, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, Chen X, Liu X, Jiang C, Li J, Yang M, Song Y, Wang X, Gao Q, Zhu F. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; **21**: 181-192 [PMID: 33217362 DOI: 10.1016/S1473-3099(20)30843-4]

46 **Goncalves-Mendes N**, Talvas J, Dualé C, Guttmann A, Corbin V, Marceau G, Sapin V, Brachet P, Evrard B, Laurichesse H, Vasson MP. Impact of Vitamin D Supplementation on Influenza Vaccine Response and Immune Functions in Deficient Elderly Persons: A Randomized Placebo-Controlled Trial. *Front Immunol* 2019; **10**: 65 [PMID: 30800121 DOI: 10.3389/fimmu.2019.00065]

47 **Sadarangani SP**, Whitaker JA, Poland GA. "Let there be light": the role of vitamin D in the immune response to vaccines. *Expert Rev Vaccines* 2015; **14**: 1427-1440 [PMID: 26325349 DOI: 10.1586/14760584.2015.1082426]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2022 March 25; 11(2): 90-112

Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents

Bimonthly Volume 11 Number 2 March 25, 2022

OPINION REVIEW

MINIREVIEWS

LETTER TO THE EDITOR

World Journal of Virology

Bimonthly Volume 11 Number 2 March 25, 2022

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
March 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 March 25; 11(2): 90-97

DOI: 10.5501/wjv.v11.i2.90

ISSN 2220-3249 (online)

OPINION REVIEW

Rifampicin for COVID-19

George D Panayiotakopoulos, Dimitrios T Papadimitriou

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wang CY

Received: July 25, 2021
Peer-review started: July 25, 2021
First decision: November 11, 2021
Revised: November 29, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 25, 2022

George D Panayiotakopoulos, Department of Clinical Pharmacology, University of Patras Medical School, Rion 26504, Greece

George D Panayiotakopoulos, The National Public Health Organization of Greece, Athens 15123, Greece

Dimitrios T Papadimitriou, Department of Pediatric, Adolescent Endocrinology & Diabetes, Athens Medical Center, Marousi 15125, Greece

Dimitrios T Papadimitriou, Endocrine Unit, Aretaieion University Hospital, Athens 11528, Greece

Corresponding author: Dimitrios T Papadimitriou, MD, MSc, PhD, Academic Fellow, Department of Pediatric, Adolescent Endocrinology & Diabetes, Athens Medical Center, 58 av. Kifisias, Marousi 15125, Greece. info@pedoendo.net

Abstract

Vaccinations for coronavirus disease-2019 (COVID-19) have begun more than a year before, yet without specific treatments available. Rifampicin, critically important for human medicine (World Health Organization's list of essential medicines), may prove pharmacologically effective for treatment and chemoprophylaxis of healthcare personnel and those at higher risk. It has been known since 1969 that rifampicin has a direct selective antiviral effect on viruses which have their own RNA polymerase (severe acute respiratory syndrome coronavirus 2), like the main mechanism of action of remdesivir. This involves inhibition of late viral protein synthesis, the virion assembly, and the viral polymerase itself. This antiviral effect is dependent on the administration route, with local application resulting in higher drug concentrations at the site of viral replication. This would suggest also trying lung administration of rifampicin by nebulization to increase the drug's concentration at infection sites while minimizing systemic side effects. Recent *in silico* studies with a computer-aided approach, found rifampicin among the most promising existing drugs that could be repurposed for the treatment of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Rifampicin; Antiviral activity; RNA polymerase

Core Tip: Rifampicin may prove pharmacologically effective, supplying a possible and cost-effective solution to the global battle against severe acute respiratory syndrome coronavirus 2, not only for treatment but also for chemoprophylaxis of those at higher risk. It is also possible to administer rifampicin by nebulization. The publications describing the *in vitro* mechanisms and providing proof of clinical efficacy of rifampicin against RNA viruses with their own RNA polymerase have emerged since 1969-1971. Recent *in silico* studies using a computer-aided approach, found rifampicin among the most promising existing drugs that can be repurposed for the treatment of coronavirus disease-2019.

Citation: Panayiotakopoulos GD, Papadimitriou DT. Rifampicin for COVID-19. *World J Virol* 2022; 11(2): 90-97
URL: https://www.wjgnet.com/2220-3249/full/v11/i2/90.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i2.90

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic presents a puzzling challenge without specific treatment yet[1], and while vaccinations have been initiated more than a year before[2], there is still a long way to go before herd immunity can be achieved, even in the developed countries[3]. In the critically ill patients, plasma transfusions from recovered patients have been tried[4] and specific severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) memory T cells could also treat moderate/severe cases of COVID-19[5]. When and with which pharmacological cocktail to intervene is under rigorous investigation worldwide[6]. Chemoprophylaxis of exposed healthcare personnel[7], along with those at higher risk for severe illness, is also equally exigent, at least until sizable worldwide immunization will be achieved[8]. And even if vaccination campaigns do make progress in the Western world, this process may take much longer in the developing countries. Even then, the possible emergence of SARS-CoV-2 new mutated strains could substantially impact the protection of currently available vaccines or the physical immunity acquired from previous illness from the previous SARS-CoV-2 variants[9] (https://theconversation.com/the-lambda-variant-is-it-more-infectious-and-can-it-escape-vaccines-a-virologist-explains-164156).

Rifampicin, discovered in 1965, was marketed in Italy in 1968, and approved in the United States in 1971. It is on the World Health Organization's (WHO) list of essential medicines, classified by the WHO as critically important for human medicine. Made by the soil bacterium *Amycolatopsis rifamycinica*, rifampicin is widely available as a generic medication with an extremely low cost compared to any other modern antiviral medication. It belongs to the *Rifamycins*, characterized as antiviral drugs which inhibit transformation of cells by viruses[10]. While in the fourth wave of this pandemic, without specific medications available yet, along with the ongoing computational analysis of potential drugs[11], it becomes clearer that - at least for now and beyond active immunization - we still need to rely on one hand on the enhancement of our immune system and on the other hand on the known anti-inflammatory and immunomodulatory effects of some antibacterials and the emerging antiviral effects of old but precious drugs, such as rifampicin. For the first task, which is to strengthen our immunity, adding zinc sulphate increased patients' discharges, decreasing the need for ventilation, intensive care unit admissions, and mortality[12]. Increased intracellular zinc concentrations seem to inhibit RNA-dependent polymerases, helping to support robust immune responses and modulating immune cell activity. For that task, researchers have tried high doses of vitamin C[13]. And last but not least, proper supplementation[14,15] or even adjunctive therapy with vitamin-D[16], to capitalize on its extra-skeletal immunomodulatory properties, may also prove valuable, playing a crucial role in enhancing and coordinating the immune system's response to SARS-CoV-2 infection[17,18]. For that purpose, personalized immunotherapy approaches with agents/monoclonal antibodies that block receptors for interleukin-1/6 have been initiated, aiming to control the macrophage activation syndrome which has been suggested as a major mechanism of lung impairment in COVID-19[19]. Monoclonal antibodies have shown promising results, with prompt administration though being a key issue to exert their benefit[20]. Bamlanivimab, a neutralizing monoclonal antibody against SARS-CoV-2, reduced the incidence of COVID-19[21].

Herein, we discuss the possibility of repurposing rifampicin for COVID-19, and we call for immediate coordinated - international if possible - collaboration[22] in *in vitro* studies, open-label pilot trials, and definitive phase 3 clinical trials.

ANTIVIRAL PROPERTIES OF RIFAMPICIN: MECHANISMS AND FACTS

Careful analysis of the COVID-19 clinical characteristics and computed tomography scans indicates that the pulmonary nontuberculous mycobacterial disease, in which azithromycin and rifampicin are among

first line treatment options, seems to share a striking analogy with SARS-CoV-2 pneumonia[23]. Going back to 1969, a conventional antibacterial of proved pharmacological acceptability in man, rifampicin (or rifampin: https://www.accessdata.fda.gov/drugsatfda_docs/Label/2018/050420s077,050627s020Lbl.pdf), was found to have a direct antiviral effect in some mammalian viruses as poxviruses including the causative agent of smallpox and mainly on viruses which have their own RNA polymerase[24], which is the case for SARS-CoV-2 and the main mechanism of action of remdesivir. Initially developed against Ebola, remdesivir raised hope, as it incorporates into nascent viral RNA chains and results in premature termination of viral replication. Remdesivir showed higher recovery and hospital discharge rates, but no significant reduction in mean time to clinical improvement or mortality[25].

Regarding large DNA viruses, the antiviral activity of rifampicin arises from its binding to the F-ring, highly conserved across mammalian poxviruses, which cannot mutate in response to rifampicin inhibition and thus provide a potential base for the development of broad-spectrum inhibitors against infectious poxviruses species in animals and humans[26]. However, the efficacy of rifampicin against viruses with their own RNA polymerase shares the same mechanism with its antibacterial activity against microbial RNA polymerases. The inhibitory mechanism of rifampicin on the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function[27]. The rifampicin molecule is a condensation product of 3-formyl rifamycin SV and 1-amino 4-methyl piperazine with the antiviral activity existing in the rifamycin part of the molecule. Its antiviral effect is reversible as removal of the drug late in the virus cycle leads to a mature and infectious virus even within 1 h. This would mean that careful monitoring of rifampicin levels may assure effectiveness. The selective antiviral effect of rifampicin involves inhibition of late viral protein synthesis[28], virion assembly[29], and the viral polymerase itself[30].

Table 1 summarizes the studies on the possible antiviral properties of rifampicin against SARS-CoV-2 presenting their main findings.

ADMINISTRATION ROUTE AND POTENTIALS

Studies in volunteers have also shown a dependence of rifampicin's antiviral effect on administration route, with local application resulting in higher concentrations of the drug at the site of viral replication [31]. This would suggest trying lung administration of rifampicin by nebulization[32], increasing the drug's concentration at infection sites while minimizing systemic side effects. This approach, using aerosolized rifampicin-loaded polymeric microspheres, reduced most measures of tuberculosis infection in experimental animals[33]. However, since the major cell entry receptor for SARS-CoV-2 is the metallocarboxyl peptidase angiotensin receptor 2[34], whose expression is very low in the lung, the approach of lung administration may not exhibit the expected systemic antiviral effects of rifampicin and requires further investigation.

An effective intracellular concentration of rifampicin without serious toxicity seems possible and probable, given its pharmacokinetic profile, suitable also for chemoprophylaxis (https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin#section=Drug-Classes). Current studies have evaluated intravenous rifampicin 20 mg/kg for 2 wk followed by high dose oral formulation (35 mg/kg for 6-8 wk) for improved survival from adult tuberculous meningitis[35]. Data concerning intracellular rifampicin concentrations to exhibit effective antiviral activity against influenza virus A[36], African swine fever virus[37], and cytomegalovirus[38] have been already available.

IN SILICO STUDIES INDICATE POSSIBLE EFFECTIVENESS OF RIFAMPICIN

The above finding may have just been verified by a recent *in silico* study using a computer-aided drug designing approach: Rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19[39]. Moreover, using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir[40]. Rifabutin, however, belongs to the rifamycins (rifampicin, rifapentine, and rifabutin), but with rifampicin being the most used[41]. *In silico* virtual screening within the United States Food and Drug Administration (FDA)-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, also placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics[42]. Virtual screening of FDA-approved drugs targeting not only the main protease of SARS-CoV-2 but also TNF-α, IL-6, and IL-1β, which are the key molecules involved in the 'cytokine storm' occurring in COVID-19, indicated rifampicin as one of the most promising drugs for the treatment of COVID-19, together with letermovir [43]. These were systematic docking studies, further confirmed by molecular dynamics simulations and molecular calculations; however, such studies are prone to the high probability of artifacts needing experimental verification.

Table 1 Studies on the possible antiviral properties of rifampicin against severe acute respiratory syndrome coronavirus 2

Ref.	Year	Findings
Becker[10]	1976	Rifampicin belongs to the *rifamycins*, characterized as antiviral drugs which inhibit transformation of cells by viruses
[24]	1969	Rifampicin has a direct antiviral effect in mammalian viruses as poxviruses including the causative agent of smallpox and on viruses which have their own RNA polymerase
Campbell *et al*[27]	2001	The inhibition mechanism of rifampicin to the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function
Ben-Ishai *et al*[28], Moss *et al*[29], McAuslan *et al*[30]	1969	Rifampicin inhibits the late viral protein synthesis, the virion assembly, and the viral polymerase itself
Moshkowitz *et al*[31]	1971	Rifampicin's antiviral effect is dependent on the administration route, with local application resulting in higher concentrations at the site of viral replication
Tewes *et al*[32]	2008	Administration of rifampicin by nebulization is possible using aerosolized rifampicin-loaded polymeric microspheres
And *et al*[36]	1980	Intracellular rifampicin concentrations exhibit effective antiviral activity against: Influenza virus A, African swine fever virus and cytomegalovirus
Dardiri *et al*[37]	1971	
Halsted *et al*[38]	1972	

The SARS-CoV-2 RNA-dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs (A-G), and discovered the interactions with rifabutin and rifampicin, among other ligands. Both of them interacted with at least two nsp12 motifs, indicating that they could be both used as inhibitors of SARS-CoV-2 nsp12 protein[44]. Another *in silico* docking approach also found that rifampicin has good binding affinity with the COVID-19 protease[45], proposing its use as therapeutic treatment as well as prophylaxis.

Of course, all the above findings require further validation by *in vitro* studies and clinical trials. Table 2 summarizes the *in silico* studies indicating effectiveness of rifampicin against SARS-CoV-2.

DRUG MONITORING AND INTERACTIONS

Experience from coadministration of antitubercular use of rifampicin with antiretroviral therapy may, however, be complicated by drug-to-drug interactions concerning drug metabolism and transport[46], which warrants caution in clinical trials designed to test the efficacy of rifampicin against SARS-CoV-2 in case of co-administration with other drugs that are also metabolized in the liver. A plan is needed to treat COVID-19 in the special group of patients with advanced liver disease[47], as rifampicin is an agonist of the nuclear pregnane nuclear receptor that regulates CYP3A4[48,49], a part of cytochrome P450 enzymes that metabolizes 60% of prescribed drugs. Thus, rifampicin can cause serious drug-to-drug interactions in combination with other medications for COVID-19 treatment. Also, it should be noted that concerning rifampicin, therapeutic drug monitoring is needed when extracorporeal membrane oxygenation is to be used as a life-saving system for critically ill patients with cardiac and/or respiratory failure[50]. The co-administration of plant-derived compounds such as gallic acid and tannic acid, which are effective potentiators resulting in a 4-fold increase in the potency of rifampicin, warrants further study[51]. A known infrequent occurrence, with few cases reported in the literature, of rifampicin-induced pneumonitis mimicking acute respiratory distress syndrome and requiring SARS-CoV-2 testing[52], merits caution. Because of an uncommon immuno-allergic reaction, following intermittent rifampin administration, with disseminated intravascular coagulation including fever, hypotension, abdominal pain, and vomiting within hours of ingestion[53], awareness is warranted for COVID-19 patients suffering from the life-threatening cytokine storm syndrome[54]. Hence, even in the latter case, as in an allergic reaction to rifampicin, apart from targeted anti-cytokine therapy[55], broadly immunosuppressive glucocorticoids would be of value.

SAFETY AND ADVANTAGES OF RIFAMPICIN

Rifampicin is not the only antibiotic that could be repurposed for COVID-19. Quinupristin, for example, is an antibiotic in clinical use for two decades now with minor side effects and has also proven *in silico*

Table 2 *In silico* studies indicating rifampicin's possible effectiveness against coronavirus disease-2019

Ref.	Year	Findings
Mishra *et al*[39]	2020	Using a computer-aided drug designing approach, rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19
Parvez *et al*[40]	2020	Using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir
Forrest *et al*[41]	2010	Rifabutin belongs to the rifamycins (rifampicin, rifapentine and rifabutin); rifampicin is the most used
Pokhrel *et al*[42]	2020	In silico virtual screen within the United States Food and Drug Administration-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics
Pathak *et al*[43]	2021	A similar approach, by targeting the main protease of SARS-CoV-2 but also TNF-α, IL-6, IL-1β, revealed rifampicin as one of the most promising drugs
Elkarhat *et al*[44]	2020	The SARS-CoV-2 RNA dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs, and discovered the interactions with rifabutin and rifampicin, concluding that both could function as inhibitors of the SARS-CoV-2 nsp12 protein
Soni *et al* [45]	2020	An *in silico* docking approach also found that rifampicin has good binding affinity with the COVID-19 protease, proposing its use as therapeutic treatment as well as prophylaxis

COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

potentially effective against SARS-CoV-2[42]. However, the knowledge and clinical experience as well as the safety profile of rifampicin even in neonates, infants[56], and pregnant woman[57] make a compelling case where alternative therapeutic options are limited. Last, but not least in this instance, the particularly low cost and the potential for worldwide availability of rifampicin as a generic medication may prove a worthy solution, for early intervention protocols against SARS-CoV-2.

RIFAMPICIN IN COVID-19 IN CLINICAL PRACTICE

A recent case report described the favorable outcome under treatment with chloroquine and rifampin of an unusual association of COVID-19, pulmonary tuberculosis, and human immunodeficiency virus infection[58], attributed either to rifampicin inhibiting the formation of mRNA of SARS-CoV-2 and/or the possible synergistic effect of chloroquine and rifampin, despite that anti-tubercular drugs such as rifampicin are powerful enzyme inducers that can reduce the effectiveness of chloroquine. Up to now, there are no clinical studies available on the treatment of COVID-19 patients with rifampicin. Anecdotally, experienced pediatricians have also successfully treated neonates and infants[59] found positive for SARS-CoV-2 with rifampicin, clearly aiming for their protection with their parents suffering overt COVID-19 with an eventful clinical course.

CONCLUSION

Timely administration, though, is important for all current regimens on trial: It must not be too late when treatment starts. Specifically, rifampicin interferes with the viral replication, and thus, early administration after diagnosis of COVID-19 could make a significant difference to its presumed effectiveness against SARS-CoV-2 infection. Similarly, for rifampicin's use for postexposure prophylaxis to people exposed to index cases of invasive meningococcal infection, pre-exposure together with post-exposure prophylaxis could also be a potential strategy, at least for unvaccinated people[60]. The WHO proposed a similar approach for people at elevated risk for infection, before or after exposure, during the influenza pandemic.

Call for studies

Facing this unprecedented global emergency and given the experience, safety, and knowledge behind rifampicin, we call for international collaboration proposing *in vitro* studies, open-label pilot trials, and definite phase 3 clinical trials for testing treatment and chemoprophylaxis efficacy of rifampicin against COVID-19. With all the above compelling evidence, rifampicin merits evaluation against COVID-19.

FOOTNOTES

Author contributions: Panayiotakopoulos GD contributed to the conceptualization; Papadimitriou DT contributed to the original draft; all authors contributed to review and editing of the manuscript.

Conflict-of-interest statement: George D Panayiotakopoulos serves as Vice President of The National Public Health Organization of Greece; Dimitrios T Papadimitriou has no conflict of interests to declare.

Country/Territory of origin: Greece

ORCID number: George D Panayiotakopoulos 0000-0002-9303-8854; Dimitrios T Papadimitriou 0000-0002-6083-3560.

S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Zhang H

REFERENCES

1 **Pagliano P**, Scarpati G, Sellitto C, Conti V, Spera AM, Ascione T, Piazza O, Filippelli A. Experimental Pharmacotherapy for COVID-19: The Latest Advances. *J Exp Pharmacol* 2021; **13**: 1-13 [PMID: 33442304 DOI: 10.2147/JEP.S255209]
2 **Williams J**, Degeling C, McVernon J, Dawson A. How should we conduct pandemic vaccination? *Vaccine* 2021; **39**: 994-999 [PMID: 33423839 DOI: 10.1016/j.vaccine.2020.12.059]
3 **Ghaffari A**, Meurant R, Ardakani A. COVID-19 Point-of-Care Diagnostics That Satisfy Global Target Product Profiles. *Diagnostics (Basel)* 2021; **11** [PMID: 33445727 DOI: 10.3390/diagnostics11010115]
4 **Mandel M**, Gurevich M, Mandelboim M, Amital H, Achiron A. Convalescent Whole Blood Donors Screening Strategies for Providing Efficient and Safe COVID-19 Survivors' Plasma and Other Blood Components. *Isr Med Assoc J* 2021; **23**: 7-10 [PMID: 33443334]
5 **Ferreras C**, Pascual-Miguel B, Mestre-Durán C, Navarro-Zapata A, Clares-Villa L, Martín-Cortázar C, De Paz R, Marcos A, Vicario JL, Balas A, García-Sánchez F, Eguizabal C, Solano C, Mora-Rillo M, Soria B, Pérez-Martínez A. SARS-CoV-2-Specific Memory T Lymphocytes From COVID-19 Convalescent Donors: Identification, Biobanking, and Large-Scale Production for Adoptive Cell Therapy. *Front Cell Dev Biol* 2021; **9**: 620730 [PMID: 33718360 DOI: 10.3389/fcell.2021.620730]
6 **Singh A**, Gupta V. SARS-CoV-2 therapeutics: how far do we stand from a remedy? *Pharmacol Rep* 2021; **73**: 750-768 [PMID: 33389724 DOI: 10.1007/s43440-020-00204-0]
7 **Tahiri Joutei Hassani R**, Bennis A. Hydroxychloroquine as antiviral prophylaxis for exposed caregivers to Covid-19: An urgent appraisal is needed. *J Infect Public Health* 2020; **13**: 865-867 [PMID: 32451259 DOI: 10.1016/j.jiph.2020.05.005]
8 **Neagu M**. The bumpy road to achieve herd immunity in COVID-19. *J Immunoassay Immunochem* 2020; **41**: 928-945 [PMID: 33086932 DOI: 10.1080/15321819.2020.1833919]
9 **Shim E**. Projecting the Impact of SARS-CoV-2 Variants and the Vaccination Program on the Fourth Wave of the COVID-19 Pandemic in South Korea. *Int J Environ Res Public Health* 2021; **18** [PMID: 34300029 DOI: 10.3390/ijerph18147578]
10 **Becker Y**. Antiviral Drugs which Inhibit Transformation of Cells by Viruses. *Monogr Virol* 1976; **11** [DOI: 10.1159/000398678]
11 **Murugan NA**, Kumar S, Jeyakanthan J, Srivastava V. Searching for target-specific and multi-targeting organics for Covid-19 in the Drugbank database with a double scoring approach. *Sci Rep* 2020; **10**: 19125 [PMID: 33154404 DOI: 10.1038/s41598-020-75762-7]
12 **Carlucci PM**, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol* 2020; **69**: 1228-1234 [PMID: 32930657 DOI: 10.1099/jmm.0.001250]
13 **Zhang J**, Rao X, Li Y, Zhu Y, Liu F, Guo G, Luo G, Meng Z, De Backer D, Xiang H, Peng Z. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. *Ann Intensive Care* 2021; **11**: 5 [PMID: 33420963 DOI: 10.1186/s13613-020-00792-3]
14 **Papadimitriou DT**, Vassaras AK, Holick MF. Association between population vitamin D status and SARS-CoV-2 related serious-critical illness and deaths: An ecological integrative approach. *World J Virol* 2021; **10**: 111-129 [PMID: 34079693 DOI: 10.5501/wjv.v10.i3.111]
15 **Papadimitriou DT**. The Big Vitamin D Mistake. *J Prev Med Public Health* 2017; **50**: 278-281 [PMID: 28768407 DOI: 10.3961/jpmph.16.111]
16 **Lakkireddy M**, Gadiga SG, Malathi RD, Karra ML, Raju ISSVPM, Ragini, Chinapaka S, Baba KSSS, Kandakatla M. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. *Sci Rep* 2021; **11**: 10641 [PMID: 34017029 DOI: 10.1038/s41598-021-90189-4]
17 **Morabia A**, Costanza MC. Vitamin D as in different. *Prev Med* 2010; **51**: 195-196 [PMID: 20837203 DOI: 10.1016/j.ypmed.2010.08.007]

18 **Maghbooli Z**, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, Hadadi A, Montazeri M, Nasiri M, Shirvani A, Holick MF. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. *PLoS One* 2020; **15**: e0239799 [PMID: 32976513 DOI: 10.1371/journal.pone.0239799]

19 **Iqubal A**, Hoda F, Najmi AK, Haque SE. Macrophage Activation and Cytokine Release Syndrome in COVID-19: Current Updates and Analysis of Repurposed and Investigational Anti-Cytokine Drugs. *Drug Res (Stuttg)* 2021; **71**: 173-179 [PMID: 33434935 DOI: 10.1055/a-1291-7692]

20 **Tuccori M**, Ferraro S, Convertino I, Cappello E, Valdiserra G, Blandizzi C, Maggi F, Focosi D. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. *MAbs* 2020; **12**: 1854149 [PMID: 33319649 DOI: 10.1080/19420862.2020.1854149]

21 **Cohen MS**, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, Stemer A, Mayer SM, Wohl D, Brengle B, Montague BT, Frank I, McCulloh RJ, Fichtenbaum CJ, Lipson B, Gabra N, Ramirez JA, Thai C, Chege W, Gomez Lorenzo MM, Sista N, Farrior J, Clement ME, Brown ER, Custer KL, Van Naarden J, Adams AC, Schade AE, Dabora MC, Knorr J, Price KL, Sabo J, Tuttle JL, Klekotka P, Shen L, Skovronsky DM; BLAZE-2 Investigators. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. *JAMA* 2021; **326**: 46-55 [PMID: 34081073 DOI: 10.1001/jama.2021.8828]

22 **Bowen AC**, Tong SY, Davis JS. Australia needs a prioritised national research strategy for clinical trials in a pandemic: lessons learned from COVID-19. *Med J Aust* 2021; **215**: 56-58.e1 [PMID: 34145568 DOI: 10.5694/mja2.51143]

23 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

24 Rifampicin and viruses. *Br Med J* 1969; **2**: 588-589 [PMID: 5798465]

25 **Al-Abdouh A**, Bizanti A, Barbarawi M, Jabri A, Kumar A, Fashanu OE, Khan SU, Zhao D, Antar AAR, Michos ED. Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Contemp Clin Trials* 2021; **101**: 106272 [PMID: 33422642 DOI: 10.1016/j.cct.2021.106272]

26 **Garriga D**, Headey S, Accurso C, Gunzburg M, Scanlon M, Coulibaly F. Structural basis for the inhibition of poxvirus assembly by the antibiotic rifampicin. *Proc Natl Acad Sci U S A* 2018; **115**: 8424-8429 [PMID: 30068608 DOI: 10.1073/pnas.1810398115]

27 **Campbell EA**, Korzheva N, Mustaev A, Murakami K, Nair S, Goldfarb A, Darst SA. Structural mechanism for rifampicin inhibition of bacterial rna polymerase. *Cell* 2001; **104**: 901-912 [PMID: 11290327 DOI: 10.1016/s0092-8674(01)00286-0]

28 **Ben-Ishai Z**, Heller E, Goldblum N, Becker Y. Rifampicin and poxvirus replication. *Nature* 1969; **224**: 29-32 [PMID: 5822902 DOI: 10.1038/224029a0]

29 **Moss B**, Rosenblum EN, Katz E, Grimley PM. Rifampicin: a specific inhibitor of vaccinia virus assembly. *Nature* 1969; **224**: 1280-1284 [PMID: 5359293 DOI: 10.1038/2241280a0]

30 **Mcauslan BR**. Rifampicin inhibition of vaccinia replication. *Biochem Biophys Res Commun* 1969; **37**: 289-295 [PMID: 4898697 DOI: 10.1016/0006-291x(69)90733-5]

31 **Moshkowitz A**, Goldblum N, Heller E. Studies on the antiviral effect of rifampicin in volunteers. *Nature* 1971; **229**: 422-424 [PMID: 4323457 DOI: 10.1038/229422a0]

32 **Tewes F**, Brillault J, Couet W, Olivier JC. Formulation of rifampicin-cyclodextrin complexes for lung nebulization. *J Control Release* 2008; **129**: 93-99 [PMID: 18514353 DOI: 10.1016/j.jconrel.2008.04.007]

33 **Garcia-Contreras L**, Sethuraman V, Kazantseva M, Godfrey V, Hickey AJ. Evaluation of dosing regimen of respirable rifampicin biodegradable microspheres in the treatment of tuberculosis in the guinea pig. *J Antimicrob Chemother* 2006; **58**: 980-986 [PMID: 16971416 DOI: 10.1093/jac/dkl369]

34 **Scialo F**, Daniele A, Amato F, Pastore L, Matera MG, Cazzola M, Castaldo G, Bianco A. ACE2: The Major Cell Entry Receptor for SARS-CoV-2. *Lung* 2020; **198**: 867-877 [PMID: 33170317 DOI: 10.1007/s00408-020-00408-4]

35 **Cresswell FV**, Ssebambulidde K, Grint D, Te Brake L, Musabire A, Atherton RR, Tugume L, Muzoora C, Lukande R, Lamorde M, Aarnoutse R, Meya D, Boulware DR, Elliott AM. High dose oral and intravenous rifampicin for improved survival from adult tuberculous meningitis: a phase II open-label randomised controlled trial (the RifT study). *Wellcome Open Res* 2018; **3**: 83 [PMID: 30175245 DOI: 10.12688/wellcomeopenres.14691.1]

36 **Hamzehei M**, Ledinko N. Inhibition of influenza A virus replication by rifampicin and selenocystamine. *J Med Virol* 1980; **6**: 169-174 [PMID: 7241092 DOI: 10.1002/jmv.1890060210]

37 **Dardiri AH**, Bachrach HL, Heller E. Inhibition by rifampin of African swine fever virus replication in tissue culture. *Infect Immun* 1971; **4**: 34-36 [PMID: 5154875 DOI: 10.1128/iai.4.1.34-36.1971]

38 **Halsted CC**, Minnefor AB, Lietman PS. Inhibition of cytomegalovirus by rifampin. *J Infect Dis* 1972; **125**: 552-555 [PMID: 4336860 DOI: 10.1093/infdis/125.5.552]

39 **Kumar A**, Mishra DC, Angadi UB, Yadav R, Rai A, Kumar D. Inhibition Potencies of Phytochemicals Derived from Sesame Against SARS-CoV-2 Main Protease: A Molecular Docking and Simulation Study. *Front Chem* 2021; **9**: 744376 [PMID: 34692642 DOI: 10.3389/fchem.2021.744376]

40 **Parvez MSA**, Karim MA, Hasan M, Jaman J, Karim Z, Tahsin T, Hasan MN, Hosen MJ. Prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 using comprehensive drug repurposing and molecular docking approach. *Int J Biol Macromol* 2020; **163**: 1787-1797 [PMID: 32950529 DOI: 10.1016/j.ijbiomac.2020.09.098]

41 **Forrest GN**, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev* 2010; **23**: 14-34 [PMID: 20065324 DOI: 10.1128/CMR.00034-09]

42 **Pokhrel R**, Chapagain P, Siltberg-Liberles J. Potential RNA-dependent RNA polymerase inhibitors as prospective therapeutics against SARS-CoV-2. *J Med Microbiol* 2020; **69**: 864-873 [PMID: 32469301 DOI: 10.1099/jmm.0.001203]

43 **Pathak Y**, Mishra A, Choudhir G, Kumar A, Tripathi V. Rifampicin and Letermovir as potential repurposed drug candidate for COVID-19 treatment: insights from an in-silico study. *Pharmacol Rep* 2021; **73**: 926-938 [PMID: 33970450 DOI: 10.1007/s43440-021-00228-0]

44 **Elkarhat Z**, Charoute H, Elkhattabi L, Barakat A, Rouba H. Potential inhibitors of SARS-cov-2 RNA dependent RNA

polymerase protein: molecular docking, molecular dynamics simulations and MM-PBSA analyses. *J Biomol Struct Dyn* 2022; **40**: 361-374 [PMID: 32873176 DOI: 10.1080/07391102.2020.1813628]

45 **Soni H**, Gautam D, Sharma S, Malik J. Rifampicin as potent inhibitor of COVID-19 main protease: in-silico docking approach. *Saudi Journal of Medical and Pharmaceutical Sciences* 2020; 588 [DOI: 10.36348/sjmps.2020.v06i09.001]

46 **Semvua HH**, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aarnoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. *Ther Drug Monit* 2015; **37**: 22-32 [PMID: 24943062 DOI: 10.1097/FTD.0000000000000108]

47 **Hanafy AS**, Abd-Elsalam S. Challenges in COVID-19 drug treatment in patients with advanced liver diseases: A hepatology perspective. *World J Gastroenterol* 2020; **26**: 7272-7286 [PMID: 33362383 DOI: 10.3748/wjg.v26.i46.7272]

48 **Chen J**, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. *Ann Clin Microbiol Antimicrob* 2006; **5**: 3 [PMID: 16480505 DOI: 10.1186/1476-0711-5-3]

49 **Li T**, Chiang JY. Rifampicin induction of CYP3A4 requires pregnane X receptor cross talk with hepatocyte nuclear factor 4alpha and coactivators, and suppression of small heterodimer partner gene expression. *Drug Metab Dispos* 2006; **34**: 756-764 [PMID: 16455805 DOI: 10.1124/dmd.105.007575]

50 **Hahn J**, Choi JH, Chang MJ. Pharmacokinetic changes of antibiotic, antiviral, antituberculosis and antifungal agents during extracorporeal membrane oxygenation in critically ill adult patients. *J Clin Pharm Ther* 2017; **42**: 661-671 [PMID: 28948652 DOI: 10.1111/jcpt.12636]

51 **Sadeer NB**, Mahomoodally MF. Antibiotic Potentiation of Natural Products: A Promising Target to Fight Pathogenic Bacteria. *Curr Drug Targets* 2021; **22**: 555-572 [PMID: 32972338 DOI: 10.2174/1389450121666200924113740]

52 **Ata F**, Shaher Mousa Hussein M, Mismar AY, Sharma R, Bozom IAM, Alsiddig Ali Ibrahim Z, Ibrahim WH. Rifampicin-Induced Pneumonitis Mimicking Severe COVID-19 Pneumonia Infection. *Am J Case Rep* 2020; **21**: e927586 [PMID: 32840240 DOI: 10.12659/AJCR.927586]

53 **Sadanshiv M**, George AA, Mishra AK, Kuriakose CK. Rifampicin-induced immune allergic reaction. *Trop Doct* 2018; **48**: 156-159 [PMID: 28764592 DOI: 10.1177/0049475517724689]

54 **Cron RQ**, Caricchio R, Chatham WW. Calming the cytokine storm in COVID-19. *Nat Med* 2021; **27**: 1674-1675 [PMID: 34480126 DOI: 10.1038/s41591-021-01500-9]

55 **Kyriazopoulou E**, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, Fragkou A, Rapti A, Damoulari C, Fantoni M, Kalomenidis I, Chrysos G, Angheben A, Kainis I, Alexiou Z, Castelli F, Serino FS, Tsilika M, Bakakos P, Nicastri E, Tzavara V, Kostis E, Dagna L, Koufargyris P, Dimakou K, Savvanis S, Tzatzagou G, Chini M, Cavalli G, Bassetti M, Katrini K, Kotsis V, Tsoukalas G, Selmi C, Bliziotis I, Samarkos M, Doumas M, Ktena S, Masgala A, Papanikolaou I, Kosmidou M, Myrodia DM, Argyraki A, Cardellino CS, Koliakou K, Katsigianni EI, Rapti V, Giannitsioti E, Cingolani A, Micha S, Akinosoglou K, Liatsis-Douvitsas O, Symbardi S, Gatselis N, Mouktaroudi M, Ippolito G, Florou E, Kotsaki A, Netea MG, Eugen-Olsen J, Kyprianou M, Panagopoulos P, Dalekos GN, Giamarellos-Bourboulis EJ. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 2021; **27**: 1752-1760 [PMID: 34480127 DOI: 10.1038/s41591-021-01499-z]

56 **Smith PB**, Cotten CM, Hudak ML, Sullivan JE, Poindexter BB, Cohen-Wolkowiez M, Boakye-Agyeman F, Lewandowski A, Anand R, Benjamin DK Jr, Laughon MM; Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee. Rifampin Pharmacokinetics and Safety in Preterm and Term Infants. *Antimicrob Agents Chemother* 2019; **63** [PMID: 30910891 DOI: 10.1128/AAC.00284-19]

57 **Bothamley G**. Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Saf* 2001; **24**: 553-565 [PMID: 11444726 DOI: 10.2165/00002018-200124070-00006]

58 **Bouaré F**, Laghmari M, Etouche FN, Arjdal B, Saidi I, Hajhouji F, Ghannane H, Amro L, Tassi N, Benali SA. Unusual association of COVID-19, pulmonary tuberculosis and human immunodeficiency virus, having progressed favorably under treatment with chloroquine and rifampin. *Pan Afr Med J* 2020; **35**: 110 [PMID: 33282065 DOI: 10.11604/pamj.supp.2020.35.2.24952]

59 **Zimmermann P**, Curtis N. COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features. *Pediatr Infect Dis J* 2020; **39**: 469-477 [PMID: 32398569 DOI: 10.1097/INF.0000000000002700]

60 **Mitjà O**, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. *Lancet Glob Health* 2020; **8**: e639-e640 [PMID: 32199468 DOI: 10.1016/S2214-109X(20)30114-5]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 March 25; 11(2): 98-103

DOI: 10.5501/wjv.v11.i2.98

ISSN 2220-3249 (online)

MINIREVIEWS

Too hard to die: Exercise training mediates specific and immediate SARS-CoV-2 protection

Konstantinos I Papadopoulos, Warachaya Sutheesophon, Tar-Choon Aw

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arumugam VA, Wu QN

Received: October 16, 2021
Peer-review started: October 16, 2021
First decision: December 16, 2021
Revised: December 19, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 25, 2022

Konstantinos I Papadopoulos, Research and Development, THAI StemLife, Bangkok 10310, Bangkok, Thailand

Warachaya Sutheesophon, Laboratory, THAI StemLife, Bangkok 10310, Bangkok, Thailand

Tar-Choon Aw, Laboratory Medicine, Changi General Hospital, Singapore 529889, Singapore, Singapore

Tar-Choon Aw, Department of Medicine, National University of Singapore, Singapore 119228, Singapore, Singapore

Corresponding author: Konstantinos I Papadopoulos, MD, PhD, Chairman, Chief Doctor, Research and Development, THAI StemLife, THAI StemLife, 566/3 Soi Ramkhamhaeng 39 (Thepleela 1), Prachaouthit Road, Wangthonglang, Bangkok 10310, Bangkok, Thailand. kostas@thaistemlife.co.th

Abstract

Several mechanisms may explain how exercise training mechanistically confers protection against coronavirus disease 2019 (COVID-19). Here we propose two new perspectives through which cardiorespiratory fitness may protect against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Physical exercise-activated adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling induces endothelial nitric oxide (NO) synthase (eNOS), increases NO bio-availability, and inhibits palmitoylation, leading to specific and immediate SARS-CoV-2 protection. AMPK signaling also induces angiotensin 1-7 release and enhances eNOS activation thus further mediating cardio- and reno-protection. Irisin, a myokine released from skeletal muscles during aerobic exercise, also participates in the AMPK/Akt-eNOS/NO pathway, protects mitochondrial functions in endothelial cells, and antagonizes renin angiotensin system proinflammatory action leading to reductions in genes associated with severe COVID-19 outcomes. Collectively, all the above findings point to the fact that increased AMPK and irisin activity through exercise training greatly benefits molecular processes that mediate specific, immediate, and delayed SARS-CoV-2 protection. Maintaining regular physical activity levels is a safe and affordable lifestyle strategy against the current and future pandemics and may also mitigate against obesity and cardiometabolic disease syndemics. Move more because a moving target is harder to kill.

Key Words: Adenosine monophosphate-activated protein kinase; Irisin; Physical exercise; Nitric oxide; Endothelial nitric oxide synthase; Severe acute respiratory syndrome coronavirus-2

Core Tip: Increased nitric oxide bio-availability through exercise training-induced activation of the master regulator of metabolism, the energy-sensing cellular enzyme adenosine monophosphate-activated protein kinase and irisin, the fat browning exercise hormone, released from skeletal muscles during aerobic exercise may mediate specific, immediate, and delayed severe acute respiratory syndrome coronavirus-2 protection. Move more because a moving target is harder to kill.

Citation: Papadopoulos KI, Sutheesophon W, Aw TC. Too hard to die: Exercise training mediates specific and immediate SARS-CoV-2 protection. *World J Virol* 2022; 11(2): 98-103
URL: https://www.wjgnet.com/2220-3249/full/v11/i2/98.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i2.98

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (COVID-19), has to date (December 2021) infected over 270 million people worldwide and the death tally approaches 5.5 million[1]. Evolutionary evidence supports the survival of the fittest through natural selection for pathogen resistance, with effects mediated through younger age, lifestyle choices and importantly, genetics[2]. Epidemiological data support a lower COVID-19 incidence and severity in children and adolescents[3], individuals with high cardiorespiratory fitness (CRF) and muscle strength[4] as well as certain protective erythropoietin (EPO) augmenting genetic variants[3]. At the other end of the spectrum, inactivity, obesity, insulin resistance, diabetes, and hypertension, are associated with worse SARS-CoV-2 infection course and disproportionate COVID-19 mortality risk[5,6]. Public policies should promote increased physical activity and endeavor to increase the overall physical fitness in society by all available means. This is especially imperative for the population groups associated with worse SARS-CoV-2 prognosis[7]. The scope of this minireview is to focus on the mechanistical perspectives of two novel pathways, namely adenosine monophosphate (AMP)-activated protein kinase (AMPK) and irisin, through which exercise training may mitigate against SARS-CoV-2 infection and improve COVID-19 prognosis.

We conducted a PubMed literature search for publications in the English language since the start of the pandemic until September 2021, using the keywords: "AMPK"; "Irisin"; "physical exercise"; "renin angiotensin system (RAS)"; "angiotensin-converting enzyme 2 (ACE2)"; "nitric oxide (NO)"; "endothelial nitric oxide (NO) synthase (eNOS)"; "beta common receptor (βcR)"; "SARS-CoV-2"; and "COVID-19". We noticed a veritable dearth of publications, especially when the keywords "eNOS", "Irisin", "AMPK" were used in different combinations together with "physical exercise" and "SARS-CoV-2 or COVID-19" which prompted us to focus on AMPK/eNOS and Irisin. Those pathways are known for their cardiometabolic, and vascular protective properties and suggest concrete mechanisms that offer immediate and delayed SARS-CoV-2 protection[8].

HOW DOES EXERCISE IMPROVE IMMUNITY?

Several reviews have described numerous immune mechanisms which may explain how exercise training mechanistically confers protection against COVID-19. First, exercise downregulates the expression/activation of proinflammatory Toll-like receptors (TLR)[5]. Second, exercise training demonstrates an anti-inflammatory cytokine profile with increased levels of anti-inflammatory interleukin (IL)-10, IL-1 receptor antagonist (IL-1ra), and IL-37, which in turn inhibits the TLR-inflammation pathway and counteracts the inflammatory response induced by the inflammasomes[5]. In general, exercise promotes the recirculation of key immune cells and mediates an anti-inflammatory and antioxidant state through multiple mechanisms[5]. Effective rehabilitation programs for sarcopenia, could reduce inflammation and the need for IL-37 to exert its negative feedback to control the release of inflammatory cytokines[9].

NEWER PERSPECTIVES ON EXERCISE PROTECTION IN COVID-19

AMPK

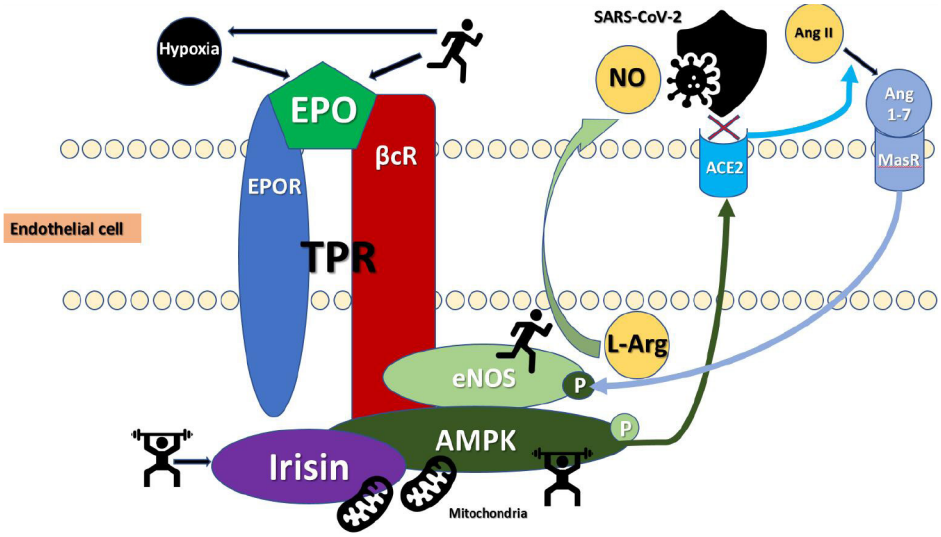
A more specific mechanism with immediate antiviral effects involves AMPK. We propose two new perspectives through which high CRF may protect from SARS-CoV-2. AMPK is an energy-sensing heterotrimeric enzyme, able to detect minute changes in cellular ADP and AMP as well as glucose availability[10]. Located in various cells and organs, AMPK modulates numerous downstream targets through switching phosphorylation on-off, including targets in the RAS[11]. AMPK is activated through several physiological and pathological conditions, such as hypoxia, caloric restriction, and physiological exercise but also *via* certain well known pharmacological agents as metformin, aspirin, canagliflozin, telmisartan, and herbal substances such as resveratrol, berberine, and quercetin[11,12]. Since activating AMPK has been shown to suppresses the Angiotensin II-induced vascular smooth muscle proliferative pathway and improve cardiometabolic disease, we believe that physical exercise-induced AMPK regulation of diverse cellular pathways is a reasonable mechanism in mediating both immediate and delayed SARS-CoV-2 protection (Figure 1)[11,13,14]. Physiological exercise induces AMPK activation as an important molecular mechanism of adaptation after physical activity. AMPK-eNOS phosphorylation-activated formation of NO appears to be a signal that impacts metabolic activity[15]. Mice with an eNOS mutation that prevents AMPK-dependent phosphorylation and impedes NO-biosynthesis develop hyperinsulinemia and insulin resistance with high fasting blood sugar, increased adiposity, elevated inflammatory markers and weight gain when fed a high-fat diet[16]. eNOS phosphorylation through AMPK will lead to increased NO generation and NO bio-availability in the lung and blood vessels[17]. Host endothelium is where the critical COVID-19 battle between SARS-CoV-2 and the host is fought with NO as one of the main contenders (Figure 1)[18]. SARS-CoV-2 spike (S) protein induces endotheliitis *via* downregulation of angiotensin-converting enzyme 2 (ACE2) and NO impairment[18]. At the same time, increased generation and bio-availability of NO inhibits SARS-CoV-1/2[19] replication through two clearly different mechanisms: (1) Decline in the production of viral RNA in the very first stages of viral replication; and (2) decrease in the palmitoylation of nascently-expressed S protein that impacts the fusion of the S protein with ACE2[20]. Similar NO effects are presumed for SARS-CoV-2, given both SARS-CoV-1/2 engage ACE2 in the same manner[21]. Palmitoylation of SARS-CoV-2 S protein is critical in controlling membrane fusion and virion infectivity[22]. Inhibition of acetyl-CoA carboxylase by AMPK will directly inhibit palmitate synthesis thus engendering additional SARS-CoV-2 protection[23]. In addition, orlistat, a pharmaceutical substance used in weight loss treatment also inhibits fatty acid synthase[23]. Through both mechanisms of increased NO bio-availability and directly reducing palmitate synthesis, physical exercise engenders specific and immediate SARS-CoV-2 protection[20,22,23].

Chronic exercise induces EPO elevation, a well-known neuroprotective hormone, which mediates COVID-19 protection[3]. EPO's protective effects are mediated through AMPK-dependent signaling, leading to enhanced phosphorylation of the beta common receptor (βcR) and eNOS, increased βcR-AMPK-eNOS complex formation, NO production, increased NO bio-availability, and ultimately tissue protection (Figure 1)[24]. Elevated, protective EPO mRNA levels were recently reported to be 2.6 times higher in nasopharyngeal swab samples of adult SARS-CoV-2 patients that were asymptomatic or showing mild COVID-19 symptoms, as compared to a control group[25]. Patients with acute respiratory distress syndrome (ARDS) in a moderate-sized COVID-19 cohort showed lower soluble eNOS levels, implying that greater eNOS activity and the presumed increased NO synthesis probably prevent patients from serious lung complications[26]. Fluvoxamine, intensely investigated as a SARS-CoV-2 protective agent, also mediates its action through sigma-1 receptor (S1R) agonism that induces eNOS, albeit *via* phosphatidylinositol-3-kinase and protein kinase B signaling[27].

Moreover, AMPK signaling exerts beneficial effects through RAS by elevating the protective arm of ACE2 and angiotensin (Ang) 1-7 through the Mas receptor (MasR) (Figure 1)[11]. Phosphorylation of ACE2 by AMPK enhances the stability of ACE2 and increases Ang 1-7 and eNOS-derived NO bio-availability further sustaining increased, protective NO levels[28]. Reduced inflammatory responses in lung emphysema, mitigation of pulmonary hypertension and protection against lipopolysaccharide-induced acute lung injury and ARDS have been reported with increased AMPK signaling[28-30]. Later in the course of SARS-CoV-2 infection, AMPK/ACE2/Ang 1-7/MasR-induced NO-increase may be cardio-, and renoprotective through lower oxidative stress, apoptosis, and systemic inflammatory responses[11,31].

Irisin perspectives in COVID-19

Irisin is a myokine, cleaved as a peptide hormone of 112 amino acids from fibronectin type III domain containing 5 in skeletal muscle and secreted during aerobic exercise[32]. Irisin is positively correlated with an active lifestyle and vigorous intensity physical activity[32]. Both aerobic and resistance exercise are associated with high irisin levels, especially in older age groups[32]. Irisin is involved in muscle hyper-trophy and controls energy levels in muscle, participates in glucose homeostasis and browning of white adipose tissue, and has been implicated in exercise-induced neuroprotection as it is highly expressed in the brain[33,34]. Furthermore, exercise-derived irisin reduces arterial stiffness and lowers



DOI: 10.5501/wjv.v11.i2.98

Figure 1 Molecular mechanisms of exercise. Chronic exercise induces transient hypoxia and elevates erythropoietin (EPO) that induces endothelial nitric oxide synthase (eNOS) *via* the tissue protective receptor (EPOR/βcR). Exercise activates adenosine monophosphate-activated protein kinase (AMPK) and releases Irisin, resulting in eNOS activation and subsequent nitric oxide production inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication and mitigating cell entry (X). AMPK stabilizes angiotensin-converting enzyme (ACE) 2 and increases protective angiotensin (Ang) 1-7 conversion which in turn activates eNOS *via* the MasR. Irisin also exerts protective functions on mitochondria. AMPK: Adenosine monophosphate-activated protein kinase; EPO: Erythropoietin; EPOR: EPO receptor; βcR: β-common receptor; TPR: Tissue protective receptor; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; L-Arg: Arginine; ACE2: Angiotensin-converting enzyme 2; Ang II: Angiotensin II; Ang1-7: Angiotensin 1-7; MasR: Mas receptor; P: Phosphorylation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

blood pressure through activation of the AMPK/Akt-eNOS/NO pathway and has thus the potential to impact cardiovascular health (Figure 1)[8,35]. Irisin also protects mitochondrial function in endothelial cells and benefits endothelial barrier integrity through the integrin αVβ5 receptor and activated AMPK signaling[36]. Moreover, irisin can directly antagonize Ang II-induced cardiac profibrotic response *in vitro* as well as *in vivo*[37]. In addition, serum irisin levels were decreased and negatively correlated with disease severity and mortality in ARDS patients[36]. Recently, irisin modulation of genes associated with severe COVID-19 outcomes was reported in human subcutaneous adipocyte cell culture[38].

Collectively, all the above findings point to the fact that increased AMPK and irisin activity with exercise training greatly benefits molecular processes that mediate specific, immediate, and delayed SARS-CoV-2 protection.

CONCLUSION

Evolution arms us with ingenious and adaptive defense structures - our immune system, musculature, and cardiovascular system. Increased CRF through regular aerobic exertion and resistance exercise, greatly benefits all the above systems promoting survival and longevity[5]. Regular physical exercise enhances vaccination response and immunoprotection[5]. Maintaining regular physical activity levels along with prudent and balanced nutrition are safe and affordable lifestyle strategies against the current and future pandemics. Physical exercise may also reverse insulin resistance, alleviate hypertension, and mitigate against obesity and cardiometabolic disease syndemics[39]. While observing social distancing, exercise is still possible in public indoor spaces or outdoors. Exercise prescription for vulnerable groups and free or subsidized use of digital technology with online platforms delivering exercise classes could be employed to achieve the recommended exercise guidelines. For greater health benefits, 300 min of aerobic activity is recommended along with strength training exercises for all major muscle groups at least two times a week[40]. "Work from home" directives along with time savings from daily commuting have potentially freed up time for exercise that can be achievable in the home environment. The beneficial effects of exercise training in communicable and non-communicable disease prevention must remain central when deciding appropriate public health policies and subsidies. Government bodies should heed the Damoclean warning in this pandemic of the excess mortality threatening over 500 million people affected with obesity and diabetes worldwide or risk new hecatombs. We may have to learn to live with the virus for many years to come. It is thus imperative, on an individual level, to devise personal strategies for exercise training that do not depend on access to public gymnasiums. The takeaway message is once again to move more because a moving target is harder to kill.

FOOTNOTES

Author contributions: Papadopoulos KI had the original idea on the hypothesis concept and composed the manuscript; Sutheesophon W and Aw TC assisted in literature search, and all have made substantial, direct, and intellectual contributions to the work; all authors critically assessed the manuscript and approved it for publication.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Country/Territory of origin: Thailand

ORCID number: Konstantinos I Papadopoulos 0000-0003-0041-7853; Warachaya Sutheesophon 0000-0002-1823-3852; Tar-Choon Aw 0000-0002-7814-8836.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). 2021 [DOI: 10.21203/rs.3.rs-15447/v1]
2 **Karlsson EK**, Kwiatkowski DP, Sabeti PC. Natural selection and infectious disease in human populations. *Nat Rev Genet* 2014; **15**: 379-393 [PMID: 24776769 DOI: 10.1038/nrg3734]
3 **Papadopoulos KI**, Sutheesophon W, Manipalviratn S, Aw TC. Age and genotype dependent erythropoietin protection in COVID-19. *World J Stem Cells* 2021; **13**: 1513-1529 [PMID: 34786155 DOI: 10.4252/wjsc.v13.i10.1513]
4 **Af Geijerstam A**, Mehlig K, Börjesson M, Robertson J, Nyberg J, Adiels M, Rosengren A, Åberg M, Lissner L. Fitness, strength and severity of COVID-19: a prospective register study of 1 559 187 Swedish conscripts. *BMJ Open* 2021; **11**: e051316 [PMID: 34226237 DOI: 10.1136/bmjopen-2021-051316]
5 **Nieman DC**, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019; **8**: 201-217 [PMID: 31193280 DOI: 10.1016/j.jshs.2018.09.009]
6 **Gammone MA**, D'Orazio N. COVID-19 and Obesity: Overlapping of Two Pandemics. *Obes Facts* 2021; **14**: 579-585 [PMID: 34569546 DOI: 10.1159/000518386]
7 **O'Rourke RW**, Lumeng CN. Pathways to Severe COVID-19 for People with Obesity. *Obesity (Silver Spring)* 2021; **29**: 645-653 [PMID: 33270351 DOI: 10.1002/oby.23099]
8 **Inoue K**, Fujie S, Hasegawa N, Horii N, Uchida M, Iemitsu K, Sanada K, Hamaoka T, Iemitsu M. Aerobic exercise training-induced irisin secretion is associated with the reduction of arterial stiffness *via* nitric oxide production in adults with obesity. *Appl Physiol Nutr Metab* 2020; **45**: 715-722 [PMID: 31860334 DOI: 10.1139/apnm-2019-0602]
9 **La Rosa F**, Agostini S, Saresella M, Costa AS, Piancone F, Miglioli R, Trecate F, Clerici M. Deregulation of IL-37 and its miRNAs modulators in sarcopenic patients after rehabilitation. *J Transl Med* 2021; **19**: 172 [PMID: 33902634 DOI: 10.1186/s12967-021-02830-5]
10 **Steinberg GR**, Carling D. AMP-activated protein kinase: the current landscape for drug development. *Nat Rev Drug Discov* 2019; **18**: 527-551 [PMID: 30867601 DOI: 10.1038/s41573-019-0019-2]
11 **Liu J**, Li X, Lu Q, Ren D, Sun X, Rousselle T, Li J, Leng J. AMPK: a balancer of the renin-angiotensin system. *Biosci Rep* 2019; **39** [PMID: 31413168 DOI: 10.1042/BSR20181994]
12 **Myojo M**, Nagata D, Fujita D, Kiyosue A, Takahashi M, Satonaka H, Morishita Y, Akimoto T, Nagai R, Komuro I, Hirata Y. Telmisartan activates endothelial nitric oxide synthase *via* Ser1177 phosphorylation in vascular endothelial cells. *PLoS One* 2014; **9**: e96948 [PMID: 24827148 DOI: 10.1371/journal.pone.0096948]
13 **Carapeto PV**, Aguayo-Mazzucato C. Effects of exercise on cellular and tissue aging. *Aging (Albany NY)* 2021; **13**: 14522-14543 [PMID: 34001677 DOI: 10.18632/aging.203051]
14 **Nagata D**, Takeda R, Sata M, Satonaka H, Suzuki E, Nagano T, Hirata Y. AMP-activated protein kinase inhibits angiotensin II-stimulated vascular smooth muscle cell proliferation. *Circulation* 2004; **110**: 444-451 [PMID: 15262850 DOI: 10.1161/01.CIR.0000136025.96811.76]
15 **Kashiwagi S**, Atochin DN, Li Q, Schleicher M, Pong T, Sessa WC, Huang PL. eNOS phosphorylation on serine 1176 affects insulin sensitivity and adiposity. *Biochem Biophys Res Commun* 2013; **431**: 284-290 [PMID: 23291238 DOI: 10.1016/j.bbrc.2012.12.110]
16 **Tenopoulou M**, Doulias PT. Endothelial nitric oxide synthase-derived nitric oxide in the regulation of metabolism. *F1000Res* 2020; **9** [PMID: 33042519 DOI: 10.12688/f1000research.19998.1]
17 **Nosarev AV**, Smagliy LV, Anfinogenova Y, Popov SV, Kapilevich LV. Exercise and NO production: relevance and implications in the cardiopulmonary system. *Front Cell Dev Biol* 2014; **2**: 73 [PMID: 25610830 DOI: 10.3389/fcell.2014.00073]

18 **Lei Y**, Zhang J, Schiavon CR, He M, Chen L, Shen H, Zhang Y, Yin Q, Cho Y, Andrade L, Shadel GS, Hepokoski M, Lei T, Wang H, Yuan JX, Malhotra A, Manor U, Wang S, Yuan ZY, Shyy JY. SARS-CoV-2 Spike Protein Impairs Endothelial Function *via* Downregulation of ACE 2. *Circ Res* 2021; **128**: 1323-1326 [PMID: 33784827 DOI: 10.1161/CIRCRESAHA.121.318902]

19 **Akaberi D**, Krambrich J, Ling J, Luni C, Hedenstierna G, Järhult JD, Lennerstrand J, Lundkvist Å. Mitigation of the replication of SARS-CoV-2 by nitric oxide in vitro. *Redox Biol* 2020; **37**: 101734 [PMID: 33007504 DOI: 10.1016/j.redox.2020.101734]

20 **Akerström S**, Gunalan V, Keng CT, Tan YJ, Mirazimi A. Dual effect of nitric oxide on SARS-CoV replication: viral RNA production and palmitoylation of the S protein are affected. *Virology* 2009; **395**: 1-9 [PMID: 19800091 DOI: 10.1016/j.virol.2009.09.007]

21 **Jackson CB**, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* 2022; **23**: 3-20 [PMID: 34611326 DOI: 10.1038/s41580-021-00418-x]

22 **Wu Z**, Zhang Z, Wang X, Zhang J, Ren C, Li Y, Gao L, Liang X, Wang P, Ma C. Palmitoylation of SARS-CoV-2 S protein is essential for viral infectivity. *Signal Transduct Target Ther* 2021; **6**: 231 [PMID: 34117209 DOI: 10.1038/s41392-021-00651-y]

23 **Tanner JE**, Alfieri C. The Fatty Acid Lipid Metabolism Nexus in COVID-19. *Viruses* 2021; **13** [PMID: 33440724 DOI: 10.3390/v13010090]

24 **Su KH**, Yu YB, Hou HH, Zhao JF, Kou YR, Cheng LC, Shyue SK, Lee TS. AMP-activated protein kinase mediates erythropoietin-induced activation of endothelial nitric oxide synthase. *J Cell Physiol* 2012; **227**: 3053-3062 [PMID: 22021095 DOI: 10.1002/jcp.23052]

25 **Mpekoulis G**, Frakolaki E, Taka S, Ioannidis A, Vassiliou AG, Kalliampakou KI, Patas K, Karakasiliotis I, Aidinis V, Chatzipanagiotou S, Angelakis E, Vassilacopoulou D, Vassilaki N. Alteration of L-Dopa decarboxylase expression in SARS-CoV-2 infection and its association with the interferon-inducible ACE2 isoform. *PLoS One* 2021; **16**: e0253458 [PMID: 34185793 DOI: 10.1371/journal.pone.0253458]

26 **Vassiliou AG**, Zacharis A, Keskinidou C, Jahaj E, Pratikaki M, Gallos P, Dimopoulou I, Kotanidou A, Orfanos SE. Soluble Angiotensin Converting Enzyme 2 (ACE2) Is Upregulated and Soluble Endothelial Nitric Oxide Synthase (eNOS) Is Downregulated in COVID-19-induced Acute Respiratory Distress Syndrome (ARDS). *Pharmaceuticals (Basel)* 2021; **14** [PMID: 34358119 DOI: 10.3390/ph14070695]

27 **Papadopoulos KI**, Sutheesophon W, Aw TC. Anti-SARS-CoV-2 Action of Fluvoxamine may be Mediated by Endothelial Nitric Oxide Synthase. *Pharmacopsychiatry* 2021 [PMID: 34555857 DOI: 10.1055/a-1641-0357]

28 **Zhang J**, Dong J, Martin M, He M, Gongol B, Marin TL, Chen L, Shi X, Yin Y, Shang F, Wu Y, Huang HY, Zhang J, Zhang Y, Kang J, Moya EA, Huang HD, Powell FL, Chen Z, Thistlethwaite PA, Yuan ZY, Shyy JY. AMP-activated Protein Kinase Phosphorylation of Angiotensin-Converting Enzyme 2 in Endothelium Mitigates Pulmonary Hypertension. *Am J Respir Crit Care Med* 2018; **198**: 509-520 [PMID: 29570986 DOI: 10.1164/rccm.201712-2570OC]

29 **Cheng XY**, Li YY, Huang C, Li J, Yao HW. AMP-activated protein kinase reduces inflammatory responses and cellular senescence in pulmonary emphysema. *Oncotarget* 2017; **8**: 22513-22523 [PMID: 28186975 DOI: 10.18632/oncotarget.15116]

30 **Wu YX**, Wang YY, Gao ZQ, Chen D, Liu G, Wan BB, Jiang FJ, Wei MX, Zuo J, Zhu J, Chen YQ, Qian F, Pang QF. Ethyl ferulate protects against lipopolysaccharide-induced acute lung injury by activating AMPK/Nrf2 signaling pathway. *Acta Pharmacol Sin* 2021; **42**: 2069-2081 [PMID: 34417573 DOI: 10.1038/s41401-021-00742-0]

31 **Pourbagher-Shahri AM**, Farkhondeh T, Talebi M, Kopustinskiene DM, Samarghandian S, Bernatoniene J. An Overview of NO Signaling Pathways in Aging. *Molecules* 2021; **26** [PMID: 34361685 DOI: 10.3390/molecules26154533]

32 **Cosio PL**, Crespo-Posadas M, Velarde-Sotres Á, Pelaez M. Effect of Chronic Resistance Training on Circulating Irisin: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Int J Environ Res Public Health* 2021; **18** [PMID: 33802329 DOI: 10.3390/ijerph18052476]

33 **Jodeiri Farshbaf M**, Alviña K. Multiple Roles in Neuroprotection for the Exercise Derived Myokine Irisin. *Front Aging Neurosci* 2021; **13**: 649929 [PMID: 33935687 DOI: 10.3389/fnagi.2021.649929]

34 **De Sousa RAL**, Improta-Caria AC, Aras-Júnior R, de Oliveira EM, Soci ÚPR, Cassilhas RC. Physical exercise effects on the brain during COVID-19 pandemic: links between mental and cardiovascular health. *Neurol Sci* 2021; **42**: 1325-1334 [PMID: 33492565 DOI: 10.1007/s10072-021-05082-9]

35 **Fu J**, Han Y, Wang J, Liu Y, Zheng S, Zhou L, Jose PA, Zeng C. Irisin Lowers Blood Pressure by Improvement of Endothelial Dysfunction *via* AMPK-Akt-eNOS-NO Pathway in the Spontaneously Hypertensive Rat. *J Am Heart Assoc* 2016; **5** [PMID: 27912206 DOI: 10.1161/JAHA.116.003433]

36 **Bi J**, Zhang J, Ren Y, Du Z, Zhang Y, Liu C, Wang Y, Zhang L, Shi Z, Wu Z, Lv Y, Wu R. Exercise hormone irisin mitigates endothelial barrier dysfunction and microvascular leakage-related diseases. *JCI Insight* 2020; **5** [PMID: 32516137 DOI: 10.1172/jci.insight.136277]

37 **Chen RR**, Fan XH, Chen G, Zeng GW, Xue YG, Liu XT, Wang CY. Irisin attenuates angiotensin II-induced cardiac fibrosis *via* Nrf2 mediated inhibition of ROS/ TGFβ1/Smad2/3 signaling axis. *Chem Biol Interact* 2019; **302**: 11-21 [PMID: 30703374 DOI: 10.1016/j.cbi.2019.01.031]

38 **de Oliveira M**, De Sibio MT, Mathias LS, Rodrigues BM, Sakalem ME, Nogueira CR. Irisin modulates genes associated with severe coronavirus disease (COVID-19) outcome in human subcutaneous adipocytes cell culture. *Mol Cell Endocrinol* 2020; **515**: 110917 [PMID: 32593740 DOI: 10.1016/j.mce.2020.110917]

39 **Di Ciaula A**, Krawczyk M, Filipiak KJ, Geier A, Bonfrate L, Portincasa P. Noncommunicable diseases, climate change and iniquities: What COVID-19 has taught us about syndemic. *Eur J Clin Invest* 2021; **51**: e13682 [PMID: 34551123 DOI: 10.1111/eci.13682]

40 **Flack KD**, Hays HM, Moreland J, Long DE. Exercise for Weight Loss: Further Evaluating Energy Compensation with Exercise. *Med Sci Sports Exerc* 2020; **52**: 2466-2475 [PMID: 33064415 DOI: 10.1249/MSS.0000000000002376]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 March 25; 11(2): 104-106

DOI: 10.5501/wjv.v11.i2.104

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Therapeutic potential of N-acetyl cysteine during COVID-19 epoch

Ajita Kapur, Munish Sharma, Geetanjali Sageena

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Abasimel NA

Received: August 7, 2021
Peer-review started: August 7, 2021
First decision: November 11, 2021
Revised: November 22, 2021
Accepted: February 23, 2022
Article in press: February 23, 2022
Published online: March 25, 2022

Ajita Kapur, Department of Pharmacology, V.P. Chest Institute, University of Delhi, Delhi 110007, India

Munish Sharma, Hindu Rao Hospital and NDMC Medical College, Delhi 110007, India

Geetanjali Sageena, Environmental Studies, Keshav Mahavidyalaya University of Delhi, New Delhi 110034, India

Corresponding author: Geetanjali Sageena, PhD, Assistant Professor, Environmental Studies, Keshav Mahavidyalaya University of Delhi, H-4-5 Zone Pitampura, New Delhi 110034, India. geetanjali.sageena@keshav.du.ac.in

Abstract

N-acetyl cysteine (NAC) is a promising drug for prophylaxis and treatment of coronavirus disease 2019 (COVID-19) based on antioxidant and anti-inflammatory mechanisms. Further studies with cautious approach are needed to establish the benefits and risks before considering NAC as an adjuvant treatment for COVID-19.

Key Words: N-acetyl cysteine; COVID-19; Coagulopathy; Therapeutic potential; Prophylaxis; Treatment

Core Tip: Risk of coagulopathy is noteworthy in coronavirus disease 2019 (COVID-19) and cerebral hemorrhage could be a potential risk in COVID-19 patients receiving N-acetyl cysteine (NAC). Results of well-designed randomized controlled trials should be awaited before NAC becomes a common practice for prophylaxis and treatment of patients with COVID-19.

Citation: Kapur A, Sharma M, Sageena G. Therapeutic potential of N-acetyl cysteine during COVID-19 epoch. *World J Virol* 2022; 11(2): 104-106
URL: https://www.wjgnet.com/2220-3249/full/v11/i2/104.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i2.104

TO THE EDITOR

The impact of coronavirus disease 2019 (COVID-19) pandemic resulting in substantial mortalities and morbidities has driven the quest to accelerate the treatment options for containment of this public health emergency. We read with interest the review by Dominari *et al*[1]. The authors have reviewed the pharmacology, efficacy, and safety of N-acetyl cysteine (NAC) as an adjuvant therapy of COVID-19. NAC is a nutraceutical precursor of vital antioxidant glutathione. Based on a broad range of antioxidant and anti-inflammatory mechanisms, NAC seems to be a promising drug to attenuate the risk of developing COVID-19, and in high doses might play an adjuvant role in the treatment of severe COVID-19 and alleviate its fatal complications[2]. We agree with author's insight that NAC is a worthy candidate to be evaluated for COVID-19; however, we consider that a cautiously optimistic approach is required to assess the risk–benefit profile of this medication in the current scenario.

Patients with COVID-19 suffer from coagulopathy and prolonged prothrombin time (PT)[3]. Hypercoagulation due to elevated D dimer and fibrinogen could lead to ischemic stroke in COVID-19 patients. Though less common, intracerebral haemorrhage resulting from consumption coagulopathy related to fibrinogen depletion has been reported in more than 10% of COVID-19 patients with stroke [4].

As documented in the review, adverse effects from NAC could vary from mild gastrointestinal symptoms to severe anaphylactoid reactions[1]. Abnormal hemostatic activity, such as anticoagulant and platelet-inhibiting properties with increased bleeding risk, has been documented in patients receiving NAC[5]. NAC interacts with human vitamin K epoxide reductase at the same binding site and causes interruption in the vitamin K reduction pathway. A recent study warns regarding prolonged use of NAC in COVID-19 patients and suggests the monitoring of international normalized ratio, PT, and partial thromboplastin time. In addition, considering the lipophilicity, and hence, easy passage of NAC through blood brain barrier, this study cautioned about the risk of cerebral hemorrhage in COVID-19[6].

The possible benefits of NAC in COVID-19 seem to outweigh the risks, but an important issue plaguing the usefulness of NAC is its uncertain efficacy in mild cases[7] and potential of unregulated use in the current scenario where there are limited drugs available for the management of COVID-19. Hence, as is rightly stressed upon by the author[1], before the use of NAC in COVID-19 spreads, further research is warranted to avoid another failure story[8]. Clinical trials are already underway to establish efficacy of NAC in COVID-19[9,10], and recent review by Wong *et al*[11] (2021) elaborated the potential role of NAC as adjunctive remedy for COVID-19[11]. However, there is no in vivo research to specifically examine its effects in COVID-19.

A retrospective cohort study of hospitalized patients with moderate or severe COVID-19 pneumonia documented lower risk of progression to serious respiratory failure in patients treated with NAC[12]. However, we would like to emphasize that the results of the randomized controlled trials should be awaited before incorporating NAC to improve prognosis and clinical outcomes in the treatment of COVID-19.

FOOTNOTES

Author contributions: Kapur A designed the editorial; Kapur A, Sharma M, and Sageena G wrote the manuscript; All authors gave final approval for publication.

Conflict-of-interest statement: All authors declare no conflict of interest.

Country/Territory of origin: India

ORCID number: Ajita Kapur 0000-0003-3449-6959; Munish Sharma 0000-0003-1334-5844; Geetanjali Sageena 0000-0001-7248-4356.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **Dominari A**, Hathaway Iii D, Kapasi A, Paul T, Makkar SS, Castaneda V, Gara S, Singh BM, Agadi K, Butt M, Retnakumar V, Chittajallu S, Taugir R, Sana MK, Kc M, Razzack S, Moallem N, Alvarez A, Talalaev M. Bottom-up analysis of emergent properties of N-acetylcysteine as an adjuvant therapy for COVID-19. *World J Virol* 2021; **10**: 34-52 [PMID: 33816149 DOI: 10.5501/wjv.v10.i2.34]

2 **De Flora S**, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. *FASEB J* 2020; **34**: 13185-13193 [PMID: 32780893 DOI: 10.1096/fj.202001807]

3 **Levi M**, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020; **7**: e438-e440 [PMID: 32407672 DOI: 10.1016/S2352-3026(20)30145-9]

4 **Nannoni S**, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke* 2021; **16**: 137-149 [PMID: 33103610 DOI: 10.1177/1747493020972922]

5 **Niemi TT**, Munsterhjelm E, Pöyhiä R, Hynninen MS, Salmenperä MT. The effect of N-acetylcysteine on blood coagulation and platelet function in patients undergoing open repair of abdominal aortic aneurysm. *Blood Coagul Fibrinolysis* 2006; **17**: 29-34 [PMID: 16607076 DOI: 10.1097/01.mbc.0000195922.26950.89]

6 **Hashemi SA**, Kyani A, Bathaie SZ. The *in silico* mechanism of hVKOR interaction with acetaminophen and its metabolite, as well as N-acetyl cysteine: caution on application in COVID-19 patients. *J Biomol Struct Dyn* 2021; 1-12 [PMID: 33879035 DOI: 10.1080/07391102.2021.1910570]

7 **Schloss J**, Leach M, Brown D, Hannan N, Kendall-Reed P, Steel A. The effects of *N*-acetyl cysteine on acute viral respiratory infections in humans: A rapid review. *Adv Integr Med* 2020; **7**: 232-239 [PMID: 32837898 DOI: 10.1016/j.aimed.2020.07.006]

8 **Saag MS**. Misguided Use of Hydroxychloroquine for COVID-19: The Infusion of Politics Into Science. *JAMA* 2020; **324**: 2161-2162 [PMID: 33165507 DOI: 10.1001/jama.2020.22389]

9 **Lai-Becker M**, Duncan MK. Efficacy of N-Acetylcysteine (NAC) in Preventing COVID-19 From Progressing to Severe Disease. September 23 2020 - May 31, 2021 [cited 10 March 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04419025101

10 A Study to Evaluate OP-101 (Dendrimer N-acetyl-cysteine) in Severe Coronavirus Disease 2019 (COVID-19) Patients (PRANA). July 1, 2020 - November 10, 2020 [cited 10 March 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04458298

11 **Wong KK**, Lee SWH, Kua KP. N-Acetylcysteine as Adjuvant Therapy for COVID-19 - A Perspective on the Current State of the Evidence. *J Inflamm Res* 2021; **14**: 2993-3013 [PMID: 34262324 DOI: 10.2147/JIR.S306849]

12 **Assimakopoulos SF**, Aretha D, Komninos D, Dimitropoulou D, Lagadinou M, Leonidou L, Oikonomou I, Mouzaki A, Marangos M. N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study. *Infect Dis (Lond)* 2021; **53**: 847-854 [PMID: 34182881 DOI: 10.1080/23744235.2021.1945675]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 March 25; 11(2): 107-110

DOI: 10.5501/wjv.v11.i2.107

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Bacterial and fungal co-infection is a major barrier in COVID-19 patients: A specific management and therapeutic strategy is required

Tarun Sahu, Henu Kumar Verma, Lakkakula V K S Bhaskar

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lozada-Martinez I

Received: August 14, 2021
Peer-review started: August 14, 2021
First decision: September 2, 2021
Revised: September 8, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 25, 2022

Tarun Sahu, Department of Physiology, All India Institute of Medical Science, Raipur 492001, Chhattisgarh, India

Henu Kumar Verma, Department of Immunopathology, Institute of Lung Health and Immunity, Comprehensive Pneumology Center, Helmholtz Zentrum, Munich 85764, Germany

Lakkakula V K S Bhaskar, Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur 495001, Chhattisgarh, India

Corresponding author: Henu Kumar Verma, PhD, Research Scientist, Senior Researcher, Department of Immunopathology, Institute of Lung Health and Immunity, Comprehensive Pneumology Center, Helmholtz Zentrum, Neuherberg Inglostäder Landstrapβe 1, Munich 85764, Germany. henu.verma@yahoo.com

Abstract

Microbial co-infections are another primary concern in patients with coronavirus disease 2019 (COVID-19), yet it is an untouched area among researchers. Preliminary data and systematic reviews only show the type of pathogens responsible for that, but its pathophysiology is still unknown. Studies show that these microbial co-infections are hospital-acquired/nosocomial infections, and patients admitted to intensive care units with invasive mechanical ventilation are highly susceptible to it. Patients with COVID-19 had elevated inflammatory cytokines and a weakened cell-mediated immune response, with lower $CD4^+$ T and $CD8^+$ T cell counts, indicating vulnerability to various co-infections. Despite this, there are only a few studies that recommend the management of co-infections.

Key Words: COVID-19; Co-infection; Bacterial co-infection; Fungal co-infection

Core Tip: The immune systems of coronavirus disease 2019 patients are already compromised, making them vulnerable to bacterial, fungal, and viral co-infections. These secondary infections, also known as co-infections, are hospital-acquired/nosocomial infections, and mechanically ventilated patients are especially vulnerable. There are no specific guidelines or treatment options for these types of co-infections at the moment, which is contributing to an increase in morbidity and mortality among these patients.

Citation: Sahu T, Verma HK, Bhaskar LVKS. Bacterial and fungal co-infection is a major barrier in COVID-19 patients: A specific management and therapeutic strategy is required. *World J Virol* 2022; 11(2): 107-110
URL: https://www.wjgnet.com/2220-3249/full/v11/i2/107.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i2.107

TO THE EDITOR

The first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China, in December 2019, and the World Health Organization declared it a pandemic in March 2019. Approximately one-third of patients experienced severe complications of COVID-19 and required hospitalization[1]. Recently, secondary bacterial/fungal infections or co-infections are another major concern in COVID-19 patients, impacting mortality but lacking attention. Less evidence of bacterial and fungal infection was documented in earlier coronavirus pandemics and epidemics, such as severe acute respiratory syndrome (SARS)-1 and Middle East respiratory syndrome[2]. Recently, we have seen a paper by Saeed *et al*[3] entitled "Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain"[3] in your well-regarded journal *World J Virol*. We appreciate the work done by Saeed *et al*[3] as they reported the microbial infections in patients with COVID-19 in the Kingdom of Bahrain.

The most common bacterial species they reported were *K. pneumonia, P. aeruginosa, A. baumannii, E. coli, S. aureus, E. faecalis,* and *E. faecium*. Among all of these, hospital-acquired (HAI)/nosocomial infection was higher (73.8%) than community-acquired infection. Similar results were reported by Mahmoudi[4] and Sharifipour *et al*[5] in the neighboring country Iran. Both authors reported the same species of bacterial strains, which are the most common. Later on, a descriptive study conducted in the United Arab Emirates found bacterial co-infection in patients with COVID-19 and especially *Klebsiella pneumonia, Escherichia coli, Staphylococcus aureus,* and *Acinetobacter baumannii* were most predominant strains[6]. The recent reviews and meta-analysis also show that *Klebsiella pneumonia, Haemophiles influenzae, Streptococcus pneumoniae,* and *Staphylococcus aureus* are the most frequently identified bacteria among co-infected patients[7,8]. A unique case series from Saudi Arabia reported Middle East respiratory syndrome coronavirus co-infection in 12% of patients already suffering from severe acute respiratory syndrome coronavirus 2[9]. At the same time, another case series from Saudi Arabia by Shabrawishi *et al*[10] reported 7 cases of COVID-19 and tuberculosis co-infection[10]. The interesting results of Hashemi *et al*[11] showed influenza A (H1N1) virus, human metapneumovirus, bocavirus, adenovirus, respiratory syncytial virus (RSV), and parainfluenza viruses in 105 dead patients with COVID-19 in northeastern Iran[11].

Other than bacteria, fungal and viral co-infections are also severe issues with COVID-19 patients. In the present article, the authors reported fungal co-infection in about 10% of total microbial co-infection. The most common isolated fungi were *Candida galabrata, Candida tropicalis, Candida albicans,* and *Aspergillus fumigatus*. They also found that the death rates in patients with fungal co-infection were very high (70.4%)[3]. Studies from other different regions found aspergillosis or invasive candidiasis as the common fungal co-infections[12]. In contrast, influenza type A, type B, and RSV were the most common viral co-infections in patients with COVID-19[7]. These co-infections are associated with an increased probability of death. Most of the articles reported that microbial co-infections were HAI/nosocomial infections, similar to Saeed *et al*[3], who found 71% were HAI.

Further, the authors have described well different microbial co-infections in patients of COVID-19. Furthermore, the study has some limitations, such as the authors not providing any treatment or management options for COVID-19 infected patients. That is the most crucial concern for the patient's benefit. In this context, we would like to draw your attention to the management and recommendations for the infection. Chedid *et al*[13] reviewed the most common antibiotics used by COVID-19 hospitalized patients, primarily in an intensive situation, by analyzing the use of antibiotics in different types of bacterial secondary and co-infection[13].

On the other hand, Sieswerda *et al*[14] gave evidence-based recommendations for antibacterial therapy for secondary microbial and co-infection[14]. Wu *et al*[15] described the management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19[15]. For the treatment of fungal co-infections, Song *et al*[16] suggested the regimen, which is currently in an induction phase and includes amphotericin B deoxycholate and flucytosine, followed by (1) Fluconazole; alternative options for fluconazole + flucytosine or amphotericin B deoxycholate +

fluconazole; (2) Consolidation phase for fluconazole; and (3) Maintenance (or secondary prophylaxis) phase for fluconazole[16].

Depending upon disease severity, patients with influenza A or B viral co-infection should be treated with oseltamivir or its substitute[17]. Treatment options for other viral co-infection, such as RSV, are restricted and beneficial only in specific circumstances, such as immunosuppression or hypogammaglobulinemia[18,19].

Patients with COVID-19 had elevated levels of inflammatory cytokines and a debilitated cell-mediated immune response, with lower $CD4^+$ T and $CD8^+$ T cell counts, indicating vulnerability to various co-infections. Furthermore, COVID-19 patients who are immunocompromised, such as those with extended neutropenia, hematopoietic stem cell transplantation, hereditary or acquired immunodeficiencies, or tumor, are more likely to develop co-infection. Co-infection and superinfection of pathogens in COVID-19 patients is a critical issue as it is difficult to distinguish the associated complications. Specific diagnostic tests should be recommended for proper treatment and management of these infections to reduce morbidity and mortality.

FOOTNOTES

Author contributions: Sahu T, Verma HK, and Bhaskar LVKS wrote and revised the letter.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: Germany

ORCID number: Tarun Sahu 0000-0002-2721-7432; Henu Kumar Verma 0000-0003-1130-8783; Lakkakula V K S Bhaskar 0000-0003-2977-6454.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **Sahu T**, Mehta A, Ratre YK, Jaiswal A, Vishvakarma NK, Bhaskar LVKS, Verma HK. Current understanding of the impact of COVID-19 on gastrointestinal disease: Challenges and openings. *World J Gastroenterol* 2021; **27**: 449-469 [PMID: 33642821 DOI: 10.3748/wjg.v27.i6.449]

2 **Rawson TM**, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. *Clin Infect Dis* 2020; **71**: 2459-2468 [PMID: 32358954 DOI: 10.1093/cid/ciaa530]

3 **Saeed NK**, Al-Khawaja S, Alsalman J, Almusawi S, Albalooshi NA, Al-Biltagi M. Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain. *World J Virol* 2021; **10**: 168-181 [PMID: 34367932 DOI: 10.5501/wjv.v10.i4.168]

4 **Mahmoudi H**. Bacterial co-infections and antibiotic resistance in patients with COVID-19. *GMS Hyg Infect Control* 2020; **15**: Doc35 [PMID: 33391970 DOI: 10.3205/dgkh000370]

5 **Sharifipour E**, Shams S, Esmkhani M, Khodadadi J, Fotouhi-Ardakani R, Koohpaei A, Doosti Z, Ej Golzari S. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC Infect Dis* 2020; **20**: 646 [PMID: 32873235 DOI: 10.1186/s12879-020-05374-z]

6 **Senok A**, Alfaresi M, Khansaheb H, Nassar R, Hachim M, Al Suwaidi H, Almansoori M, Alqaydi F, Afaneh Z, Mohamed A, Qureshi S, Ali A, Alkhajeh A, Alsheikh-Ali A. Coinfections in Patients Hospitalized with COVID-19: A Descriptive Study from the United Arab Emirates. *Infect Drug Resist* 2021; **14**: 2289-2296 [PMID: 34188495 DOI: 10.2147/IDR.S314029]

7 **Musuuza JS**, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PLoS One* 2021; **16**: e0251170 [PMID: 33956882 DOI: 10.1371/journal.pone.0251170]

8 **Westblade LF**, Simon MS, Satlin MJ. Bacterial Coinfections in Coronavirus Disease 2019. *Trends Microbiol* 2021; **29**: 930-941 [PMID: 33934980 DOI: 10.1016/j.tim.2021.03.018]

9 **Elhazmi A**, Al-Tawfiq JA, Sallam H, Al-Omari A, Alhumaid S, Mady A, Al Mutair A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) coinfection: A unique case series. *Travel Med Infect Dis* 2021; **41**: 102026 [PMID: 33727175 DOI: 10.1016/j.tmaid.2021.102026]

10 **Shabrawishi M**, AlQarni A, Ghazawi M, Melibari B, Baljoon T, Alwafi H, Samannodi M. New disease and old threats: A case series of COVID-19 and tuberculosis coinfection in Saudi Arabia. *Clin Case Rep* 2021; **9**: e04233 [PMID: 34084515 DOI: 10.1002/ccr3.4233]

11 **Hashemi SA**, Safamanesh S, Ghasemzadeh-Moghaddam H, Ghafouri M, Azimian A. High prevalence of SARS-CoV-2 and influenza A virus (H1N1) coinfection in dead patients in Northeastern Iran. *J Med Virol* 2021; **93**: 1008-1012 [PMID: 32720703 DOI: 10.1002/jmv.26364]

12 **Fungal Diseases and COVID-19**. Coronavirus disease-19: The First 7,755 Cases in the Republic of Korea. 2021 Preprint. Available from: medRxiv2020.03.15.20036368

13 **Chedid M**, Waked R, Haddad E, Chetata N, Saliba G, Choucair J. Antibiotics in treatment of COVID-19 complications: a review of frequency, indications, and efficacy. *J Infect Public Health* 2021; **14**: 570-576 [PMID: 33848886 DOI: 10.1016/j.jiph.2021.02.001]

14 **Sieswerda E**, de Boer MGJ, Bonten MMJ, Boersma WG, Jonkers RE, Aleva RM, Kullberg BJ, Schouten JA, van de Garde EMW, Verheij TJ, van der Eerden MM, Prins JM, Wiersinga WJ. Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline. *Clin Microbiol Infect* 2021; **27**: 61-66 [PMID: 33010444 DOI: 10.1016/j.cmi.2020.09.041]

15 **Wu CP**, Adhi F, Highland K. Recognition and management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19. *Cleve Clin J Med* 2020; **87**: 659-663 [PMID: 32393593 DOI: 10.3949/ccjm.87a.ccc015]

16 **Song G**, Liang G, Liu W. Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China. *Mycopathologia* 2020; **185**: 599-606 [PMID: 32737747 DOI: 10.1007/s11046-020-00462-9]

17 **Uyeki TM**, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clin Infect Dis* 2019; **68**: 895-902 [PMID: 30834445 DOI: 10.1093/cid/ciy874]

18 **Beigel JH**, Nam HH, Adams PL, Krafft A, Ince WL, El-Kamary SS, Sims AC. Advances in respiratory virus therapeutics - A meeting report from the 6th isirv Antiviral Group conference. *Antiviral Res* 2019; **167**: 45-67 [PMID: 30974127 DOI: 10.1016/j.antiviral.2019.04.006]

19 **Ruan Q**, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46**: 846-848 [PMID: 32125452 DOI: 10.1007/s00134-020-05991-x]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 March 25; 11(2): 111-112

DOI: 10.5501/wjv.v11.i2.111

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Novel appearance of hyperglycemia/diabetes, associated with COVID-19

Ioannis Ilias

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Gonzalez FM, Chile; Gupta S, United States; Wang TJ, China

Received: September 29, 2021
Peer-review started: September 29, 2021
First decision: January 12, 2022
Revised: January 12, 2022
Accepted: March 15, 2022
Article in press: March 15, 2022
Published online: March 25, 2022

Ioannis Ilias, Department of Endocrinology, Diabetes & Metabolism, Elena Venizelou Hospital, Athens GR-11521, Greece

Corresponding author: Ioannis Ilias, MD, PhD, Consultant Physician-Scientist, Department of Endocrinology, Diabetes & Metabolism, Elena Venizelou Hospital, 2 Elena Venizelou Sq., Athens GR-11521, Greece. iiliasmd@yahoo.com

Abstract

In a recent meta-analysis the prevalence of coronavirus disease 2019 (COVID-19)-associated hyperglycemia was 25%, and that of COVID-19-associated new-onset diabetes was 19%. An association between hyperglycemia or new-onset diabetes and COVID-19 has been suggested. In a recent relevant study of critically and non-critically ill patients with COVID-19, we found that indeed beta-cell function was compromised in critically ill patients with COVID-19 and that these patients showed a high glycemic gap. Nevertheless, one quarter of critically ill patients with no history of diabetes have stress hyperglycemia, a finding which could obscure the prevalence of hyperglycemia or new-onset diabetes that could be attributed to COVID-19 *per se*.

Key Words: Blood glucose; Pandemics; Severe acute respiratory syndrome coronavirus 2; Humans; Hyperglycemia; Hospitalization

Core Tip: An association between hyperglycemia or new-onset diabetes and coronavirus disease 2019 (COVID-19) has been suggested. Nevertheless, one quarter of critically ill patients with no history of diabetes have stress hyperglycemia, a finding which could obscure the prevalence of hyperglycemia or new-onset diabetes that could be attributed to COVID-19 *per se*.

Citation: Ilias I. Novel appearance of hyperglycemia/diabetes, associated with COVID-19. *World J Virol* 2022; 11(2): 111-112
URL: https://www.wjgnet.com/2220-3249/full/v11/i2/111.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i2.111

TO THE EDITOR

We have read with great interest the work by Shrestha *et al*[1] regarding new-onset hyperglycemia/diabetes (DM) in patients with coronavirus disease 2019 (COVID-19). With an erudite meta-analysis the authors found that the pooled prevalence of COVID-19-associated hyperglycemia was 25.23% and that the prevalence of COVID-19-associated new-onset DM was 19.70%[1].

An association between hyperglycemia/new-onset DM and COVID-19 has been suggested[2], *via* decreased insulin secretion and increased insulin resistance[2,3]. In a recent relevant study, of critically and non-critically ill patients with COVID-19, we found that indeed beta cell function (based on glucose and insulin measurements and using the Homeostasis Model Assessment HOMA2 estimate of steady state beta cell function[4]) was compromised in critically ill patients with COVID-19. Furthermore, these patients showed a high glycemic gap (based on admission glucose and glycated hemoglobin measurements)[5]. Nevertheless, we acknowledged that on average, 25% of critically ill patients with no history of DM have stress hyperglycemia[5-7], a finding which could obscure the prevalence of hyperglycemia/new-onset DM that could be attributed to COVID-19 *per se*.

Thus, it would be interesting if the results of the study by Shrestha *et al*[1] were presented separately-if possible-for critically and non-critically ill patients with COVID-19 and compared to non-COVID-19 patients.

FOOTNOTES

Author contributions: Ilias I conceived and wrote this letter.

Conflict-of-interest statement: The author declares no conflict of interest.

Country/Territory of origin: Greece

ORCID number: Ioannis Ilias 0000-0001-5718-7441.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Shrestha DB**, Budhathoki P, Raut S, Adhikari S, Ghimire P, Thapaliya S, Rabaan AA, Karki BJ. New-onset diabetes in COVID-19 and clinical outcomes: A systematic review and meta-analysis. *World J Virol* 2021; **10**: 275-287 [PMID: 34631477 DOI: 10.5501/wjv.v10.i5.275]
2 **Muniangi-Muhitu H**, Akalestou E, Salem V, Misra S, Oliver NS, Rutter GA. Covid-19 and Diabetes: A Complex Bidirectional Relationship. *Front Endocrinol (Lausanne)* 2020; **11**: 582936 [PMID: 33133024 DOI: 10.3389/fendo.2020.582936]
3 **Lim S**, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol* 2021; **17**: 11-30 [PMID: 33188364 DOI: 10.1038/s41574-020-00435-4]
4 **Wallace TM**, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; **27**: 1487-1495 [PMID: 15161807 DOI: 10.2337/diacare.27.6.1487]
5 **Ilias I**, Diamantopoulos A, Pratikaki M, Botoula E, Jahaj E, Athanasiou N, Tsipilis S, Zacharis A, Vassiliou AG, Vassiliadi DA, Kotanidou A, Tsagarakis S, Dimopoulou I. Glycemia, Beta-Cell Function and Sensitivity to Insulin in Mildly to Critically Ill Covid-19 Patients. *Medicina (Kaunas)* 2021; **57** [PMID: 33466617 DOI: 10.3390/medicina57010068]
6 **Bellaver P**, Schaeffer AF, Dullius DP, Viana MV, Leitão CB, Rech TH. Association of multiple glycemic parameters at intensive care unit admission with mortality and clinical outcomes in critically ill patients. *Sci Rep* 2019; **9**: 18498 [PMID: 31811218 DOI: 10.1038/s41598-019-55080-3]
7 **Ali Abdelhamid Y**, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, Horowitz M, Deane AM. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. *Crit Care* 2016; **20**: 301 [PMID: 27677709 DOI: 10.1186/s13054-016-1471-6]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2022 May 25; 11(3): 113-169

Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents

Bimonthly Volume 11 Number 3 May 25, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Observational Study

World Journal of Virology

Bimonthly Volume 11 Number 3 May 25, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Virology*, Basavraj Nagoba, PhD, Professor, Research Dean, Department of Microbiology, MIMSR Medical College, Latur 413512, Maharashtra, India. dr_bsnagoba@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
May 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 May 25; 11(3): 113-128

DOI: 10.5501/wjv.v11.i3.113

ISSN 2220-3249 (online)

REVIEW

Severe acute respiratory syndrome coronavirus 2 infection: Role of interleukin-6 and the inflammatory cascade

Mohaddeseh Bahmani, Rojin Chegini, Elham Ghanbari, Elham Sheykhsaran, Parisa Shiri Aghbash, Hamed Ebrahimzadeh Leylabadlo, Ehsan Moradian, Amir Masoud Kazemzadeh Houjaghan, Hossein Bannazadeh Baghi

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Singh AK, India; Wang H

Received: December 14, 2021
Peer-review started: December 14, 2021
First decision: February 15, 2022
Revised: March 3, 2022
Accepted: April 28, 2022
Article in press: April 28, 2022
Published online: May 25, 2022

Mohaddeseh Bahmani, Department of Virology, Student Research Committee, Tabriz University of Medical Sciences, Tabriz 15731, Iran

Rojin Chegini, Department of Medical Science, Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan 81745-33871, Iran

Elham Ghanbari, Department of Medical Science, Fertility and Infertility Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah 67159-59167, Iran

Elham Sheykhsaran, Department of Microbiology, Student Research Committee, Tabriz University of Medical Sciences, Tabriz 15731, Iran

Elham Sheykhsaran, Parisa Shiri Aghbash, Immunology Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran

Parisa Shiri Aghbash, Department of Virology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz 15731, Iran

Hamed Ebrahimzadeh Leylabadlo, Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran

Ehsan Moradian, Department of Medical Science, Medical Faculty, Tabriz University of Medical Sciences, Tabriz 5165665931, Iran

Amir Masoud Kazemzadeh Houjaghan, Department of Internal Medicine, Medical Faculty, Tehran University of Medical Sciences, Tehran 14155-6559, Iran

Hossein Bannazadeh Baghi, Department of Virology, Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran

Corresponding author: Hossein Bannazadeh Baghi, PhD, Associate Professor, Department of Virology, Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran. hbannazadeh@tbzmed.ac.ir

Abstract

Since December 2019, a novel coronavirus that represents a serious threat to human lives has emerged. There is still no definite treatment for severe cases of

the disease caused by this virus, named coronavirus disease 2019 (COVID-19). One of the most considered treatment strategies targets the exaggerated immune regulator, and interleukin (IL)-6 is a crucial pro-inflammatory mediator. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases show an elevated level of IL-6 related to disease severity. IL-6 activity can be inhibited by the following: IL-6 itself, IL-6 signaling pathways such as Janus kinase and signal transducer and activator of transcription (JAK-STAT), gp130, IL-6R, and downstream activated ILs, such as IL-17 and IL-6 cytokine. Currently, according to these studies and their results, IL-6 blockade with anti-IL-6 or its receptor antibodies such as tocilizumab in COVID-19 is beneficial in severe cases and may reduce the mortality rate. JAK-STAT inhibitors block the cytokine storm by inhibiting several crucial pro-inflammatory mediators such as TNF-α and IL-6 and have shown various results in clinical trials. IL-6 induces IL-17 secretion, and IL-17 is involved in the pathogenesis of inflammatory processes. Clinical trials of anti-IL-17 drugs are currently recruiting, and anti-gp130 antibody is preclinical. However, this agent has shown positive effects in inflammatory bowel disease clinical trials and could be tested for SARS-CoV-2. This study aimed to review the role of IL-6 in the cytokine storm and studies regarding IL-6 and blockade of its inflammatory pathways in COVID-19 to determine if any of these agents are beneficial for COVID-19 patients.

Key Words: Anti-interleukin-6; COVID-19; Inflammation; Interleukin-6; Interleukin-6 receptor; SARS-CoV-2

Core Tip: One of the most considered treatment strategies for severe acute respiratory syndrome coronavirus 2 is targeting the immune response and pro-inflammatory cytokines such as interleukin (IL)-6. Patients with severe acute respiratory syndrome coronavirus 2 show elevated levels of IL-6, which is related to disease severity. Current studies have shown that IL-6 blockade by anti-IL-6 or its receptor antibodies such as tocilizumab is beneficial in severe cases and may reduce the mortality rate. Moreover, the combination of anti-inflammatory agents is more effective than single therapy.

Citation: Bahmani M, Chegini R, Ghanbari E, Sheykhsaran E, Shiri Aghbash P, Leylabadlo HE, Moradian E, Kazemzadeh Houjaghan AM, Bannazadeh Baghi H. Severe acute respiratory syndrome coronavirus 2 infection: Role of interleukin-6 and the inflammatory cascade. *World J Virol* 2022; 11(3): 113-128
URL: https://www.wjgnet.com/2220-3249/full/v11/i3/113.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i3.113

INTRODUCTION

In December 2019, an epidemic of secretive pneumonia which started in Wuhan city, Hubei province, China, quickly spread to many other countries and finally resulted in a pandemic[1]. The causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a single-stranded enveloped RNA virus belonging to Nidovirales and the family Coronaviridae. The analysis of SARS-CoV-2 genome structure has shown that this virus is related to the beta-coronavirus genus, containing bat SARS-identical coronavirus and two previous invasive coronaviruses Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV[2]. Universally, as of September 2021, there have been 226,844,344 recognized cases of SARS-CoV-2, including 4,666,334 victims[3]. The disease caused by the novel coronavirus, coronavirus disease 2019 (COVID-19), is similar to these previous viruses, which is mainly pulmonary disease[4], and all of them have a zoonotic origin. In addition to pulmonary involvement, various organs such as the kidney, gastrointestinal system, nervous system, liver, and coagulation system, may be targets of the virus, leading to serious complications such as acute kidney injury (AKI), acute pulmonary failure, and disseminated intravascular coagulation (DIC) that may lead to death[5]. Currently, this virus is a serious global concern with enormous social and economic damage to societies worldwide[6].

Moreover, the fatality rate is high in severe cases[7]. At present, we do not have any definite treatment for severe cases of this disease, and the management of severe SARS-CoV-2 patients is still challenging. Therefore, various treatment options have been assumed according to the different levels of viral pathogenesis, including viral entry, replication, and effects of the virus on target cells. The antiviral agent remdesivir is the only treatment with Food and Drug Administration (FDA) approval for this disease, and dexamethasone is the only drug to reduce mortality in hospitalized patients with

decreased oxygen saturation but not in others[8]. However, the World Health Organization (WHO) has suggested mortality trials for some repurposed anti-viral drugs, including lopinavir, interferon beta 1a (INF-β1a), and hydroxychloroquine in hospitalized patients with SARS-CoV-2[9].

In this regard, IL-6 is known as a crucial inflammatory mediator with essential roles in the pathogenesis of inflammatory diseases in addition to several chronic disorders such as diabetes mellitus [10]. This cytokine is widely expressed by different immune cells and affects immune function[11]. Thus, the disease has a wide range of symptoms. Clinical deterioration in COVID-19 is mainly due to the effects of inflammatory cytokines such as IL-1, IL-6, IFN-α, and tumor necrosis factor (TNF) that are increased in the cytokine storm phase, and the role of immune cells including neutrophils[12-15]. In this process, when a neutrophil encounters a pathogen, the extensive release of cytokines such as IL-1 and IL-6 may become harmful to the body and lead to multi-organ damage[13]. In this rationale, targeting the cytokine release syndrome (CRS) symbolizes a possible therapeutic goal in managing SARS-CoV-2 related cytokine storms and IL-6[16].

In this study, we aim to review the role of IL-6, the rationale of IL-6 blockade in COVID-19, and the results of recent studies on this topic to determine whether any available anti-IL-6 agents or any other drugs with the ability to inhibit inflammatory pathways induced by this cytokine have shown efficacy in improving patient prognosis in SARS-CoV-2 infection.

STUDY METHOD

PubMed, Google Scholar, Scopus, and the Web of Science were searched with the following keywords or their combinations, without any time limits: COVID-19, IL-6, IL-6 receptor, SARS-CoV-2, anti-IL-6, Inflammation. Related articles of any type were selected and reviewed. Extracted information included: SARS-CoV-2 pathophysiology and characteristics, IL-6 activities in the immune system and associated pathways, studies focused on the concept of anti-IL-6 antibodies in the treatment of COVID-19, and other methods of IL-6 inhibition [Janus kinase and signal transducer and activator of transcription (JAK-STAT) inhibition and anti-IL-17 therapies] and are discussed further.

SARS-COV-2 PATHOPHYSIOLOGY AND CHARACTERISTICS

In the last two decades, the third most common coronavirus to cause a pandemic of acute respiratory disease in humans is SARS-CoV-2. These viruses enter the body through respiratory aerosols and are attached to the nasal or paranasal epithelial cells[17]. Angiotensin-converting enzyme 2 (ACE-2) is the major receptor for these viruses to enter host cells, which is expressed in nasal epithelial cells[18,19].

The virus, along with the infection of ciliated cells in the airways, undergoes local replication and dissemination. This stage lasts a few days, and a slight immune response is produced during this process. Despite having a low viral load at this time, infected individuals are highly contagious, and the virus can be identified following a nasal swab[20].

Virus entry into the host cell

Through its spike (S) protein, the virus enters the host cell by binding to ACE-2 on the cellular surface. Transmembrane serine protease 2 (TMPRSS2), then mediates S protein cleavage, and the virus enters the cell[21]. A high virus infectivity rate is associated with mutations in the binding domain of the receptor and the acquisition of a furin cleavage site in the S protein. The association of the virus with ACE-2 can decrease anti-inflammatory function and increase angiogenic activity[22]. The virus migrates from the nasal epithelium to the upper respiratory tract within the conducting airways[23]. The disease presents various signs and symptoms such as fever and dry cough due to involvement of the upper respiratory tract[24].

At this stage, a higher immune response occurs due to the virus-infected cells and results in the secretion of C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and -λ). As a result of the sufficient immune response to control the spread of infection, the majority of patients do not advance beyond this point[25]. About one-fifth of infected individuals advance to this point and may experience severe symptoms. The virus, *via* the host receptor ACE-2, targets alveolar epithelial cells type 2 and continues to undergo replication to create more and more viral nucleocapsids[26].

Many distinct cytokines and inflammatory markers are now produced by virus-laden pneumocytes such as ILs (IL-1, IL-6, IL-8, and IL-12), tumor necrosis factor-alpha (TNF-α), IFN-λ and IFN-β, monocyte chemoattractant protein-1 (MCP-1), CXCL-10, and macrophage inflammatory protein-1 alpha (MIP-1α). This 'cytokine storm' serves as a chemoattractant to neutrophils, CD4 helper, and CD8 cytotoxic T cells, and these cells then become sequestered in the pulmonary tissue[27,28]. In addition to being crucial in fighting the virus, these cells cause inflammation and damage to the lungs and other organs. The host cell undergoes apoptosis and releases new viruses, which will then infect the neighboring type 2 alveolar epithelial cells in the same way. Diffuse trauma to the alveoli eventually results in an acute

respiratory syndrome and finally respiratory distress, owing to the recurrent injuries triggered by the sequestered immune cells and viral replication, contributing to the annihilation of both type 1 and type 2 pneumocytes[29,30].

COVID-19 spreads mainly by the transmission of respiratory droplets from person to person and occurs when someone is in close contact with an infected individual who is coughing or sneezing violently. This occurs as the host's mucosal surfaces, *i.e.*, the eyes, nose, and mouth, are exposed to the infected respiratory droplets[31]. Virus transmission may also occur by fomites, such as bedsheets, towels, kitchen utensils, thermometers, and stethoscopes, used by or used on the infected person. Airborne transmission of COVID-19 can occur especially in situations where aerosol-generating procedures are conducted, *i.e.*, endotracheal intubation, bronchoscopy, open suction, oxygen nebulization, bronchodilators, or steroids, ventilation using a bag and mask, tracheostomy, and cardiopulmonary resuscitation[32]. In this way, the incubation time for SARS-CoV-2 (between the onset of symptoms and exposure to the virus) is about 5 to 6 d. However, it can be up to 14 d. During this time, also known as the 'pre-symptomatic' phase, the affected individual can be contagious and transmit the virus to the healthy population[33,34]. The most frequent symptoms include fever, muscle aches, shortness of breath, malaise, and a dry cough.

While patients can remain asymptomatic or develop a mild, moderate, or severe illness, gastrointestinal manifestations such as stomach pain, vomiting, and loose stools can also occur. Many of the complications seen in SARS-CoV-2 infected individuals are attributed to the CRS[35,36].

Cytokine storm

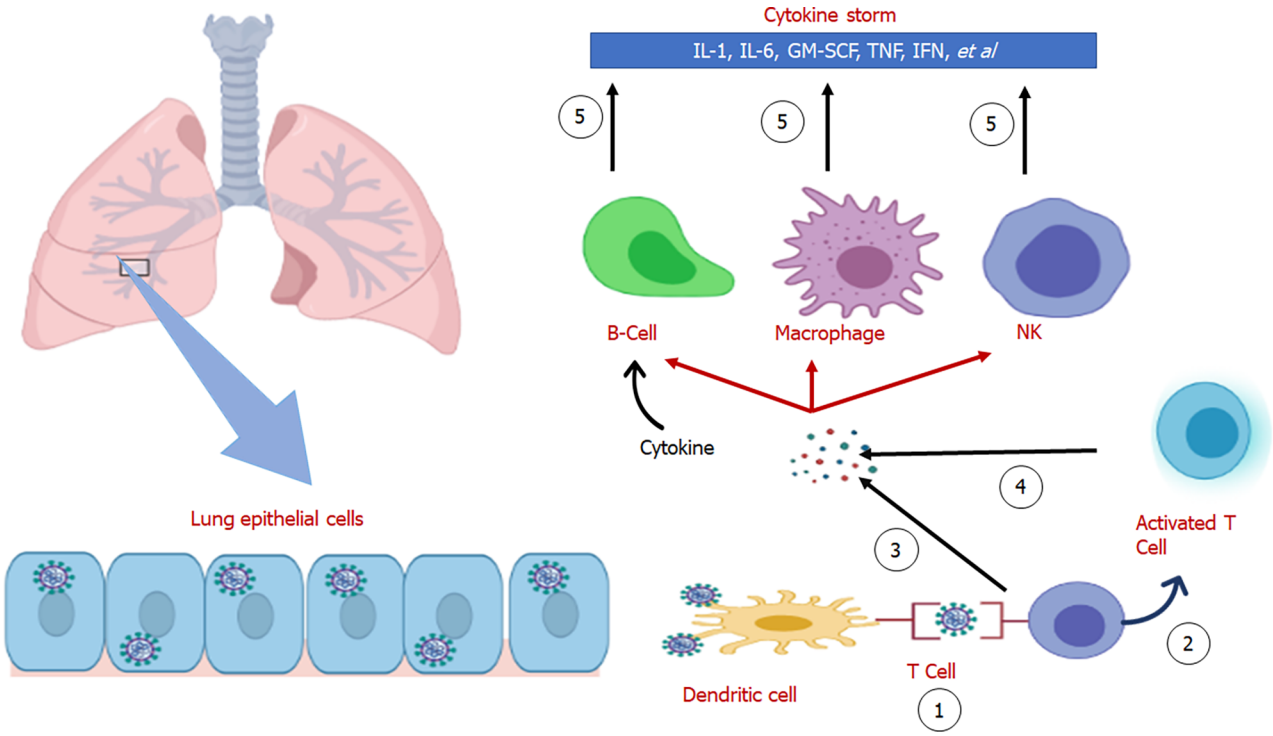
The cytokine storm was historically referred to as an influenza-like syndrome that occurred during systemic diseases such as sepsis and after immunotherapies such as Coley's toxins. *Yersinia pestis* (causative agent of plague or black death) infection has led to extreme pandemics; it induces alveolar macrophages to produce disproportionate quantities of cytokines, resulting in the cytokine storm and has subsequently caused massive pandemics[37]. An intensive inflammatory response and fast release of various cytokines (such as TNF-α-1, 2, IL-6, and IFN-γ) to the circulation are activated by pathogen infection (Figure 1). Patients with viral infections are especially vulnerable to acute respiratory failure due to the cytokine storm[38]. For instance, in other coronaviruses (SARS and MERS), cytokine cascades and low lymphocytes are positively linked to the course and severity of the disease. Recent experiments have supported this conclusion in most cases of SARS-CoV-2, indicating low lymphocyte counts and heightened levels of inflammatory mediators[12,39]. Furthermore, it has been shown that pro-inflammatory cytokines such as IL-6 play an essential role in the progression of COVID-19.

IMMUNE SYSTEM AND ROLES OF IL-6

IL-6 is a soluble mediator with various functions in the immune system[40]. For example, controlling the differentiation and migration of immune cells, apoptosis of target cells[41], and assembly of acute-phase proteins such as C-reactive protein (CRP), haptoglobin, and fibrinogen. In contrast, IL-6 reduces the production of other proteins such as albumin. Human IL-6 comprises 212 amino acids (28-amino-acid signal peptide), and its controlling gene is located on chromosome 7p21[40]. This interleukin contributes to hypothalamic-pituitary-adrenal axis regulation and glucose homeostasis. It induces the differentiation of T-helper cells, which secrete IL-17. These cells are related to the pathogenesis of chronic inflammatory diseases[42]. IL-6 is produced in the immune system by various cells including endothelial cells and contributes to the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis, atherosclerosis, and systemic lupus erythematosus[41]. This cytokine acts by binding to its receptor on the target cells that consist of CD126 (IL-6 Receptor-α) and glycoprotein 130 (gp130). Therefore, it activates signaling pathways such as JAK-STAT[43] and mitogen-activated protein kinase[11]. Conformational alterations in the gp130 cytoplasmic domain when IL-6 binds to the IL-6 receptor induces activation of JAK-STAT[43], and JAK-STAT signaling pathway activation leads to cytokine release[44]. However, these signaling pathways downregulate IL-6 expression[11].

While the membrane-bound receptor (IL-6Rα) is expressed only on the surface of a small number of cells such as leukocytes and hepatocytes (known as IL-6 classic signaling), IL-6 can affect many other cells through its soluble receptor (sIL-6Rα). It was recently discovered that endothelial cells also express IL-6R. This receptor forms a complex with IL-6 that binds to gp130. This complex then mediates a signal known as IL-6 trans-signaling through which pro-inflammatory responses are mainly mediated. In contrast, the classic signaling pathway is related to anti-inflammatory pathways[41]. Furthermore, IL-6 is produced by the innate immune cells after encountering a pathogen and is critical in the body's defense against the respiratory syncytial virus and influenza virus in the early infection phases[45]. However, in CRS, IL-6 and IL-5 can induce coagulation cascade and complement system overactivation, capillary leakage, hypotension, and myocardial dysfunction[46].

In severe SARS-CoV-2 infection, high levels of pro-inflammatory mediators are present, such as IL-6. Although one study showed that monocytes were a source of IL-1β and IL-8, the exact source of IL-6 remains unclear[47]. In the presence of immune dysregulation, in addition to a non-sufficient anti-viral



DOI: 10.5501/wjv.v11.i3.113

Figure 1 The mechanism of the inflammatory storm. ① Antigen presenting; Dendritic cells activate T-cells by processing the antigen and delivering it to these cells; ② Start reproducing; Native T cells become activated by receiving antigens from dendritic cells; ③ A significant quantity of cytokines is secreted during the activation of T cells. These cytokines can activate B cells, macrophages, and NK cells; ④ Activated T cells also release cytokines and further activate macrophages, B cells and NK cells; ⑤ Cytokines secreted; These activated cells, in turn, lead to the secretion of inflammatory and pro-inflammatory cytokines; the resulting cytokine storm leads to the development of clinical signs of infection.

response, there is also a continuous secretion of pro-inflammatory mediators such as IL-6 that resembles the macrophage activation syndrome and lead to multi-organ damage[45]. Also, in COVID-19, multifocal interstitial pneumonia is the chief reason for pulmonary failure and death. In this process, there are inflammatory infiltrates in the interstitial tissue of the lungs, which lead to alveolar damage [48]. These infiltrates consist of mononuclear cells that will be induced after the pro-inflammatory pathways are activated by trans-signal transduction of IL-6[45]. In this way, one study showed that patients with high levels of ACE-2 expression experience more severe tissue damage by IL-6 and the cytokine storm after infection with SARS-CoV-2. These individuals also have a suppressed immune system to fight against the virus[7]. In summary, IL-6 is crucial in both pro-inflammatory and anti-pathogen responses, and trans-signaling is the critical pathway of inflammatory processes conducted by IL-6. A diagram of the significant roles of IL-6 and its location in the immune cascade is summarized in Figure 2.

DRUGS AVAILABLE TO INHIBIT IL-6 ACTIVITY

According to the signaling pathways induced by IL-6 and its components, IL-6 activity can be inhibited by the following: IL-6 itself, IL-6 signaling pathways such as JAK-STAT, gp130, IL-6R, or the IL-6/sIL-6R complex[49]. Two main drugs in the class of IL-6 receptor blockers are tocilizumab (TCZ) and slumab, which are FDA approved monoclonal antibodies for rheumatoid arthritis, and TCZ is also approved for juvenile idiopathic arthritis (JIA) and giant cell arteritis[50].

TCZ blocks both soluble and membrane-bound receptors and accordingly blocks signal transduction *via* JAK-STAT[51]. JIA, a chimeric antigen receptor (CAR)-T cell-induced CRS, giant cell arteritis, rheumatoid arthritis, and Still's disease are examples of the conditions in which TCZ has been used to control the disease[52]. Siltuximab is an anti-IL-6 agent that has shown more effectiveness than TCZ in some aspects, and although it is not FDA approved, it is used in refractory CRS cases. Data regarding Siltuximab in COVID-19 are currently restricted[46].

The specific gp130FC named Olamkicept specifically blocks the trans-signaling pathway. In animals, it showed more effectiveness in controlling the hyper-inflammatory status due to sepsis than anti-IL-6 antibodies. Significantly, it did not impair the anti-inflammatory responses of IL-6 *via* classic signal-transduction[45]. JAK-STAT inhibition is another option. Some of these agents are currently on COVID-19 clinical trials, such as ruxolitinib. A list of these drugs is shown in Table 1.

Table 1 Drugs with anti-interleukin-6 activity and their side effects with examples of clinical trials in coronavirus disease 2019

Ref.	SARS-CoV-2 clinical trials on Clinicaltrial.gov	Side effects	Examples	Category
[93]	NCT04661527, NCT04315298, NCT04357808, NCT04386239, NCT04341870, NCT04359901, NCT04380519	Cytopenia, intestinal perforation, Hypersensitivity, immunosuppression, and the possibility of infections, impairment of liver enzymes	Sarilumab	The anti-receptor of IL-6
[94, 95]	NCT04445272, NCT04331795, NCT04346355, NCT04320615, NCT04356937, NCT04403685, NCT04339712	Intestinal perforation, Hypersensitivity, immunosuppression, and the possibility of infections, acute liver dysfunction, demyelination, cardiac injury, and hepatitis	Tocilizumab	
[96]	NCT04322188, NCT04329650, NCT04330638	Hypersensitivity disorders, intestinal perforation, risk of infections	Siltuximab	Anti-IL-6
[97]	-	Preclinical; in a phase 2 trial of IBD, it showed effectiveness. Patients in this study who were treated with the drug had hypersensitivity skin reactions and respiratory infections. In animal studies, it did not show serious immunosuppression	Olamkicept	Specific gp130fc
[98]	NCT04358614, NCT04401579, NCT04640168, NCT04381936 (RECOVERY Trial), NCT04320277	Increased risk of infections including reactivation of latent infections, lymphoproliferative disorder, cytopenia, liver enzymes disturbances, clot formation, intestinal perforations	Baricitinib	JAK inhibitors
[99]	NCT04348071, NCT04377620, NCT04362137, NCT04366232	Skin malignancy, exacerbation with drug discontinuation, cytopenia, and immunosuppression, increased risk of infection	Ruxolitinib	

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IL: Interleukin; IBD: Inflammatory bowel disease; JAK: Janus kinase.

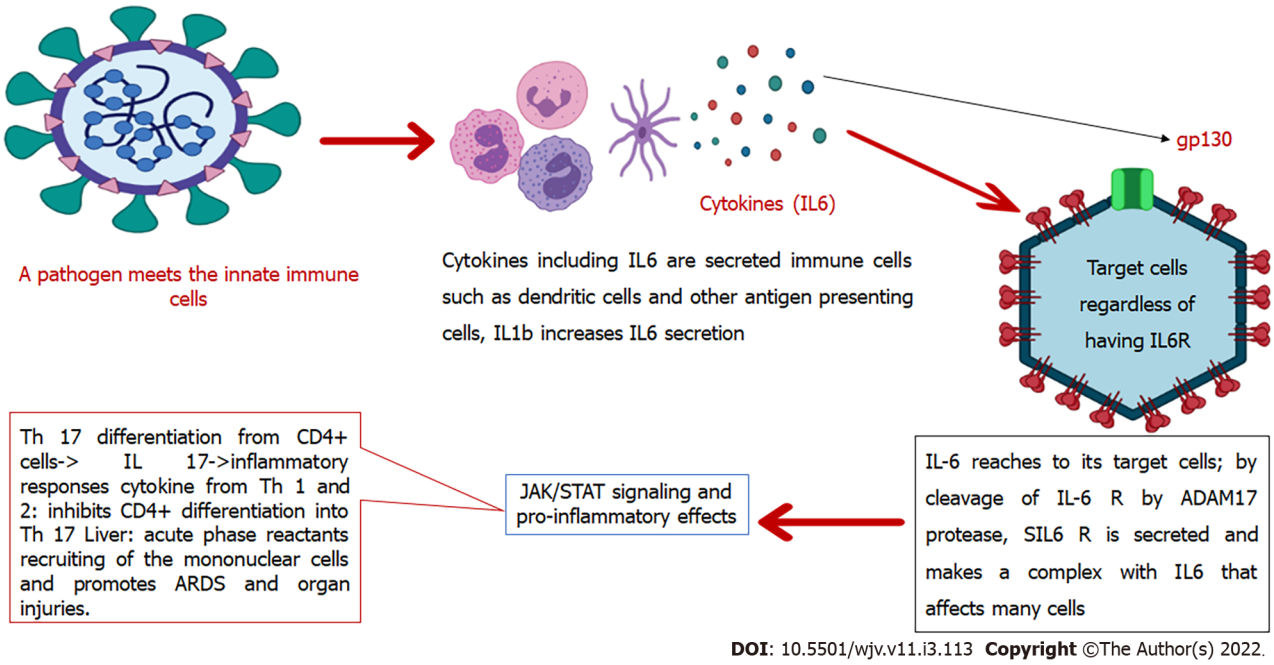


Figure 2 Interleukin-6 in the immune system. IL: Interleukin; JAK-STAT: Janus kinase and signal transducer and activator of transcription.

EXPERIENCE OF IL-6 BLOCKADE IN COVID-19

The cytokine storm is associated with disease intensity in SARS-CoV-2, as also shown in SARS-CoV-1 and MERS-CoV. Although the reports from different studies focused on IL-6 blockade in COVID-19 are inconsistent, it was first shown to reduce the mortality rate in critically ill patients[53].

Considering the presence of lymphopenia in SARS-CoV-2 patients, administration of immunosuppressive agents might increase the risk of secondary fungal or bacterial infections[54]. In a previous study, TCZ induced necrotizing fasciitis and candidemia[55]. Accordingly, the exact place for immunosuppression and anti-IL-6 agents in COVID-19 is crucial. The possible effects of TCZ on management of the COVID-19 related cytokine storm first originated from observational studies that showed it to be effective in the clinical improvement of COVID-19 patients[56]. In a recent clinical trial,

the effect of a single dose of 8 mg/kg TCZ administration *via* the intravenous route in addition to the standard of care in the management of COVID-19 was investigated. In this study, 46 adult patients who were positive for SARS-CoV-2 and had multifocal interstitial pneumonia on imaging studies were enrolled soon after showing clinical worsening. The drug was influential in the clinical improvement of severely ill patients and patients in the early clinical worsening state. However, it did not show significant efficacy in reducing the mortality rate and was accompanied by adverse effects[48].

According to a recent observational study, having an IL-6 level of more than 30 pg/mL is related to the disease severity and need for respiratory support in COVID-19 patients. This study showed the positive effects of TCZ in patients with higher IL-6 levels at baseline, but no positive trends were seen in the group with low IL-6 levels[51].

A recent case series showed the efficacy of subcutaneous TCZ in three severely ill COVID-19 patients in reducing inflammatory-related indices and improving the clinical condition[57]. The results of a prospective phase two cohort study (TOCIVID-19) showed that TCZ effectively reduced the mortality rate at 30 d, especially in severe patients who did not require mechanical ventilation. This effect was independent of corticosteroids and was not accompanied by significant adverse events[58].

One of the concerns regarding the use of anti-immune drugs in SARS-CoV-2 is that they may interfere with the proper immune response to the virus. Cytokines, especially IL-6, play a significant role in the host's fight against viruses through the humoral and cellular responses by affecting helper and cytotoxic T cells. Accordingly, a cohort study conducted in Spain found that these drugs do not pose a problem in the body's fight against the virus. Although the study found that patients treated with anti-cytokines had a longer viral clearance time, they initially had higher virus levels, and their disease was more severe[59]. A preprint study that showed an unexpected increase in inflammatory mediators after TCZ administration supports the fact that IL-6 blockade alone may not be effective in the management of COVID-19[60]. Recently, two studies showed a transient elevation in the D-dimer level in SARS-CoV-2 patients receiving TCZ[61,62]. A recent meta-analysis also demonstrated that IL-6 blockade alone does not lower the mortality rate, although it may effectively reduce the risk of respiratory failure in hospitalized patients[63]. According to another study, administration time is another crucial factor, and treatment with TCZ ten days after disease onset is more beneficial[64]. In contrast, other studies, including the RECOVERY trial, have shown that early administration of TCZ in severe cases before intensive care unit (ICU) admission and the need for mechanical ventilation is effective in reducing the mortality rate,[65,66] and when the patient requires mechanical ventilation, it will not have much effect[66,67]. In general, different methods and inclusion criteria in studies do not result in the same conclusions. A list of recent studies in this regard is summarized in Table 2. According to some clinical trials, TCZ, when added to a corticosteroid, markedly reduces the mortality rate compared with corticosteroids (CSs) alone. Treatments that include agents to target more ILs in addition to IL-6 have more efficacy than only IL-6 blockade[63,68]. IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF, IL-1, and IL-8 are the primary inflammatory mediators that could be targeted in CRS. IL-1 is proximal to IL-6 in the inflammatory cascade, and its blockade has recently been considered. A recent study compared the effectiveness of IL-1 and IL-6 blockade with the standard of care, and it was observed that IL-1 inhibition is more effective in reducing the mortality rate, while positive effects of IL-6 antibodies were restricted to a group of severely ill patients with high CRP levels[50]. Another clinical trial of TCZ in COVID-19 patients with a hyperinflammatory state also stopped recruiting as it failed to reach its primary endpoints (improving the patient's clinical status or reducing the mortality rate)[69]. In general, despite the effect that IL-6 blockade has on the suppression of inflammation, it cannot completely control inflammation as it does not affect the distal inflammatory pathways[70]. However, in severe and critical SARS-CoV-2 patients with a hyperinflammatory state, IL-6 blockade with monoclonal antibodies seems to be effective in reducing the mortality rate, reducing the risk of mechanical ventilation, and improving the clinical condition[67,71-74]. Although all of these studies have been performed in adult patients, the effect of TCZ in the treatment of COVID-19 in children is also being investigated in the RECOVERY trial[67].

To date, several clinical trials have failed to show the efficiency of TCZ in COVID-19 treatment. However, the RECOVERY trial and some other clinical trials showed positive results[67,75,76]. Although meta-analysis had previously demonstrated an 11% reduction in 28-d mortality following TCZ administration in patients with severe SARS-CoV-2 infection, this reduction was significant when the results of the RECOVERY trial were added[67]. In conclusion, this drug can effectively improve the prognosis in extreme cases.

TCZ inhibits both classic and trans-signal transduction through IL-6, thus interfering with this cytokine's anti- and pro-inflammatory functions. As mentioned previously, IL-6 signaling pathways involve the JAK-STAT that could be targeted with drugs such as ruxolitinib, a JAK 1 and 2 inhibitor. This drug lowers the levels of IL-6 and is currently being evaluated for SARS-CoV-2 and had positive effects in one study[77]. However, RUXCOVID, a phase 3 clinical trial of ruxolitinib, revealed no significant efficacy in reducing the death rate and serious complications[78]. Another JAK inhibitor is baricitinib. A recent clinical trial (ACTT2) that evaluated baricitinib in hospitalized patients with SARS-CoV-2 infection indicated that it reduced the recovery time when added to remdesivir, compared with remdesivir alone[79,80]. Another study also investigated the potency of the anti-myeloproliferative agent ruxolitinib and included the patients requiring supplementary oxygen but not with respiratory

Table 2 List of recent clinical trials and observational studies regarding interleukin-6 blocker monoclonal antibodies in severe acute respiratory syndrome coronavirus 2

Study design	Inclusion criteria	Interventions	Number of patients	Results	Ref.
Observational retrospective	Severe SARS-CoV-2 positive ICU admitted patients, with or without respiratory failure	Single 400 mg TCZ dose, without antimicrobialpro-phylaxis	55 severe patients were treated,Compared with 41 untreated (non-severe) patients	Lower mortality rate among treated patients against more disease severity, with no serious side effects and no significantly different increased infection rates	[53]
Quasi-experi-mental	SARS-CoV-2 positive patients with respiratory failure or a need for supplemental oxygen, with clinical or laboratory signs of acute inflammation	Comparing CSs, and TCZ (8 mg/kg up to 800 mg/dose up to 3 doses)	33 patients in the TCZ group and 60 in the CS group.	These drugs both reduced the need for supplemental oxygen and ICU stay to the same level, but in the CS group the survival rate was higher, use of TCZ was safe	[100]
Cohort	COVID-19 patients with respiratory failure and acute inflammatory laboratory findings, such as an elevated CRP level	Anakinra: 5 mg/kg BD until clinical improvement; TCZ: 400 mg single dose, repeated according to the clinical condition; Sarilumab: 400 mg single dose	62 patients received IL-1 blocker and 55 IL-6 blocker (26 sarilumab and 29 TCZ) (severe patients); 275 without IL blockade (standard of care only)	IL-6 blockade had only limited effectiveness in individuals with high concentrations of CRP, but IL-1 blockade reduced the mortality rate in all patients	[50]
Retrospective observational	Severe patients	Tocilizumab use was compared with standard of care in ICU patients	78 severe patients received tocilizumab and were compared with 112 severe patients who received standard of care	Patients on tocilizumab had a longer hospital and ICU stay and more costs with no reduction in the mortality rate	[101]
Retrospective observational	Severe SARS-CoV-2 patients with respiratory failure	TCZ 8 mg/kg	30 severe patients with respiratory failure who received TCZ were evaluated for inflam-matory markers and clinical condition after treatment	Patients had better oxygenation and inflam-matory markers decreased after treatment with TCZ	[102]
Randomized, double-blindclinical trial	Hospitalized patients without respiratory failure and mechanical ventilation, but with decreased SpO2 in room air	8 mg/kg up to 800 mg, TCZ; One-two doses	249 TCZ; 128 SOC	Likelihood ratio of; serious adverse outcomes were significantly lower in the treatment group; But no reduction in all-cause mortality rate	[8]
Clinical trial	Moderate and severe patients according to the clinical status, with higher IL-6 levels, neither ICU admitted nor on mechanical ventilation	TCZ 400 mg; Single-dose	29 patients were treated with TCZ and 32 received standard of care only	TCZ was safe but did not show any significant difference in clinical improvement	[103]
Cross-sectional, observational	Severe patients with high levels of inflammatory markers	TCZ 4 mg/kg	54 patients were treated with TCZ	Significant reduction in neutrophil count and CRP	[104]
Clinical trial	Patients with hyper-inflam-matory state and acute respiratory failure	TCZ 8 mg/kg (up to 800 mg); After 12 h: second dosage	66 severe patients received TCZ and were compared with 60 patients who received standard of care	Not effective in decreasing the risk of disease deteri-oration	[105]
Open-label clinical trial	Proven SARS-CoV-2 infection, with the need for respiratory support and recent worsening in the clinical condition	TCZ 8 mg/kg	46 moderate and severe patients were treated with TCZ	Treatment improved respiratory function	[48]
Clinical trial	High levels of IL-6Moderate and severe disease severity	TCZ 400 mg (second dosage after 24h)	34 patients were treated and 31 were not	Treatment with TCZ improved respiratory condition without reducing the mortality rate	[106]
Clinical trial	Severe and critical patients	Sarilumab 400 mg	Total = 416 (Sarilumab 400 mg, n = 173; Placebo, n = 84; Sarilumab 200 mg, n = 159); Primary analysis between 194 severely ill	Did not meet the primary and secondary endpoints in improving disease progression and the study stopped further	NCT04315298 [107,108]

			patients who needed respiratory support	recruitment	
Randomized, double-blindclinical trial	Severe patients with decreased SpO2 without supplemental oxygen	TCZ 8 mg/kg up to 800 mg	2:1 Placebo+ Standard of care (151); TCZ+ SOC (301)	No significant benefits on mortality rate or clinical improvement, but a positive effect on hospitalization duration was observed with no significant side effects compared with the control group	NCT04320615 [109]
Retrospective cohort	SARS-CoV-2 positive patients with severe pneumonia	TCZ one to two doses, 400–800 mg every 12 h	n = 62 treated, n = 86 untreated	Treated patients showed significantly lower leukocytosis compared to the control group after 14 d. D-dimer and ferritin initially increased and then decreased in the treated group. The mortality rate at 28 d was statistically lower in the TCZ group. A longer hospital stay was shown in these patients although this was not statistically significant. Ten patients developed an infection during hospitalization	[62]
Retrospective cohort	Moderate to severe SARS-CoV-2 patients	One to two doses of TCZ 8 mg/kg	170 treated; 655 untreated	Clinical improvement was significantly better in the treatment group compared with the control group. A significant reduction in the mortality rate at 21 and 28 d was found in patients with respiratory failure and patients with IL-6 levels above 100 pg/mL	[110]
Randomized clinical trial	Critical patients with respiratory failure who were admitted to the ICU	TCZ one to two doses (8 mg/kg); Sarilumab (a single dose of 400 mg); Other interventions: Anakinra and interferon beta-1a	350 on TCZ; 45 on sarilumab; 1136 on another immunomodulator; 397 on no immunomodulation	IL-6 blocking agents were effective in reducing the mortality rate. When added to corticosteroids, this effect was stronger compared with IL-6 blockade alone	NCT02735707 [74]
Randomized, controlled, open-label clinical trial	COVID-19 patients with worsening clinical status or with high CRP levels after 21 d of the first randomization to dexamethasone, lopinavir–ritonavir, hydroxychloroquine, azithromycin, or colchicine or convalescent plasma or a combination of two anti-SARS-CoV-2 spike protein antibodies (REGN-COV2) or aspirin	A single dose of TCZ according to the patient's weight	2022 received TCZ; 2094 received standard of care	TCZ group had a significantly lower mortality rate, need for mechanical ventilation, and higher chance of hospital discharge at day 28. This effect was similar in patients randomized less than or more than two days from hospitalization. In patients who were on mechanical ventilation at the time of drug administration, this drug had no significant effect on improving prognosis	[67]
Randomized, double-blindclinical trial	Severe COVID-19 patients	Sarilumab 200 or 400 mg, single dose	n = 153 sarilumab 400 mg, n = 141 sarilumab 200 mg, n = 75 placebo	No significant effectiveness was found in the treatment groups compared with the control group	[111]
Randomized, double-Blind, placebo-controlled trial	Patients with COVID-19 in a hyper-inflammatory state	TCZ 8 mg/kg up to 800 mg	TCZ (n = 161); Placebo (n = 81) + standard of care	No significant benefits from early TCZ administration in COVID-19 were observed	[112]

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ICU: Intensive care unit; TCZ: Tocilizumab; CSs: Corticosteroids; COVID-19: Coronavirus disease 2019.

failure. This study found that inflammatory mediators significantly reduced after ruxolitinib administration which also improved clinical conditions. These successes were not accompanied by any severe effects[81]. Another effect of JAK inhibitors in hampering the cytokine storm is related to TNF, the other crucial inflammatory mediator in the cytokine storm that uses JAK signaling and can be inhibited by JAK inhibitors. A recent study evaluated the concurrent administration of an IL-1 blocker antibody and ruxolitinib in critical patients with SARS-CoV-2. The preliminary report of this study demonstrated that this combination was beneficial in clinical improvement, and the lymphocyte count increased after this treatment[82]. In addition, no treatment-related severe complications were observed. Tofacitinib is another JAK inhibitor that was shown to reduce adverse outcomes and mortality in COVID-19 patients in a previous retrospective cohort study[83]. Another exciting intervention for IL blockade with positive effects in patients on ECMO in previous research was extracorporeal cytokine adsorption which showed a significant decrease in IL-6 in treated patients[84,85]. Other agents with anti-IL-6 properties have not yet been entered in clinical trials of COVID-19. However, targeting the trans-signaling pathway seems more efficient than non-specific IL-6 blockade with monoclonal antibodies.

IL-6 INDUCES TH17 LINEAGE DIFFERENTIATION

Th17 is related to inflammatory processes. As mentioned in Figure 2, when the IL-6-sIL-6R complex reaches CD4+ T cells, it causes them to differentiate into Th17 cell lineage. This action is mediated through the JAK-STAT signaling pathway (IL-6 recruits JAK 1 and 2). These cells can secrete IL-17, 21, and 22 and GM-CSF, and therefore contribute to the pathogenesis of inflammatory processes and chronic diseases. Viral diseases also promote Th17 related responses, and severe cases show higher Th17-related cytokines. Accordingly, Th17 blockade seems to be another way to fight against COVID-19, especially in extreme cases. One study showed that fedratinib reduced Th17 related cytokines in mouse models. Fedratinib is a JAK 2 inhibitor[86].

It was shown that the Th17 subgroup of T cells is increased relative to the other subgroups in severe COVID-19 cases. The role of these cells in SARS-CoV-2 patients with lung injuries has been revealed. Drugs with anti-IL-17 activities include ixekizumab, secukinumab, and brodalumab, and they are used in moderate to severe cases of psoriasis[87,88]. Ixekizumab is an anti-IL-17 antibody and is currently being evaluated in a COVID-19 clinical trial. Inclusion criteria in this study are those with high serum levels of IL-6 and not admitted to the ICU[89]. When IL-17 is secreted from Th17 cells, it causes target cells to produce inflammatory mediators, including IL-6, TNF-α, chemokine C-C motif 2 (CCL2), and IL-1β. These procedures lead to CRS and clinical worsening in SARS-CoV-2[87]. IL-17 is also related to the cutaneous manifestations of COVID-19[90]. However, recent evidence has shown undetectable quantities of IL-17A expression in COVID-19 patients[91]. In a previous study, secukinumab, an anti-IL-17A selective antibody, resulted in clinical improvement in severe SARS-CoV-2 patients[92].

CONCLUSION

According to the above-mentioned data, IL-6 blockade alone with anti-IL-6R monoclonal antibodies has no significant benefits in improving the prognosis of patients, except for those in a critical condition and in the hyper-inflammatory state before mechanical ventilation. Many factors are related to a patient's response to IL-6 blockade, such as baseline IL-6 level and disease severity. It may also be associated with some worrying side effects. According to recent data, a combination of anti-inflammatory agents is more effective than any one agent alone. Other ways to inhibit IL-6, such as a selective trans-signaling pathway and JAK-STAT inhibition, should be investigated further.

ACKNOWLEDGEMENTS

The authors would like to thank the Clinical Research Development Unit and Tabriz University of Medical Sciences Faculty of Medicine for providing the expertise that greatly assisted in this work.

FOOTNOTES

Author contributions: Bahmani M, Bannazadeh Baghi H, and Chegini R contributed to the conceptualization; Bahmani M, Chegini R, and Ghanbari E contributed to writing - original draft; Shiri Aghbash P, and Bannazadeh Baghi H contributed to writing - review and editing; Shiri Aghbash P, Bannazadeh Baghi H, Chegini R, and Sheykhsaran E contributed to the visualization; Leylabadlo HE, Bannazadeh Baghi H, Shiri Aghbash P, Ghanbari E, and Sheykhsaran E contributed to the supervision; Bannazadeh Baghi H and Shiri Aghbash P contributed to the project administration; Moradian E, and Kazemzadeh Houjaghan AM contributed to the language editing.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Country/Territory of origin: Iran

ORCID number: Mohaddeseh Bahmani 0000-0002-7438-7653; Rojin Chegini 0000-0001-8505-1728; Elham Ghanbari 0000-0001-6040-1912; Elham Sheykhsaran 0000-0002-9273-433X; Parisa Shiri Aghbash 0000-0001-6733-4556; Hamed Ebrahimzadeh Leylabadlo 0000-0002-3790-9176; Ehsan Moradian 0000-0003-1218-1059; Amir Masoud Kazemzadeh Houjaghan 0000-0001-5456-3835; Hossein Bannazadeh Baghi 0000-0002-2513-5361.

S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

REFERENCES

1 **Wu YC**, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. *J Chin Med Assoc* 2020; **83**: 217-220 [PMID: 32134861 DOI: 10.1097/JCMA.0000000000000270]
2 **Shahrajabian MH**, Sun W, Cheng Q. Product of natural evolution (SARS, MERS, and SARS-CoV-2); deadly diseases, from SARS to SARS-CoV-2. *Hum Vaccin Immunother* 2021; **17**: 62-83 [PMID: 32783700 DOI: 10.1080/21645515.2020.1797369]
3 **World Health Organization**. WHO Coronavirus (COVID-19) Dashboard. [cited September 19, 2021] Available from: https://covid19.who.int/
4 **Castelnovo L**, Tamburello A, Lurati A, Zaccara E, Marrazza MG, Olivetti M, Mumoli N, Mastroiacovo D, Colombo D, Ricchiuti E, Vigano' P, Paola F, Mazzone A. Anti-IL6 treatment of serious COVID-19 disease: A monocentric retrospective experience. *Medicine (Baltimore)* 2021; **100**: e23582 [PMID: 33429732 DOI: 10.1097/MD.0000000000023582]
5 **Sarkesh A**, Daei Sorkhabi A, Sheykhsaran E, Alinezhad F, Mohammadzadeh N, Hemmat N, Bannazadeh Baghi H. Extrapulmonary Clinical Manifestations in COVID-19 Patients. *Am J Trop Med Hyg* 2020; **103**: 1783-1796 [PMID: 32940201 DOI: 10.4269/ajtmh.20-0986]
6 **IHME COVID-19 Forecasting Team**. Modeling COVID-19 scenarios for the United States. *Nat Med* 2021; **27**: 94-105 [PMID: 33097835 DOI: 10.1038/s41591-020-1132-9]
7 **Bao Z**, Wang LJ, He K, Lin X, Yu T, Li J, Gong J, Xiang G. High expression of ACE2 in the human lung leads to the release of IL6 by suppressing cellular immunity: IL6 plays a key role in COVID-19. *Eur Rev Med Pharmacol Sci* 2021; **25**: 527-540 [PMID: 33506945 DOI: 10.26355/eurrev_202101_24425]
8 **Salama C**, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebeb-Reuter M, Lima de Menezes F, Shah R, González-Lara MF, Assman B, Freedman J, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med* 2021; **384**: 20-30 [PMID: 33332779 DOI: 10.1056/NEJMoa2030340]
9 **WHO Solidarity Trial Consortium**, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med* 2021; **384**: 497-511 [PMID: 33264556 DOI: 10.1056/NEJMoa2023184]
10 **Hunter CA**, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol* 2015; **16**: 448-457 [PMID: 25898198 DOI: 10.1038/ni.3153]
11 **Jordan SC**, Choi J, Kim I, Wu G, Toyoda M, Shin B, Vo A. Interleukin-6, A Cytokine Critical to Mediation of Inflammation, Autoimmunity and Allograft Rejection: Therapeutic Implications of IL-6 Receptor Blockade. *Transplantation* 2017; **101**: 32-44 [PMID: 27547870 DOI: 10.1097/TP.0000000000001452]
12 **Tang Y**, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front Immunol* 2020; **11**: 1708 [PMID: 32754163 DOI: 10.3389/fimmu.2020.01708]
13 **Hemmat N**, Derakhshani A, Bannazadeh Baghi H, Silvestris N, Baradaran B, De Summa S. Neutrophils, Crucial, or Harmful Immune Cells Involved in Coronavirus Infection: A Bioinformatics Study. *Front Genet* 2020; **11**: 641 [PMID: 32582303 DOI: 10.3389/fgene.2020.00641]
14 **Hemmat N**, Asadzadeh Z, Karim-ahangar N, Alemohammad H, Najafzadeh B, Derakhshani A, Baghbanzadeh A,

Bannazadeh Baghi H, Javadrashid D, Najafi S, Gouilh MA, Baradaran B. The alterations of cellular signaling pathways in the host cell upon the high pathogenic Coronaviruses infection, SARS-CoV and MERS-CoV. What could be expected from the SARS-CoV-2? 2020. Available from: https://www.researchgate.net/publication/344729169_The_alterations_of_cellular_signaling_pathways_in_the_host_cell_upon_the_high_pathogenic_Coronaviruses_infection_SARS-CoV_and_MERS-CoV_What_could_be_expected_from_the_SARS-CoV-2

15 **Shiri Aghbash P**, Eslami N, Shamekh A, Entezari-Maleki T, Bannazadeh Baghi H. SARS-CoV-2 infection: The role of PD-1/PD-L1 and CTLA-4 axis. *Life Sci* 2021; **270**: 119124 [PMID: 33508291 DOI: 10.1016/j.lfs.2021.119124]

16 **Liu B**, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun* 2020; **111**: 102452 [PMID: 32291137 DOI: 10.1016/j.jaut.2020.102452]

17 **Wiersinga WJ**, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; **324**: 782-793 [PMID: 32648899 DOI: 10.1001/jama.2020.12839]

18 **Oroojalian F**, Haghbin A, Baradaran B, Hemmat N, Shahbazi MA, Bannazadeh Baghi H, Mokhtarzadeh A, Hamblin MR. Novel insights into the treatment of SARS-CoV-2 infection: An overview of current clinical trials. *Int J Biol Macromol* 2020; **165**: 18-43 [PMID: 32991900 DOI: 10.1016/j.ijbiomac.2020.09.204]

19 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

20 **Azer SA**. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New Microbes New Infect* 2020; **37**: 100738 [PMID: 32834902 DOI: 10.1016/j.nmni.2020.100738]

21 **Huang Y**, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacol Sin* 2020; **41**: 1141-1149 [PMID: 32747721 DOI: 10.1038/s41401-020-0485-4]

22 **Li W**, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454 [PMID: 14647384 DOI: 10.1038/nature02145]

23 **Parasher A**. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. *Postgrad Med J* 2021; **97**: 312-320 [PMID: 32978337 DOI: 10.1136/postgradmedj-2020-138577]

24 **Hassan SA**, Sheikh FN, Jamal S, Ezeh JK, Akhtar A. Coronavirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment. *Cureus* 2020; **12**: e7355 [PMID: 32328367 DOI: 10.7759/cureus.7355]

25 **Ahmad T**, Chaudhuri R, Joshi MC, Almatroudi A, Rahmani AH, Ali SM. COVID-19: The Emerging Immunopathological Determinants for Recovery or Death. *Front Microbiol* 2020; **11**: 588409 [PMID: 33335518 DOI: 10.3389/fmicb.2020.588409]

26 **Wu J**, Deng W, Li S, Yang X. Advances in research on ACE2 as a receptor for 2019-nCoV. *Cell Mol Life Sci* 2021; **78**: 531-544 [PMID: 32780149 DOI: 10.1007/s00018-020-03611-x]

27 **Tufan A**, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk J Med Sci* 2020; **50**: 620-632 [PMID: 32299202 DOI: 10.3906/sag-2004-168]

28 **Shiri Aghbash P**, Hemmat N, Nahand JS, Shamekh A, Memar MY, Babaei A, Bannazadeh Baghi H. The role of Th17 cells in viral infections. *Int Immunopharmacol* 2021; **91**: 107331 [PMID: 33418239 DOI: 10.1016/j.intimp.2020.107331]

29 **Zhang Y**, Geng X, Tan Y, Li Q, Xu C, Xu J, Hao L, Zeng Z, Luo X, Liu F, Wang H. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. *Biomed Pharmacother* 2020; **127**: 110195 [PMID: 32361161 DOI: 10.1016/j.biopha.2020.110195]

30 **Labbé K**, Saleh M. Cell death in the host response to infection. *Cell Death Differ* 2008; **15**: 1339-1349 [PMID: 18566602 DOI: 10.1038/cdd.2008.91]

31 **Dhand R**, Li J. Coughs and Sneezes: Their Role in Transmission of Respiratory Viral Infections, Including SARS-CoV-2. *Am J Respir Crit Care Med* 2020; **202**: 651-659 [PMID: 32543913 DOI: 10.1164/rccm.202004-1263PP]

32 **Noorimotlagh Z**, Jaafarzadeh N, Martínez SS, Mirzaee SA. A systematic review of possible airborne transmission of the COVID-19 virus (SARS-CoV-2) in the indoor air environment. *Environ Res* 2021; **193**: 110612 [PMID: 33309820 DOI: 10.1016/j.envres.2020.110612]

33 **Hu B**, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021; **19**: 141-154 [PMID: 33024307 DOI: 10.1038/s41579-020-00459-7]

34 **Yuki K**, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol* 2020; **215**: 108427 [PMID: 32325252 DOI: 10.1016/j.clim.2020.108427]

35 **Sharma R**, Agarwal M, Gupta M, Somendra S, Saxena SK. Clinical Characteristics and Differential Clinical Diagnosis of Novel Coronavirus Disease 2019 (COVID-19). In: Saxena S (eds). Coronavirus Disease 2019 (COVID-19). Medical Virology: From Pathogenesis to Disease Control. Springer, Singapore [DOI: 10.1007/978-981-15-4814-7_6]

36 **Bohn MK**, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression. *Physiology (Bethesda)* 2020; **35**: 288-301 [PMID: 32783610 DOI: 10.1152/physiol.00019.2020]

37 **Fajgenbaum DC**, June CH. Cytokine Storm. *N Engl J Med* 2020; **383**: 2255-2273 [PMID: 33264547 DOI: 10.1056/NEJMra2026131]

38 **Younan P**, Iampietro M, Nishida A, Ramanathan P, Santos RI, Dutta M, Lubaki NM, Koup RA, Katze MG, Bukreyev A. Ebola Virus Binding to Tim-1 on T Lymphocytes Induces a Cytokine Storm. *mBio* 2017; **8** [PMID: 28951472 DOI: 10.1128/mBio.00845-17]

39 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

40 **Tanaka T**, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014; **6**: a016295 [PMID: 25190079 DOI: 10.1101/cshperspect.a016295]

41 **Ljungberg LU**, Zegeye MM, Kardeby C, Fälker K, Repsilber D, Sirsjö A. Global Transcriptional Profiling Reveals Novel Autocrine Functions of Interleukin 6 in Human Vascular Endothelial Cells. *Mediators Inflamm* 2020; **2020**: 4623107 [PMID: 32410854 DOI: 10.1155/2020/4623107]

42 **Jones SA**, Scheller J, Rose-John S. Therapeutic strategies for the clinical blockade of IL-6/gp130 signaling. *J Clin Invest* 2011; **121**: 3375-3383 [PMID: 21881215 DOI: 10.1172/JCI57158]

43 **Moshapa FT**, Riches-Suman K, Palmer TM. Therapeutic Targeting of the Proinflammatory IL-6-JAK-STAT Signalling Pathways Responsible for Vascular Restenosis in Type 2 Diabetes Mellitus. *Cardiol Res Pract* 2019; **2019**: 9846312 [PMID: 30719343 DOI: 10.1155/2019/9846312]

44 **Saha A**, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Tocilizumab: A Therapeutic Option for the Treatment of Cytokine Storm Syndrome in COVID-19. *Arch Med Res* 2020; **51**: 595-597 [PMID: 32482373 DOI: 10.1016/j.arcmed.2020.05.009]

45 **Magro G**. SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? *Cytokine X* 2020; **2**: 100029 [PMID: 32421092 DOI: 10.1016/j.cytox.2020.100029]

46 **Murthy H**, Iqbal M, Chavez JC, Kharfan-Dabaja MA. Cytokine Release Syndrome: Current Perspectives. *Immunotargets Ther* 2019; **8**: 43-52 [PMID: 31754614 DOI: 10.2147/ITT.S202015]

47 **Kahn R**, Schmidt T, Golestani K, Mossberg A, Gullstrand B, Bengtsson AA, Kahn F. Mismatch between circulating cytokines and spontaneous cytokine production by leukocytes in hyperinflammatory COVID-19. *J Leukoc Biol* 2021; **109**: 115-120 [PMID: 32794348 DOI: 10.1002/JLB.5COVBCR0720-310RR]

48 **Pomponio G**, Ferrarini A, Bonifazi M, Moretti M, Salvi A, Giacometti A, Tavio M, Titolo G, Morbidoni L, Frausini G, Onesta M, Amico D, Rocchi MLB, Menzo S, Zuccatosta L, Mei F, Menditto V, Svegliati S, Donati A, D'Errico MM, Pavani M, Gabrielli A. Tocilizumab in COVID-19 interstitial pneumonia. *J Intern Med* 2021; **289**: 738-746 [PMID: 33511686 DOI: 10.1111/joim.13231]

49 **Heo TH**, Wahler J, Suh N. Potential therapeutic implications of IL-6/IL-6R/gp130-targeting agents in breast cancer. *Oncotarget* 2016; **7**: 15460-15473 [PMID: 26840088 DOI: 10.18632/oncotarget.7102]

50 **Cavalli G**, Larcher A, Tomelleri A, Campochiaro C, Della-Torre E, De Luca G, Farina N, Boffini N, Ruggeri A, Poli A, Scarpellini P, Rovere-Querini P, Tresoldi M, Salonia A, Montorsi F, Landoni G, Castagna A, Ciceri F, Zangrillo A, Dagna L. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. *Lancet Rheumatol* 2021; **3**: e253-e261 [PMID: 33655218 DOI: 10.1016/S2665-9913(21)00012-6]

51 **Galván-Román JM**, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, Alcaraz-Serna A, Mateu-Albero T, Rodríguez-Cortes P, Sánchez-Cerrillo I, Esparcia L, Martínez-Fleta P, López-Sanz C, Gabrie L, Del Campo Guerola L, Suárez-Fernández C, Ancochea J, Canabal A, Albert P, Rodríguez-Serrano DA, Aguilar JM, Del Arco C, de Los Santos I, García-Fraile L, de la Cámara R, Serra JM, Ramírez E, Alonso T, Landete P, Soriano JB, Martín-Gayo E, Fraile Torres A, Zurita Cruz ND, García-Vicuña R, Cardeñoso L, Sánchez-Madrid F, Alfranca A, Muñoz-Calleja C, González-Álvaro I; REINMUN-COVID Group. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study. *J Allergy Clin Immunol* 2021; **147**: 72-80.e8 [PMID: 33010257 DOI: 10.1016/j.jaci.2020.09.018]

52 **Soto GP**. Potential therapeutic agents against COVID-19 based on blocking and inhibition of the viral life cycle and the cytokine storm syndrome. *An Fac Cienc Méd (Asunción)* 2020; **53**: 131-146 [DOI: 10.18004/anales/2020.053.03.131]

53 **Huang E**, Isonaka S, Yang H, Salce E, Rosales E, Jordan SC. Tocilizumab treatment in critically ill patients with COVID-19: A retrospective observational study. *Int J Infect Dis* 2021; **105**: 245-251 [PMID: 33609773 DOI: 10.1016/j.ijid.2021.02.057]

54 **Deana C**, Vetrugno L, Bassi F, De Monte A. Tocilizumab administration in COVID-19 patients: Water on the fire or gasoline? *Med Mycol Case Rep* 2021; **31**: 32-34 [PMID: 33520634 DOI: 10.1016/j.mmcr.2021.01.002]

55 **Setliff E**, Kosmisky D, Ngeve R. 683: Necrotizing Fasciitis and Candidemia After Tocilizumab Initiation: A Case Report. *Crit Care Med* 2021; **49**: 336 [DOI: 10.1097/01.ccm.0000728620.08082.ed]

56 **Sciascia S**, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R, Bonora S, Calcagno A, Cecchi I, Cinnirella G, Converso M, Cozzi M, Crosasso P, De Iaco F, Di Perri G, Eandi M, Fenoglio R, Giusti M, Imperiale D, Imperiale G, Livigni S, Manno E, Massara C, Milone V, Natale G, Navarra M, Oddone V, Osella S, Piccioni P, Radin M, Roccatello D, Rossi D. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19. *Clin Exp Rheumatol* 2020; **38**: 529-532

57 **Mazzitelli M**, Arrighi E, Serapide F, Pelle MC, Tassone B, Lionello R, Marrazzo G, Laganà D, Costanzo FS, Matera G, Trecarichi EM, Torti C. Use of subcutaneous tocilizumab in patients with COVID-19 pneumonia. *J Med Virol* 2021; **93**: 32-34 [PMID: 32410234 DOI: 10.1002/jmv.26016]

58 **Perrone F**, Piccirillo MC, Ascierto PA, Salvarani C, Parrella R, Marata AM, Popoli P, Ferraris L, Marrocco-Trischitta MM, Ripamonti D, Binda F, Bonfanti P, Squillace N, Castelli F, Muiesan ML, Lichtner M, Calzetti C, Salerno ND, Atripaldi L, Cascella M, Costantini M, Dolci G, Facciolongo NC, Fraganza F, Massari M, Montesarchio V, Mussini C, Negri EA, Botti G, Cardone C, Gargiulo P, Gravina A, Schettino C, Arenare L, Chiodini P, Gallo C; TOCIVID-19 investigators, Italy. Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. *J Transl Med* 2020; **18**: 405 [PMID: 33087150 DOI: 10.1186/s12967-020-02573-9]

59 **Masiá M**, Fernández-González M, Padilla S, Ortega P, García JA, Agulló V, García-Abellán J, Telenti G, Guillén L, Gutiérrez F. Impact of interleukin-6 blockade with tocilizumab on SARS-CoV-2 viral kinetics and antibody responses in patients with COVID-19: A prospective cohort study. *EBioMedicine* 2020; **60**: 102999 [PMID: 32950003 DOI: 10.1016/j.ebiom.2020.102999]

60 **Ponthieux F**, Dauby N, Maillart E, Fils JF, Smet J, Claus M, Besse-Hammer T, Bels D, Corazza F, Nagant C. Tocilizumab-Induced Unexpected Increase of Several Inflammatory Cytokines in Critically Ill COVID-19 Patients: The Anti-Inflammatory Side of IL-6. *Viral Immunol* 2022; **35**: 60-70 [PMID: 35085462 DOI: 10.1089/vim.2021.0111]

61 **Chan KH**, Patel B, Podel B, Szablea ME, Shaaban HS, Guron G, Slim J. Tocilizumab and Thromboembolism in COVID-19: A Retrospective Hospital-Based Cohort Analysis. *Cureus* 2021; **13**: e15208 [PMID: 34178527 DOI: 10.7759/cureus.15208]

62 **Al-Baadani A**, Eltayeb N, Alsufyani E, Albahrani S, Basheri S, Albayat H, Batubara E, Ballool S, Al Assiri A, Faqihi F, Musa AB, Robert AA, Alsherbeeni N, Elzein F. Efficacy of tocilizumab in patients with severe COVID-19: Survival and clinical outcomes. *J Infect Public Health* 2021; **14**: 1021-1027 [PMID: 34153727 DOI: 10.1016/j.jiph.2021.05.015]

63 **Kow CS**, Hasan SS. The effect of tocilizumab on mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol* 2021; **77**: 1089-1094 [PMID: 33532896 DOI: 10.1007/s00228-021-03087-z]

64 **Moreno Diaz R**, Amor García MA, Teigell Muñoz FJ, Saldaña Perez LE, Mateos Gonzalez M, Melero Bermejo JA, López Hernández A, Reyes Marquez L, De Guzman García-Monge MT, Perez Quero JL, Homez Guzman MP. Does timing matter on tocilizumab administration? *Eur J Hosp Pharm* 2021 [PMID: 33627476 DOI: 10.1136/ejhpharm-2020-002669]

65 **Eşkazan AE**, Balkan İİ, Demirbaş KC, Ar MC, Karaali R, Sekibağ Y, Mulamahmutoğlu S, Yartaş Dumanlı G, Çakmak F, Özgür Yurttaş N, Kurt F, Aladağ Kurt S, Kuşkucu M, Ürkmez S, Börekçi Ş, Saribal D, Mete B, Bavunoğlu I, Dikmen Y, Aygün G, Midilli K, Tabak F. Tocilizumab in COVID-19: The Cerrahpaşa-PREDICT score. *J Infect Chemother* 2021; **27**: 1329-1335 [PMID: 34120824 DOI: 10.1016/j.jiac.2021.05.007]

66 **Li P**, Lu Z, Li Q, Wang Z, Guo Y, Cai C, Wang S, Liu P, Su X, Huang Y, Dong Y, Qiu W, Ling Y, Yarmus L, Luo F, Zeng L, Bai C, Zhang W. Administration Timing and Efficacy of Tocilizumab in Patients With COVID-19 and Elevated IL-6. *Front Mol Biosci* 2021; **8**: 651662 [PMID: 33937333 DOI: 10.3389/fmolb.2021.651662]

67 **RECOVERY Collaborative Group**. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397**: 1637-1645 [PMID: 33933206 DOI: 10.1016/S0140-6736(21)00676-0]

68 **Van den Eynde E**, Gasch O, Oliva JC, Prieto E, Calzado S, Gomila A, Machado ML, Falgueras L, Ortonobes S, Morón A, Capilla S, Navarro G, Oristrell J, Cervantes M, Navarro M. Corticosteroids and tocilizumab reduce in-hospital mortality in severe COVID-19 pneumonia: a retrospective study in a Spanish hospital. *Infect Dis (Lond)* 2021; **53**: 291-302 [PMID: 33620019 DOI: 10.1080/23744235.2021.1884286]

69 Efficacy of Early Administration of Tocilizumab in COVID-19 Patients - American College of Cardiology. [cited March 28, 2021] Available from: https://www.acc.org/Latest-in-cardiology/clinical-trials/2020/12/31/20/42/rct-tcz-covid-19

70 **Akinosoglou K**, Velissaris D, Ziazias D, Davoulos C, Tousis A, Tsiotsios K, Kalogeropoulou C, Spyridonidis A, Marangos M, Fligkou F, Gogos C. Remdesivir and tocilizumab: Mix or match. *J Med Virol* 2021; **93**: 56-58 [PMID: 32492200 DOI: 10.1002/jmv.26117]

71 **Antony SJ**, Davis MA, Davis MG, Almaghlouth NK, Guevara R, Omar F, Del Rey F, Hassan A, Arian MU, Antony N, Prakash BV. Early use of tocilizumab in the prevention of adult respiratory failure in SARS-CoV-2 infections and the utilization of interleukin-6 levels in the management. *J Med Virol* 2021; **93**: 491-498 [PMID: 32644254 DOI: 10.1002/jmv.26288]

72 **Bhandari S**, Rankawat G, Singh A. Tocilizumab: An Effective Therapy for Severely and Critically Ill COVID-19 Patients. *Indian J Crit Care Med* 2021; **25**: 260-266 [PMID: 33790504 DOI: 10.5005/jp-journals-10071-23747]

73 **Chilimuri S**, Sun H, Alemam A, Kang KS, Lao P, Mantri N, Schiller L, Sharabun M, Shehi E, Tejada J, Yugay A, Nayudu SK. Tocilizumab use in patients with moderate to severe COVID-19: A retrospective cohort study. *J Clin Pharm Ther* 2021; **46**: 440-446 [PMID: 33098139 DOI: 10.1111/jcpt.13303]

74 **REMAP-CAP Investigators**, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; **384**: 1491-1502 [PMID: 33631065 DOI: 10.1056/NEJMoa2100433]

75 **Furlow B**. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. *Lancet Rheumatol* 2020; **2**: e592 [PMID: 32929415 DOI: 10.1016/S2665-9913(20)30313-1]

76 **Hasanin A**, Mostafa M. Tocilizumab in patients with COVID-19: which patient, time, and dose? *J Anesth* 2021; **35**: 896-902 [PMID: 34264384 DOI: 10.1007/s00540-021-02974-0]

77 **Satarker S**, Tom AA, Shaji RA, Alosious A, Luvis M, Nampoothiri M. JAK-STAT Pathway Inhibition and their Implications in COVID-19 Therapy. *Postgrad Med* 2021; **133**: 489-507 [PMID: 33245005 DOI: 10.1080/00325481.2020.1855921]

78 **Novartis**. Novartis provides update on RUXCOVID study of ruxolitinib for hospitalized patients with COVID-19. [cited March 20, 2021] Available from: https://www.novartis.com/news/media-releases/novartis-provides-update-ruxcovid-study-ruxolitinib-hospitalized-patients-covid-19

79 **Eli Lilly and Company**. Baricitinib in Combination with Remdesivir Reduces Time to Recovery in Hospitalized Patients with COVID-19 in NIAID-Sponsored ACTT-2 Trial. [cited March 20, 2021]. Available from: https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery

80 **Kalil AC**, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, Tapson V, Iovine NM, Jain MK, Sweeney DA, El Sahly HM, Branche AR, Regalado Pineda J, Lye DC, Sandkovsky U, Luetkemeyer AF, Cohen SH, Finberg RW, Jackson PEH, Taiwo B, Paules CI, Arguinchona H, Erdmann N, Ahuja N, Frank M, Oh MD, Kim ES, Tan SY, Mularski RA, Nielsen H, Ponce PO, Taylor BS, Larson L, Rouphael NG, Saklawi Y, Cantos VD, Ko ER, Engemann JJ, Amin AN, Watanabe M, Billings J, Elie MC, Davey RT, Burgess TH, Ferreira J, Green M, Makowski M, Cardoso A, de Bono S, Bonnett T, Proschan M, Deye GA, Dempsey W, Nayak SU,

Dodd LE, Beigel JH; ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021; **384**: 795-807 [PMID: 33306283 DOI: 10.1056/NEJMoa2031994]

81 **Mortara A**, Mazzetti S, Margonato D, Delfino P, Bersano C, Catagnano F, Lauriola M, Grosso P, Perseghin G, Ippoliti G. Compassionate use of ruxolitinib in patients with SARS-Cov-2 infection not on mechanical ventilation: Short-term effects on inflammation and ventilation. *Clin Transl Sci* 2021; **14**: 1062-1068 [PMID: 33403775 DOI: 10.1111/cts.12971]

82 **Kaplanski G**, Bontemps D, Esnault P, Blasco V, Carvelli J, Delarbre D, Cauchois R, Forel JM, Papazian L. Combined Anakinra and Ruxolitinib treatment to rescue extremely ill COVID-19 patients: A pilot study. *Autoimmun Rev* 2021; **20**: 102726 [PMID: 33326855 DOI: 10.1016/j.autrev.2020.102726]

83 **Maslennikov R**, Ivashkin V, Vasilieva E, Chipurik M, Semikova P, Semenets V, Russkova T, Levshina A, Grigoriadis D, Magomedov S, Efremova I, Dzhakhaya N. Tofacitinib reduces mortality in coronavirus disease 2019 Tofacitinib in COVID-19. *Pulm Pharmacol Ther* 2021; **69**: 102039 [PMID: 34023513 DOI: 10.1016/j.pupt.2021.102039]

84 **Rieder M**, Wengenmayer T, Staudacher D, Duerschmied D, Supady A. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation. *Crit Care* 2020; **24**: 435 [PMID: 32664996 DOI: 10.1186/s13054-020-03130-y]

85 **Supady A**, Duerschmied D, Bode C, Rieder M, Lother A. Extracorporeal cytokine adsorption as an alternative to pharmacological inhibition of IL-6 in COVID-19. *Crit Care* 2020; **24**: 514 [PMID: 32819415 DOI: 10.1186/s13054-020-03238-1]

86 **Wu D**, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect* 2020; **53**: 368-370 [PMID: 32205092 DOI: 10.1016/j.jmii.2020.03.005]

87 **Bulat V**, Situm M, Azdajic MD, Likic R. Potential role of IL-17 blocking agents in the treatment of severe COVID-19? *Br J Clin Pharmacol* 2021; **87**: 1578-1581 [PMID: 32627226 DOI: 10.1111/bcp.14437]

88 **Martonik D**, Parfieniuk-Kowerda A, Rogalska M, Flisiak R. The Role of Th17 Response in COVID-19. *Cells* 2021; **10** [PMID: 34205262 DOI: 10.3390/cells10061550]

89 **Liu P**, Huang Z, Yin M, Liu C, Chen X, Pan P, Kuang Y. Safety and Efficacy of Ixekizumab and Antiviral Treatment for Patients with COVID-19: A structured summary of a study protocol for a Pilot Randomized Controlled Trial. *Trials* 2020; **21**: 999 [PMID: 33276811 DOI: 10.1186/s13063-020-04925-8]

90 **Carugno A**, Gambini DM, Raponi F, Vezzoli P, Robustelli Test E, Arosio MEG, Callegaro A, Sena P. Coronavirus disease 2019 (COVID-19) rash in a psoriatic patient treated with Secukinumab: Is there a role for Interleukin 17? *Dermatol Ther* 2020; **33**: e14011 [PMID: 32654404 DOI: 10.1111/dth.14011]

91 **Sette A**, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* 2021; **184**: 861-880 [PMID: 33497610 DOI: 10.1016/j.cell.2021.01.007]

92 **Hasan MJ**, Rabbani R, Anam AM, Huq SMR. Secukinumab in severe COVID-19 pneumonia: Does it have a clinical impact? *J Infect* 2021; **83**: e11-e13 [PMID: 34029628 DOI: 10.1016/j.jinf.2021.05.011]

93 **National Library of Medicine**. DailyMed - KEVZARA- sarilumab injection, solution. [cited March 20, 2021] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=827bc01c-d379-4266-a18c-c7f904b76af3

94 **National Library of Medicine**. DailyMed - ACTEMRA- tocilizumab injection, solution, concentrate ACTEMRA- tocilizumab injection, solution ACTEMRA ACTPEN- tocilizumab injection, solution. [cited March 20, 2021] Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2e5365ff-cb2a-4b16-b2c7-e35c6bf2de13

95 **Charan J**, Dutta S, Kaur R, Bhardwaj P, Sharma P, Ambwani S, Jahan I, Abubakar AR, Islam S, Hardcastle TC, Rahman NAA, Lugova H, Haque M. Tocilizumab in COVID-19: a study of adverse drug events reported in the WHO database. *Expert Opin Drug Saf* 2021; **20**: 1125-1136 [PMID: 34162299 DOI: 10.1080/14740338.2021.1946513]

96 **National Library of Medicine**. DailyMed - SYLVANT- siltuximab injection, powder, for solution. [cited March 20, 2021] Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8d663642-f52e-49c0-a023-2da083fdfc0b

97 **National Library of Medicine**. DailyMed - OLUMIANT- baricitinib tablet, film coated. [cited March 20, 2021] Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=866e9f35-9035-4581-a4b1-75a621ab55cf#s21

98 **Schreiber S**, Aden K, Bernardes JP, Conrad C, Tran F, Höper H, Volk V, Mishra N, Blase JI, Nikolaus S, Bethge J, Kühbacher T, Röcken C, Chen M, Cottingham I, Petri N, Rasmussen BB, Lokau J, Lenk L, Garbers C, Feuerhake F, Rose-John S, Waetzig GH, Rosenstiel P. Therapeutic Interleukin-6 Trans-signaling Inhibition by Olamkicept (sgp130Fc) in Patients With Active Inflammatory Bowel Disease. *Gastroenterology* 2021; **160**: 2354-2366.e11 [PMID: 33667488 DOI: 10.1053/j.gastro.2021.02.062]

99 **National Library of Medicine**. DailyMed - JAKAFI- ruxolitinib tablet. [cited March 20, 2021] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f1c82580-87ae-11e0-bc84-0002a5d5c51b

100 **Chachar AZK**, Khan KA, Iqbal J, Shahid AH, Asif M, Fatima SA, Khan AA, Younis BB. "Tocilizumab-an option for patients with COVID-19 associated cytokine release syndrome: A single center experience", a retrospective study-original article. *Ann Med Surg (Lond)* 2021; **63**: 102165 [PMID: 33585031 DOI: 10.1016/j.amsu.2021.02.011]

101 **Riggs K**, Patel V, Pittiglio M, Cavanaugh J, Sullivan J. 309: Evaluation of the Efficacy of Tocilizumab in Critically Ill COVID-19 Patients. *Crit Care Med* 2021; **49**: 141 [DOI: 10.1097/01.ccm.0000727124.78530.08]

102 **Adıyeke E**, Coşkun N, Bakan N, Demir S, Cihan M, Yiyit N. Efficacy of Tocilizumab in the treatment of severe COVID-19 patients with respiratory failure. *Med Sci Discov* 2021; **8**: 86-90 [DOI: 10.36472/msd.v8i2.473]

103 **Chen Y**, Zhang X. Preliminary Efficacy of Tocilizumab Treatment in The Patients With COVID-19. 2021 [DOI: 10.21203/rs.3.rs-147574/v1]

104 **Amin S**, Rahim F, Bahadur S, Noor M, Mahmood A, Gul H. The Effect of Tocilizumab on Inflammatory Markers in Survivors and Non-survivors of Severe COVID-19. *J Coll Physicians Surg Pak* 2021; **31**: S7-S10 [PMID: 34530530 DOI: 10.29271/jcpsp.2021.Supp1.S7]

105 **Salvarani C**, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, Para O, Scotton PG, Inojosa WO, Ravagnani V, Salerno ND, Sainaghi PP, Brignone A, Codeluppi M, Teopompi E, Milesi M, Bertomoro P, Claudio N, Salio M, Falcone M, Cenderello G, Donghi L, Del Bono

V, Colombelli PL, Angheben A, Passaro A, Secondo G, Pascale R, Piazza I, Facciolongo N, Costantini M; RCT-TCZ-COVID-19 Study Group. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**: 24-31 [PMID: 33080005 DOI: 10.1001/jamainternmed.2020.6615]

106 **Wang D**, Fu B, Peng Z, Yang D, Han M, Li M, Yang Y, Yang T, Sun L, Li W. Tocilizumab ameliorates the hypoxia in COVID-19 moderate patients with bilateral pulmonary lesions: a randomized, controlled, open-label, multicenter trial. 2020 [DOI: 10.2139/ssrn.3667681]

107 **Sanofi**. Sanofi provides update on Kevzara® (sarilumab) Phase 3 trial in severe and critically ill COVID-19 patients outside the U.S. (cited March 28, 2021). https://www.sanofi.com/en/media-room/press-releases/2020/2020-09-01-07-00-00

108 **Lescure FX**, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, Patel N, Hagino O. Sarilumab treatment of hospitalised patients with severe or critical COVID-19: a multinational, randomised, adaptive, phase 3, double-blind, placebo-controlled trial. MedRxiv 2021 [DOI: 10.1101/2021.02.01.21250769]

109 **Rosas IO**, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, Skiest D, Aziz MS, Cooper N, Douglas IS, Savic S, Youngstein T, Del Sorbo L, Cubillo Gracian A, De La Zerda DJ, Ustianowski A, Bao M, Dimonaco S, Graham E, Matharu B, Spotswood H, Tsai L, Malhotra A. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med* 2021; **384**: 1503-1516 [PMID: 33631066 DOI: 10.1056/NEJMoa2028700]

110 **Flisiak R**, Jaroszewicz J, Rogalska M, Łapiński T, Berkan-Kawińska A, Bolewska B, Tudrujek-Zdunek M, Kozielewicz D, Rorat M, Leszczyński P. Tocilizumab Improves the Prognosis of COVID-19 in Patients with High IL-6. *J Clin Med* 2021; 10 [DOI: 10.2139/ssrn.3770003]

111 **Lescure FX**, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, Patel N, Hagino O; Sarilumab COVID-19 Global Study Group. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021; **9**: 522-532 [PMID: 33676590 DOI: 10.1016/S2213-2600(21)00099-0]

112 **Stone JH**, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med* 2020; **383**: 2333-2344 [PMID: 33085857 DOI: 10.1056/NEJMoa2028836]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 May 25; 11(3): 129-136

DOI: 10.5501/wjv.v11.i3.129

ISSN 2220-3249 (online)

MINIREVIEWS

Impact of COVID-19 on mental health and emotional well-being of older adults

Letha Mullamkuzhy Joseph

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tran NMH, Viet Nam

Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: July 15, 2021
Revised: July 28, 2021
Accepted: April 1, 2022
Article in press: April 1, 2022
Published online: May 25, 2022

Letha Mullamkuzhy Joseph, Nurse Practitioner, Geriatric Research Education and Clinical Center, Durham VA Healthcare System, Durham, NC 27705, United States

Letha Mullamkuzhy Joseph, Consulting Associate, Duke University School of Nursing, Durham, NC 27710, United States

Corresponding author: Letha Mullamkuzhy Joseph, RN, Instructor, Nurse, Nurse Practitioner, Geriatric Research Education and Clinical Center, Durham VA Healthcare System, 508 Fulton Street, Durham, NC 27705, United States. letha.joseph@va.gov

Abstract

Older adults faced unique challenges in the pandemic due to their increased vulnerability to coronavirus disease 2019 (COVID-19) and its complications. Pandemic-related restrictions such as physical distancing, stay-at-home orders, lock-down, and mandatory face cover affected older adults in unique ways. Additionally, older adults experienced psychosocial concerns related to discrimination based on ageism and emotional distress from exposure to conflicting messages in the media. They experienced several forms of loss and associated grief and survivor guilt. Pandemic added to their loneliness and social isolation. Furthermore, older adults experienced the fear and anxiety related to COVID and the fear of contracting the disease and dying from it. Pandemic experience included events potential to generate the desire and capability for suicide. Several studies report varying symptoms such as loneliness, anxiety, and depression among older adults during the pandemic. However, during the initial months of the pandemic, there were reports on coping and resilience among this population. The impact of COVID-19 on older adults' mental health may have long-term implications. This narrative review examines the impact of COVID-19 on older adults' mental health and psychosocial wellbeing. Additionally, the review highlights various factors that affected their psychosocial wellbeing during the COVID-19 pandemic.

Key Words: COVID-19; Pandemic; Older adults; Geriatrics; Mental health; Psychosocial wellbeing

Core Tip: Coronavirus disease 2019 (COVID-19) disproportionately affected older adults. Several studies report varying symptoms such as loneliness, anxiety, and depression among older adults during the pandemic. However, during the initial months of the pandemic, there were reports on coping and resilience among this population. Implications of COVID-19 on older adults' mental health can have long-lasting consequences. This review focuses on several factors that impacted older adults' psychosocial wellbeing during the pandemic.

Citation: Joseph LM. Impact of COVID-19 on mental health and emotional well-being of older adults. *World J Virol* 2022; 11(3): 129-136
URL: https://www.wjgnet.com/2220-3249/full/v11/i3/129.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i3.129

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has a disparate effect on older adults due to their increased risk for developing severe disease and poor disease outcomes[1]. Stay–at–home orders, lock-down, and mandatory face-covering created unique challenges for older adults. The impact of COVID and COVID-related restrictions can have long-lasting effects on older adults' mental health and wellbeing. During the pandemic's initial months, healthcare professionals from several countries expressed their concern over the pandemic's potential mental health effects and alerted the global community[2-5]. Over a year into the pandemic, it may be beneficial to review the pandemic's psychosocial impact on the older adult population. This narrative review focuses on the pandemic's impact on older adults' psychosocial wellbeing and highlights various elements that influenced the pandemic's impact on older adults' mental health.

PANDEMIC AND MENTAL HEALTH

Several studies globally explored the pandemic's effect on older adults' mental health (Table 1). During the initial weeks of the pandemic, Klaiber *et al*[6] examined emotional wellbeing and reactivity to COVID-19 stressors among adults living in the United States and Canada and noted that older adults reported better emotional wellbeing and less reactivity to stressors with similar exposure to COVID-19 stressors as young adults. Similarly, van Tilburg *et al*[7] reported stable mental health and wellbeing despite increased loneliness among the older adults in Netherland. A large study among Spanish adults also reported that older adults had lower depression, anxiety, and post-traumatic stress in the early weeks of the pandemic than young adults[8]. However, this Spanish study[8] had a low representation of older adults.

In June 2020, the Centers for Disease Control and Prevention[9] reported the findings of a survey conducted among adults in the United States where the prevalence of depressive symptoms, anxiety and trauma-related stress, suicidal ideations, and substance abuse to cope up with the pandemic related stress was low among older adults as compared to other age groups. This survey's follow-up in September 2020 also supported the lower prevalence of mental health concerns among older adults than young adults[10]. However, in a longitudinal study, Krendl and Perry[11] reported an increase in depressive symptoms and loneliness among older adults living in the United States. Studies from some other countries also reported similar results, as noted below.

In a longitudinal study among community-dwelling older adults in Japan, Fujita *et al*[12] compared the participant's mental health before and during the pandemic. They reported worsening depressive symptoms and apathy among the participants. Additionally, participants 65 years to 75 years of age reported worse symptoms[12]. In Hong Kong, Wong *et al*[13] explored the level of loneliness, anxiety, depression, and insomnia among an established cohort of older adults with multiple chronic medical conditions. Compared to pre-COVID data, these participants reported increased loneliness, anxiety, depression, and insomnia[13]. In Greece, a cross-sectional survey[14] among older adults conducted in the early period of the pandemic noted moderate to severe depressive and anxiety symptoms in 80% of the participants. A similar study from Turkey[15] also reported depressive symptoms (37.5%) and anxiety (29.8%) among the participants.

COVID-related stress and the resulting emotional distress can be explained based on Neuman's systems model, where each client is considered a unique system[16]. Several lines of intrapersonal, interpersonal, and extrapersonal stressors act on the environment of the client system and affect its stability. Each individual has an imaginary 'central core' to survive the effect of such stressors[17]. Several imaginary 'lines of defense' protect the 'central core.' The individual's wellness and adaptation serve as the 'inner line of defense,' whereas the flexible 'outer line of defense' responds to each stressor.

Table 1 Studies exploring the impact of pandemic on mental health

Ref.	Title of the study	Type of study	Sample size and country	Outcomes
Klaiber *et al* [6], 2021	The Ups and Downs of Daily Life During COVID-19: Age Differences in Affect, Stress, and Positive Events	Short term longitudinal study	*n* = 776, Canada and the United States	Older adults showed better emotional well-being and less reactivity to COVID-related stressors
van Tilburg *et al*[7], 2020	Loneliness and mental health during the COVID-19 pandemic: A study among Dutch older adults	Longitudinal study	*n* = 1679, The Netherlands	Increased loneliness in older adults. However, mental health remained roughly stable
González-Sanguino *et al* [8], 2020	Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain	Cross-sectional study	*n* = 3480, Spain	Older age group was negatively related to depression, anxiety and post traumatic stress disorder
Czeisler *et al* [9], 2020	Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic - United States June 24-30, 2020	Representative panel surveys	*n* = 5470, United States	Prevalence of mental health symptoms 15.1% in older adults and 74.9% in young adults
Czeisler *et al* [10], 2021	Follow-up Survey of US Adult Reports of Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic, September 2020	Representative panel surveys	*n* = 5285, United States	Mental health symptoms were less prevalent among older adults than in younger adults
Krendl and Perry[11], 2021	The Impact of Sheltering in Place During the COVID-19 Pandemic on Older Adults' Social and Mental Well-Being	Longitudinal study	*n* = 93, United States	Older adults reported increased depressive symptoms over sheltering in-place period
Fujita *et al*[12], 2021	Mental Health Status of the Older Adults in Japan During the COVID-19 Pandemic	Longitudinal study	*n* = 519, Japan	Community-dwelling older adults had worsening of mood. Worse symptoms in adults 65-75 yr of age
Wong *et al* [13], 2020	Impact of COVID-19 on loneliness, mental health, and health service utilization: a prospective cohort study of older adults with multimorbidity in primary care	Longitudinal study	*n* = 583, Hong Kong	A pre-existing cohort of older adults reported significant worsening of loneliness, anxiety, and insomnia, after the onset of the pandemic
Parlapani *et al* [14], 2020	Intolerance of Uncertainty and Loneliness in Older Adults During the COVID-19 Pandemic	Cross-sectional study	*n* = 103, Greece	Moderate to severe depressive symptoms (81.6%) anxiety (84.5%), disrupted sleep (37.9%)
Cigiloglu *et al* [15], 2021	How have older adults reacted to coronavirus disease 2019?	Cross-sectional study	*n* = 104, Turkey	37.5% reported depressive symptoms and 29.8% reported anxiety; Worse symptoms in those with age ≥ 85 yr

COVID-19: Coronavirus disease 2019.

The 'line of resistance' determines the individual's response to the stressors. In Neuman's system model, the environment constitutes internal and external factors that influence the client or are influenced by the client. If the lines of defense and the line of resistance are strong enough to keep the stressors away from the core, the stressors will not impact the individual. Additionally, the individual's perception of the stressors as beneficial strengthens the core stability, whereas the opposite perception weakens the core stability[16]. The individual's immediate life circumstances impact the flexible outer line of defense. During the pandemic, older adults faced several life circumstances, potential stressors that affected the core's stability.

CONTRIBUTORS OF EMOTIONAL DISTRESS

Several elements such as culture, socio-economic status, prior mental illness, and poor access to care may determine the pandemic's impact on older adults' mental health and resilience. Physical distancing, stay-at-home mandates, anxiety about contracting Corona viral disease, and fear of death from complications of the disease may have created unique challenges for older adults. Whitehead and Torossian[18] explored the older adults' pandemic experience and assessed their 'stresses and joys.' An online survey of 825 United States adults aged 60 and above[18] reported confinement and restrictions from the lock-down, isolation, and loneliness from physical distancing and concern for others as the participants' everyday stressors during the pandemic.

Physical distancing and lock-down

In an attempt to contain the virus, government authorities and public health professionals advocated for non-essential service shutdowns, travel bans, and mandatory stay-at-home orders. Physical distancing mandates urged people to avoid or limit face-to-face interactions, group events, travel, and visiting

places of worship, shopping places, and healthcare facilities. Most of the services were closed for in-person activities. Such restrictions affected older adults, especially those with limited technology access or technology skills.

Activity restrictions

During the pandemic, concerns related to the difficulty in performing everyday activities, wearing face cover, inability to leave home for the job or voluntary activities, inability to attend religious and social activities such as entertainment and sports events, canceled healthcare visits, and the inability to go to stores and select merchandise were contributing to stress[19]. Older adults with solid religious affiliations reported unmet spiritual needs leading to social isolation and sadness[2]. Moreover, physical distancing led to stress factors such as helplessness, concerns related to dependency and timely help, and worry about the pandemic and future[19].

Bereavement and grief

During the pandemic, the global community suffered COVID-related death and loss of life from other causes. Unlike regular times, many of these people died alone. Several of them did not receive the usual religious rights and social rituals. Many people could not see their loved ones and say final goodbyes. Survivor guilt can contribute to intense grief. In the normal process, people adapt to grief gradually without additional effort. However, in situations with unresolved grief, which happens when something about the loss is troubling for the bereaved person, the stalled grief can give rise to prolonged grief disorder[20]. Death during the pandemic has characteristics such as the sudden and unexpected event in the absence of familiar people, which can precipitate grief that is difficult to resolve.

Ageism and stereotyping

As the pandemic emerged, discussion on older adults increased risk for contracting the disease, developing severe illness and complications, and poor disease outcomes dominated in healthcare, media, and public discussions. The concept of high vulnerability might have created anxiety and fear among older adults. As Previtali *et al*[21] argued, generalizing older adults' increased risk based on their chronological age was probably an expression of ageism, which was unfair. During the pandemic's initial months, the media highlighted fatality among older adults while giving a relatively minor focus on fatality in other age groups. Older adults' heightened COVID fears might have contributed to higher social isolation and basic needs dependency. Stereotyping older adults based on their age is unfair as several factors determine their overall health status. During the initial months of the pandemic, there was a shortage of resources and associated fear about 'triaging' and rationing the care, which might have created anxiety and worsened older adults' emotional discomfort. Emotional trauma from COVID positive status and isolation and fear of dying alone might have aggravated emotional discomfort among older adults who tested positive for COVID.

Effect of social media

There was an 'infodemic' related to the pandemic. Social media and communication outlets contributed to the fear and anxiety by spreading conflicting information. Social media expressions such as "Boomer Remover," a trending hashtag on Twitter in March 2020 was potentially hurtful to older adults. During the pandemic, Jimenez-Sotomayor *et al*[22] analyzed the tweets related to COVID-19 and older adults and found that 21.1% of the tweets communicated the notion that older adults' lives were less valuable. Gao *et al*[23] identified a positive association between social media exposure and mental health concerns in Chinese citizens. Though this study included adults in general, not just older adults, the results may have implications on older adults who access social media.

Data related to older adults' mental health implications mainly included the experience of community-dwelling participants who had web or telephone access and physical and cognitive ability to respond to the surveys. Long-term care facilities, assisted living facilities, and group care homes house older adults who require care for their chronic illnesses, disability related to physical or mental illness, or cognitive dysfunction. Residents in care homes encountered additional challenges during the pandemic.

CHALLENGES IN CARE FACILITIES

Van der Roest *et al*[24] examined the impact of COVID-19 measures on long-term care residents' mental health in the Netherlands. In this cross-sectional analysis, 77% of the participants reported loneliness, and 51% reported poor mental health. Furthermore, most of the staff noted increased agitation, depression, irritability, and anxiety among the residents[24]. Care facilities are high-risk settings for transmitting infectious diseases and were inadequately prepared to manage the pandemic[25]. To combat the pandemic, these facilities employed several interventions that inadvertently affected resident's psychosocial wellbeing. For instance, facilities employed strict visitation policies and physical

distancing policies. As a result, facilities canceled or modified activities such as community dining, group recreational activities and worship services, group exercises, celebrations, and out-of-facility pleasure trips. Physical distancing policies required the residents to stay in their rooms and keep the doors closed. Stopping visitations from family, volunteers, and pets limited older adults' opportunities for socialization. Several care facilities had to employ temporary staff leading to inconsistent caregiving. Receiving care from unfamiliar staff could be anxiety-provoking even for older adults without prior mental health concerns or dementia. Care from healthcare professionals wearing personal protective equipment potentially decreased the 'human touch' in the care. Healthcare professionals limited their face-to-face time with the residents due to the physical distancing policy that worsened the residents' loneliness. Fear about contracting the illness from the asymptomatic carriers and regular surveillance screening and waiting for the results can make the residents anxious. These are some of the examples of challenges that exposed care home residents' vulnerability to emotional distress.

PANDEMIC AND EMOTIONAL DISTRESS

During the pandemic, the initial three levels of Maslow's hierarchy of needs- physiological need, need for safety and security, and the need for love and belongingness dominated people's needs irrespective of their pre-pandemic position in the hierarchy of needs[26]. Therefore, a rapid change in needs and the reassignment to a lower level of need in the hierarchy could create negative emotions in people. These negative emotions manifest in several forms.

Suicide risk

Before COVID, evidence supported older adults' increased risk for suicide[27-29]. Direct impact of COVID-19 on the suicidal risk of older adults is yet to be known. However, the pandemic's mental health consequences can precipitate the risk factors of suicidal behavior. According to the interpersonal theory of suicide, the simultaneous presence of 'thwarted belongingness' and 'perceived burdensomeness' produced the desire for suicide. Furthermore, the repeated exposure to painful and fear-inducing experiences contributes to the capability of suicide behavior[30]. Pandemic's effect on mental health, such as social isolation, perceived ageism, and fear of delayed or denied healthcare, may contribute to the interpersonal constructs of thwarted belongingness and feelings of burdensomeness. Additionally, emotional distress may contribute to the feeling of hopelessness and increase older adults' risk for suicide[31]. Emotional experiences become distressing under several circumstances.

Social isolation

Heid *et al*[19] explored older adults' adherence to physical distancing mandates and their pandemic stressors. Participants were community-dwelling older adults from New Jersey, the state once considered the pandemic's epicenter in the United States. The majority of the participants reported avoidance of usual activities that required in-person presence. Participants identified that continuing their social relationships and following activity restrictions were their significant challenges related to physical distancing[19]. Participants also reported stress related to missed social interactions with family and friends, especially grandchildren, and canceled social events[19]. Kim and Jung[32] analyzed the link between social isolation and mental wellbeing in older adults from 62 countries who responded to an online survey, 'Global Behaviors and Perceptions in the COVID-19'. The survey[32] response supported social isolation related to physical distancing and its association with psychological distress. Since social connectedness positively impacts health and longevity[33-35], appropriate interventions to improve social connectedness while maintaining physical distancing were essential. A feeling of inadequate social connectedness gives rise to loneliness.

Loneliness

Loneliness, the subjective feeling of being alone, has physical and mental health effects in older adults. Kotwal *et al*[36] examined the experience of loneliness and social isolation among community-dwelling older adults in San-Francisco, California, during the shelter-in-place period. Fifty-four percent of the participants reported worsening loneliness due to the pandemic leading to worsening depression and anxiety[36]. Krendl and Perry[11] also reported increased depressive symptoms and loneliness during the shelter-in-place period. In a similar study in Austria, Stolz *et al*[37] reported increased loneliness in 2020 than in previous years, resulting from the pandemic-related social isolation. Furthermore, loneliness was more significant during the lock-down period than the reopening phase[37]. Researchers reported sleep deprivation and depressive symptoms in older adults with subjective or objective social isolation and loneliness even before the pandemic[38]. Moreover, pre-pandemic studies supported the positive impact of resilience on sleep in other populations[39,40]. Grossman *et al*[41] reported increased sleep concerns and insomnia in older adults who reported loneliness during the pandemic and attributed it to their insecurity from loneliness leading to alertness preventing them from getting a restful night's sleep. Further, the sleep deprivation-loneliness connection was stronger in those with more COVID-related worries or low resilience[41].

RESILIENCE IN OLDER ADULTS DURING THE PANDEMIC

Despite experiencing stressful situations and facing hardships associated with emotional distress, older adults used their coping skills and created resilience during the pandemic. Several studies attest that older adults did reasonably well in their emotional status compared to other age groups[42]. This observation is similar to the strength and vulnerability integration model, which suggests older adults' ability to regulate their emotions constructively and navigate their stressful experiences compared to other age groups[43]. Furthermore, coping skills accumulated over time might have helped the older adults employ better coping mechanisms and stay positive. Older adult's coping strategies during COVID-19 are yet to be explored. However, older adults tend to anticipate hardships and take proactive measures to cope with possibly stressful situations in life[44]. In addition, proactive coping might have led the older adults to employ wishful thinking, support seeking, and empathetic responding, common coping mechanisms reportedly beneficial in past disasters[45].

CONCLUSION

During the pandemic, older adults experienced unique challenges with detrimental effects on their mental health and wellbeing. Older adults' pandemic-related psychosocial challenges may harbinger their post-pandemic mental health needs. Post pandemic psychosocial implications are overwhelming. Communities and care homes implemented multidimensional interventions to mitigate the psychosocial impact of the pandemic. Evaluating those interventions' success and adopting the successful interventions as a standard of practice will help create resilience and improve older adults' coping.

FOOTNOTES

Author contributions: Joseph LM reviewed the current literature on this topic and wrote this manuscript.

Conflict-of-interest statement: The author has no conflict of interest to disclose.

Country/Territory of origin: United States

ORCID number: Letha Mullamkuzhy Joseph 0000-0001-8347-5850.

S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

REFERENCES

1 **Chen Y**, Klein SL, Garibaldi BT, Li H, Wu C, Osevala NM, Li T, Margolick JB, Pawelec G, Leng SX. Aging in COVID-19: Vulnerability, immunity and intervention. *Ageing Res Rev* 2021; **65**: 101205 [PMID: 33137510 DOI: 10.1016/j.arr.2020.101205]
2 **Buenaventura RD**, Ho JB, Lapid MI. COVID-19 and mental health of older adults in the Philippines: a perspective from a developing country. *Int Psychogeriatr* 2020; **32**: 1129-1133 [PMID: 32349826 DOI: 10.1017/S1041610220000757]
3 **Baiyewu O**, Elugbadebo O, Oshodi Y. Burden of COVID-19 on mental health of older adults in a fragile healthcare system: the case of Nigeria: dealing with inequalities and inadequacies. *Int Psychogeriatr* 2020; **32**: 1181-1185 [PMID: 32782036 DOI: 10.1017/S1041610220001726]
4 **Serafini G**, Bondi E, Locatelli C, Amore M. Aged Patients With Mental Disorders in the COVID-19 Era: The Experience of Northern Italy. *Am J Geriatr Psychiatry* 2020; **28**: 794-795 [PMID: 32360137 DOI: 10.1016/j.jagp.2020.04.015]
5 **Shaygan M**, Bahadori F. Considerations for Mitigation of the Psychological Impacts of COVID-19 in Older Adults. *Int J Community Based Nurs Midwifery* 2020; **8**: 277-279 [PMID: 32656280 DOI: 10.30476/ijcbnm.2020.86362.1340]
6 **Klaiber P**, Wen JH, DeLongis A, Sin NL. The Ups and Downs of Daily Life During COVID-19: Age Differences in Affect, Stress, and Positive Events. *J Gerontol B Psychol Sci Soc Sci* 2021; **76**: e30-e37 [PMID: 32674138 DOI: 10.1093/geronb/gbaa096]
7 **van Tilburg TG**, Steinmetz S, Stolte E, van der Roest H, de Vries DH. Loneliness and Mental Health During the COVID-19 Pandemic: A Study Among Dutch Older Adults. *J Gerontol B Psychol Sci Soc Sci* 2021; **76**: e249-e255 [PMID:

32756931 DOI: 10.1093/geronb/gbaa111]
8 **González-Sanguino C**, Ausín B, Castellanos MÁ, Saiz J, López-Gómez A, Ugidos C, Muñoz M. Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain. *Brain Behav Immun* 2020; **87**: 172-176 [PMID: 32405150 DOI: 10.1016/j.bbi.2020.05.040]
9 **Czeisler MÉ**, Lane RI, Petrosky E, Wiley JF, Christensen A, Njai R, Weaver MD, Robbins R, Facer-Childs ER, Barger LK, Czeisler CA, Howard ME, Rajaratnam SMW. Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic - United States, June 24-30, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1049-1057 [PMID: 32790653 DOI: 10.15585/mmwr.mm6932a1]
10 **Czeisler MÉ**, Lane RI, Wiley JF, Czeisler CA, Howard ME, Rajaratnam SMW. Follow-up Survey of US Adult Reports of Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic, September 2020. *JAMA Netw Open* 2021; **4**: e2037665 [PMID: 33606030 DOI: 10.1001/jamanetworkopen.2020.37665]
11 **Krendl AC**, Perry BL. The Impact of Sheltering in Place During the COVID-19 Pandemic on Older Adults' Social and Mental Well-Being. *J Gerontol B Psychol Sci Soc Sci* 2021; **76**: e53-e58 [PMID: 32778899 DOI: 10.1093/geronb/gbaa110]
12 **Fujita K**, Inoue A, Kuzuya M, Uno C, Huang CH, Umegaki H, Onishi J. Mental Health Status of the Older Adults in Japan During the COVID-19 Pandemic. *J Am Med Dir Assoc* 2021; **22**: 220-221 [PMID: 33321080 DOI: 10.1016/j.jamda.2020.11.023]
13 **Wong SYS**, Zhang D, Sit RWS, Yip BHK, Chung RY, Wong CKM, Chan DCC, Sun W, Kwok KO, Mercer SW. Impact of COVID-19 on loneliness, mental health, and health service utilisation: a prospective cohort study of older adults with multimorbidity in primary care. *Br J Gen Pract* 2020; **70**: e817-e824 [PMID: 32988955 DOI: 10.3399/bjgp20X713021]
14 **Parlapani E**, Holeva V, Nikopoulou VA, Sereslis K, Athanasiadou M, Godosidis A, Stephanou T, Diakogiannis I. Intolerance of Uncertainty and Loneliness in Older Adults During the COVID-19 Pandemic. *Front Psychiatry* 2020; **11**: 842 [PMID: 32973584 DOI: 10.3389/fpsyt.2020.00842]
15 **Cigiloglu A**, Ozturk ZA, Efendioglu EM. How have older adults reacted to coronavirus disease 2019? *Psychogeriatrics* 2021; **21**: 112-117 [PMID: 33295036 DOI: 10.1111/psyg.12639]
16 **Fawcett J**, Foust JB. Optimal Aging: A Neuman Systems Model Perspective. *Nurs Sci Q* 2017; **30**: 269-276 [PMID: 28899283 DOI: 10.1177/0894318417708413]
17 **Ahmadi Z**, Sadeghi T. Application of the Betty Neuman systems model in the nursing care of patients/clients with multiple sclerosis. *Mult Scler J Exp Transl Clin* 2017; **3**: 2055217317726798 [PMID: 28839950 DOI: 10.1177/2055217317726798]
18 **Whitehead BR**, Torossian E. Older Adults' Experience of the COVID-19 Pandemic: A Mixed-Methods Analysis of Stresses and Joys. *Gerontologist* 2021; **61**: 36-47 [PMID: 32886764 DOI: 10.1093/geront/gnaa126]
19 **Heid AR**, Cartwright F, Wilson-Genderson M, Pruchno R. Challenges Experienced by Older People During the Initial Months of the COVID-19 Pandemic. *Gerontologist* 2021; **61**: 48-58 [PMID: 32955079 DOI: 10.1093/geront/gnaa138]
20 **Goveas JS**, Shear MK. Grief and the COVID-19 Pandemic in Older Adults. *Am J Geriatr Psychiatry* 2020; **28**: 1119-1125 [PMID: 32709542 DOI: 10.1016/j.jagp.2020.06.021]
21 **Previtali F**, Allen LD, Varlamova M. Not Only Virus Spread: The Diffusion of Ageism during the Outbreak of COVID-19. *J Aging Soc Policy* 2020; **32**: 506-514 [PMID: 32507060 DOI: 10.1080/08959420.2020.1772002]
22 **Jimenez-Sotomayor MR**, Gomez-Moreno C, Soto-Perez-de-Celis E. Coronavirus, Ageism, and Twitter: An Evaluation of Tweets about Older Adults and COVID-19. *J Am Geriatr Soc* 2020; **68**: 1661-1665 [PMID: 32338787 DOI: 10.1111/jgs.16508]
23 **Gao J**, Zheng P, Jia Y, Chen H, Mao Y, Chen S, Wang Y, Fu H, Dai J. Mental health problems and social media exposure during COVID-19 outbreak. *PLoS One* 2020; **15**: e0231924 [PMID: 32298385 DOI: 10.1371/journal.pone.0231924]
24 **Van der Roest HG**, Prins M, van der Velden C, Steinmetz S, Stolte E, van Tilburg TG, de Vries DH. The Impact of COVID-19 Measures on Well-Being of Older Long-Term Care Facility Residents in the Netherlands. *J Am Med Dir Assoc* 2020; **21**: 1569-1570 [PMID: 33036911 DOI: 10.1016/j.jamda.2020.09.007]
25 **Miller EA**. Protecting and Improving the Lives of Older Adults in the COVID-19 Era. *J Aging Soc Policy* 2020; **32**: 297-309 [PMID: 32583751 DOI: 10.1080/08959420.2020.1780104]
26 **Cerbara L**, Ciancimino G, Crescimbene M, La Longa F, Parsi MR, Tintori A, Palomba R. A nation-wide survey on emotional and psychological impacts of COVID-19 social distancing. *Eur Rev Med Pharmacol Sci* 2020; **24**: 7155-7163 [PMID: 32633412 DOI: 10.26355/eurrev_202006_21711]
27 **Schmutte TJ**, Wilkinson ST. Suicide in Older Adults With and Without Known Mental Illness: Results From the National Violent Death Reporting System, 2003-2016. *Am J Prev Med* 2020; **58**: 584-590 [PMID: 32001049 DOI: 10.1016/j.amepre.2019.11.001]
28 **Fässberg MM**, Cheung G, Canetto SS, Erlangsen A, Lapierre S, Lindner R, Draper B, Gallo JJ, Wong C, Wu J, Duberstein P, Wærn M. A systematic review of physical illness, functional disability, and suicidal behaviour among older adults. *Aging Ment Health* 2016; **20**: 166-194 [PMID: 26381843 DOI: 10.1080/13607863.2015.1083945]
29 **Kawada T**. Suicide risk of old adults with special reference to aging. *Int Psychogeriatr* 2018; **30**: 603 [PMID: 29249208 DOI: 10.1017/S1041610217002496]
30 **Van Orden KA**, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE Jr. The interpersonal theory of suicide. *Psychol Rev* 2010; **117**: 575-600 [PMID: 20438238 DOI: 10.1037/a0018697]
31 **Chou HC**, Tzeng DS, Lin SL. Suicide and the Elderly During the COVID-19 Pandemic: An Overview of Different Suicide Theories. *Prim Care Companion CNS Disord* 2020; **22** [PMID: 33095519 DOI: 10.4088/PCC.20nr02676]
32 **Kim HH**, Jung JH. Social Isolation and Psychological Distress During the COVID-19 Pandemic: A Cross-National Analysis. *Gerontologist* 2021; **61**: 103-113 [PMID: 33125065 DOI: 10.1093/geront/gnaa168]
33 **Holt-Lunstad J**. Why Social Relationships Are Important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection. *Annu Rev Psychol* 2018; **69**: 437-458 [PMID: 29035688 DOI: 10.1146/annurev-psych-122216-011902]
34 **Holt-Lunstad J**, Robles TF, Sbarra DA. Advancing social connection as a public health priority in the United States. *Am Psychol* 2017; **72**: 517-530 [PMID: 28880099 DOI: 10.1037/amp0000103]

35 **Leschak CJ**, Eisenberger NI. Two Distinct Immune Pathways Linking Social Relationships With Health: Inflammatory and Antiviral Processes. *Psychosom Med* 2019; **81**: 711-719 [PMID: 31600173 DOI: 10.1097/PSY.0000000000000685]

36 **Kotwal AA**, Holt-Lunstad J, Newmark RL, Cenzer I, Smith AK, Covinsky KE, Escueta DP, Lee JM, Perissinotto CM. Social Isolation and Loneliness Among San Francisco Bay Area Older Adults During the COVID-19 Shelter-in-Place Orders. *J Am Geriatr Soc* 2021; **69**: 20-29 [PMID: 32965024 DOI: 10.1111/jgs.16865]

37 **Stolz E**, Mayerl H, Freidl W. The impact of COVID-19 restriction measures on loneliness among older adults in Austria. *Eur J Public Health* 2021; **31**: 44-49 [PMID: 33338225 DOI: 10.1093/eurpub/ckaa238]

38 **Cho JH**, Olmstead R, Choi H, Carrillo C, Seeman TE, Irwin MR. Associations of objective *vs* subjective social isolation with sleep disturbance, depression, and fatigue in community-dwelling older adults. *Aging Ment Health* 2019; **23**: 1130-1138 [PMID: 30284454 DOI: 10.1080/13607863.2018.1481928]

39 **Downing MJ Jr**, Houang ST, Scheinmann R, Yoon IS, Chiasson MA, Hirshfield S. Engagement in Care, Psychological Distress, and Resilience are Associated with Sleep Quality among HIV-Positive Gay, Bisexual, and Other Men Who Have Sex with Men. *Sleep Health* 2016; **2**: 322-329 [PMID: 28191491 DOI: 10.1016/j.sleh.2016.08.002]

40 **Li G**, Kong L, Zhou H, Kang X, Fang Y, Li P. Relationship between prenatal maternal stress and sleep quality in Chinese pregnant women: the mediation effect of resilience. *Sleep Med* 2016; **25**: 8-12 [PMID: 27823722 DOI: 10.1016/j.sleep.2016.02.015]

41 **Grossman ES**, Hoffman YSG, Palgi Y, Shrira A. COVID-19 related loneliness and sleep problems in older adults: Worries and resilience as potential moderators. *Pers Individ Dif* 2021; **168**: 110371 [PMID: 32904342 DOI: 10.1016/j.paid.2020.110371]

42 **Sterina E**, Hermida AP, Gerberi DJ, Lapid MI. Emotional Resilience of Older Adults during COVID-19: A Systematic Review of Studies of Stress and Well-Being. *Clin Gerontol* 2022; **45**: 4-19 [PMID: 34080527 DOI: 10.1080/07317115.2021.1928355]

43 **Charles ST**. Strength and vulnerability integration: a model of emotional well-being across adulthood. *Psychol Bull* 2010; **136**: 1068-1091 [PMID: 21038939 DOI: 10.1037/a0021232]

44 **Sougleris C**, Ranzijn R. Proactive coping in community-dwelling older Australians. *Int J Aging Hum Dev* 2011; **72**: 155-168 [PMID: 21639015 DOI: 10.2190/AG.72.2.d]

45 **Finlay JM**, Kler JS, O'Shea BQ, Eastman MR, Vinson YR, Kobayashi LC. Coping During the COVID-19 Pandemic: A Qualitative Study of Older Adults Across the United States. *Front Public Health* 2021; **9**: 643807 [PMID: 33898379 DOI: 10.3389/fpubh.2021.643807]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 May 25; 11(3): 137-143

DOI: 10.5501/wjv.v11.i3.137

ISSN 2220-3249 (online)

MINIREVIEWS

SARS-CoV-2 Omicron variant (B.1.1.529): A concern with immune escape

Adekunle Sanyaolu, Aleksandra Marinkovic, Stephanie Prakash, Nafees Haider, Martina Williams, Chuku Okorie, Olanrewaju Badaru, Stella Smith

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Diab R, Iran; Islam SMRU, Bangladesh; Vij M, India

Received: December 28, 2021
Peer-review started: December 28, 2021
First decision: February 8, 2022
Revised: March 5, 2022
Accepted: April 21, 2022
Article in press: April 21, 2022
Published online: May 25, 2022

Adekunle Sanyaolu, Department of Public Health, Federal Ministry of Health, Abuja 0000, Nigeria

Aleksandra Marinkovic, Stephanie Prakash, Martina Williams, Department of Basic Sciences, Saint James School of Medicine, The Valley 0000, Anguilla

Nafees Haider, Department of Basic Sciences, All Saints University School of Medicine, Roseau 0000, Dominica

Chuku Okorie, Department of Allied Sciences, Union County College, Plainfield, NJ 07060, United States

Olanrewaju Badaru, Department of Public Health, Nigeria Centre for Disease Control, Abuja 0000, Nigeria

Stella Smith, Department of Molecular Biology and Biotechnology, Nigerian Institute of Medical Research, Lagos 100001, Nigeria

Corresponding author: Adekunle Sanyaolu, PhD, Academic Research, Director, Department of Public Health, Federal Ministry of Health, New Federal Secretariat Complex, Phase III, Ahmadu Bello Way, Central Business District, Abuja 0000, Nigeria. sanyakunle@hotmail.com

Abstract

Omicron, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant that is now spreading across the world, is the most altered version to emerge so far, with mutations comparable to changes reported in earlier variants of concern linked with increased transmissibility and partial resistance to vaccine-induced immunity. This article provides an overview of the SARS-CoV-2 variant Omicron (B.1.1.529) by reviewing the literature from major scientific databases. Although clear immunological and clinical data are not yet available, we extrapolated from what is known about mutations present in the Omicron variant of SARS-CoV-2 and offer preliminary indications on transmissibility, severity, and immune escape through existing research and databases.

Key Words: SARS-CoV-2; COVID-19; Omicron; B.1.1.529; Variant of concern; Emerging variants

Core Tip: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, Omicron (B.1.1.529), was first reported to World Health Organization from South Africa on November 24, 2021. Omicron has been labeled a variant of concern because of genetic changes that increase transmissibility and decrease the effectiveness of health measures, vaccines, and therapeutics. This variant has 32 mutations in the spike protein, which is problematic because vaccinations designed to prevent SARS-CoV-2 infections target spike proteins. Despite some evidence that vaccination alone may not be enough, non-pharmaceutical practices such as continued use of face masks, proper hygiene precautions, and social distancing, are required to successfully combat this variant.

Citation: Sanyaolu A, Marinkovic A, Prakash S, Haider N, Williams M, Okorie C, Badaru O, Smith S. SARS-CoV-2 Omicron variant (B.1.1.529): A concern with immune escape. *World J Virol* 2022; 11(3): 137-143
URL: https://www.wjgnet.com/2220-3249/full/v11/i3/137.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i3.137

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, Omicron (B.1.1.529), was first reported to the World Health Organization (WHO) from South Africa on November 24, 2021[1]. The Omicron infection was first confirmed from a sample collected on November 9, 2021[1,2]. The variant was also detected in Botswana in samples collected on November 11, 2021[1,3]. As of January 10, 2021, B.1.1.529 had spread across 105 countries, with most states and territories in the United States testing positive for the variant[3,4]. The Centers for Disease Control and Prevention (CDC) reported that of the 43 Omicron cases initially detected in the United States, 34 had been fully vaccinated, and 25 cases were adults aged 18 years to 39 years[5,6]. By the week of December 25, 2021, the Omicron variant accounts for approximately 95.4% of circulating SARS-CoV-2 strains, while Delta accounts for 4.6%[3].

Many of the cases included mild symptoms such as coughing, congestion, and fatigue; among the less frequently reported symptoms are nausea and vomiting, diarrhea, shortness of breath, difficulty breathing, and loss of smell or taste[6]. As of November 28, 2021, there is no evidence that the symptoms linked with Omicron are distinct from those associated with other variants, according to the WHO[1]. The severity of the condition, as well as its precise signs and symptoms, are still unknown[3].

Omicron has been labeled a variant of concern (VOC) by the WHO and European Center for Disease Prevention and Control (ECDC) on November 26, 2021, because it contains genetic changes that are predicted to increase transmissibility and decrease the effectiveness of social and public health measures along with available vaccines and therapeutics[7,8]. Its genetic profile consists of 26 unique mutations that make it significantly different from other existing variants and indicate that it is a new lineage of SARS-CoV-2[9]. This variant carries 32 mutations in the spike protein alone[7]. Omicron poses an issue because vaccines that have been created to mitigate SARS-CoV-2 infections target spike proteins. Studies in Germany, South Africa, Sweden, and Pfizer have shown a 25 to 40 times decrease in the ability of antibodies created by the Pfizer BioNTech vaccine to neutralize the variant after two doses[10,11]. However, severe coronavirus disease 2019 (COVID-19) can still be managed with the use of corticosteroids to induce T-cell apoptosis and act as an NF-KB inhibitor, and interleukin 6 (IL-6) receptor blockers, which act by targeting the IL-6/IL-6R/JAK pathway to suppress the overreaction of the immune system in COVID-19 patients and blocking the binding of IL-6 to its receptor[1]. Other studies underway to assess treatment efficacy against the Omicron variant include British drugmaker GSK and its United States partner Vir Biotechnology. According to data from their investigation, all spike mutations are effectively treated by their antibody-based COVID-19 therapy[12]. Although science and knowledge about this variant keep changing as they emerge, this report evaluates the literature from key scientific databases to provide an overview of the SARS-CoV-2 variant Omicron (B.1.1.529).

GLOBAL EPIDEMIOLOGY OF THE OMICRON VARIANT

Despite efforts to better understand viral neutralization and how antibodies and T-cells respond to the SARS-CoV-2 variant, Omicron remains a mystery[13]. On November 11, 2021, the variation was discovered in samples collected in Botswana and then in South Africa by November 14, 2021[3,8,13]. Depicted in Figure 1, most countries and territories have been affected by the Omicron variant, with the United Kingdom, United States, Denmark, France, and Germany most severely impacted, as this variant is presumed to spread more easily, even among the vaccinated population and those who do not show

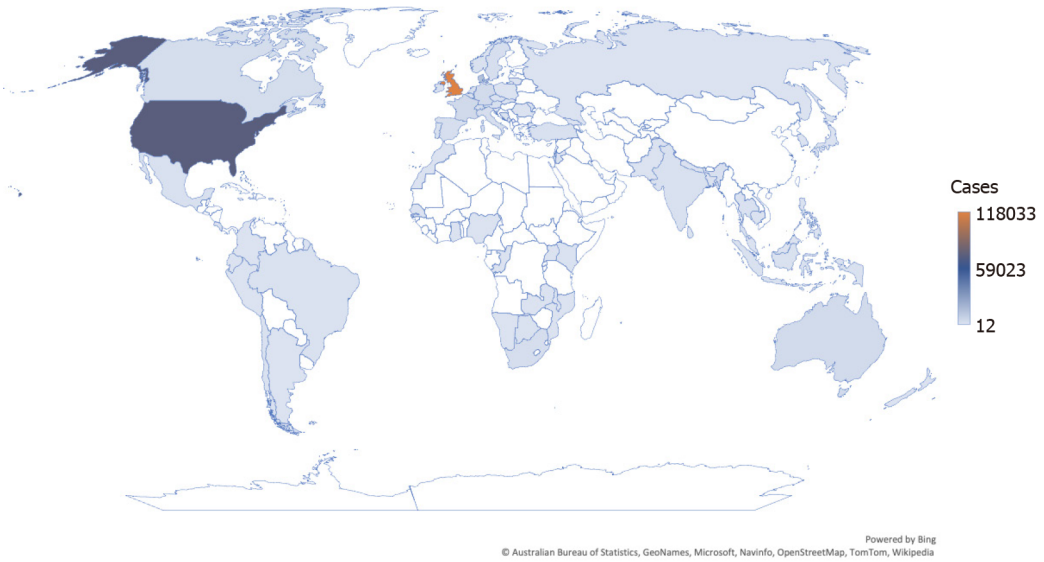


Figure 1 Confirmed Omicron cases worldwide. Data recreated and reported by GISAID as of January 10, 2022, with 242159 Omicron genome sequences reported across 105 countries[4].

symptoms; therefore, increasing the overall proportion of COVID-19 cases[3,4].

Genomic sequence

As a result of genomic surveillance, thousands of mutations have been found in the SARS-CoV-2 genome[14-16]. Numerous viral variants with mutations in the spike protein, including Alpha, Beta, and Delta, have been found[17]. These variants exhibited alterations in the receptor-binding domain (RBD), and the 25 amino acids connected to the spike protein showed an increased affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, boosting transmissibility[14,18].

A recent report presented by Dejnirattisai *et al*[14] compared neutralization titers of the SARS-CoV-2 Omicron variant with the titers of the Victoria, Beta, and Delta variants[14,19]. Sera were acquired from individuals who received the AstraZeneca or Pfizer vaccine, both of which were administered in two doses[14,20]. According to the findings, there was a considerable decrease in neutralization titers, with evidence that some individuals were unable to neutralize at all; this can lead to breakthrough vaccine infections in previously infected patients or those who completed double doses of vaccination[21-23].

Although the amino acid sequence of the Omicron spike protein can be altered by nine different mutations (S: N440K, S: G446S, S: S447N, S: T4+78K, S: E484A, S: Q493R, S: G496S, S: Q298R, and S: N501Y), the research found that antibodies can still adhere to the mutated spike protein[24]. The Omicron variant mutations do not show any structural changes that would suggest antibody evasion; nevertheless, alterations in amino acid attachments to various locations of the binding site can cause interference when engaging with antibodies[24].

Mutations

Approximately 30 mutations in the viral spike protein have been discovered, including three small deletions and one small insertion[8]. Roughly half of the mutations affect the RBD, which serves as the virus's principal site of interaction of the virus with human cells and the target protein for several current COVID-19 vaccines[8,13]. Previously, many SARS-CoV-2 variant strains revealed distinct mutations; however, the Omicron variant shows numerous types of mutations, as well as novel mutations[13]. Although the actual origin of Omicron is unknown, numerous possibilities are now being pursued, including evolution in animal reservoirs and human reinfection, or co-infection with seasonal human coronaviruses (HCoVs), such as HCoV-229E[25-27]. Chronically infected individuals are suggested to be the source of origin, as evidenced by viral sequencing[25]. Additional research revealed that when faced with a strong immune response, SARS-CoV-2 may acquire the ability to avoid antibodies through two deletions in the N-terminal domain and a mutation in the spike protein[28]. Finally, it has been proposed that natural selection can arise as a result of mutations that increase viral infectivity, antibody resistance, and vaccine breakthrough[25,29-32]. Evolutionary descent of the Omicron lineages showed that mutations arose under selection pressure due to antibodies elicited by infection, vaccination, or both, in the human population on a large scale. As of February 2022, the Omicron variant has mutated into three lineages: BA.1, BA.2, and BA.3. A sub-lineage of BA.1 with an R346K substitution in the spike protein is classified as BA.1.1. BA.1 emerged first, which was followed by BA.2 and BA.3. Like BA.1, the earlier strains of BA.2, BA.3, and BA1.1 were detected in the Gauteng Province in South Africa. It thus suggests that the diversification of Omicron occurred in South Africa.

Although BA.1 is spreading quicker than BA.2, the BA.2 lineage has become more prominent in several nations after January 2022. The genetic sequence in the spike protein of the BA.2 lineage differs from the BA.1 lineage suggesting it may confer greater immune resistance against antibodies[33-35].

Containment strategy

The U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA) diagnostic developer, DTPM, identifies and develops assays capable of diagnosing COVID-19[36]. However, due to a nine-nucleotide deletion in the N gene, exclusive to the Omicron variant, this single target test known as the reverse transcription-polymerase chain reaction (RT-PCR) of DTPM is predicted to fail, resulting in false-negative findings in patients[36]. The specific deletion of nine nucleotides is unique to the Omicron variant and poses a potential diagnostic problem, although previously detected variants should not be affected[36].

Mutations have the potential to change the accuracy of these tests, resulting in unpredictable analytical performance characteristics and false-negative results. Using a widely available commercial assay, a G-to-U transversion (nucleotide 26372) was found in the SARS-CoV-2 E gene in three cases with low viral detection efficiency[37]. Current SARS-CoV-2 PCR tests still detect the Omicron variant[7,36]. According to reports, one of the three target genes is not detected in a commonly used PCR test[7]. This targeted gene is referred to as an S gene dropout or S gene target failure[7]. As a result, pending sequencing confirmation, this test can be utilized as a marker for the Omicron variant[7]. Furthermore, the FDA is continuing to assess the impact of Omicron on SARS-CoV-2 diagnostic tests in partnership with government authorities and test producers[36]. The FDA's current investigation shows that the performance of some EUA-authorized molecular tests (*i.e.*, PCR) may be affected by the mutations in the SARS-CoV-2 Omicron variant[36]. As a response, the FDA has classified the different tests into two categories: those that are predicted to fail to identify the Omicron variant and those that are expected to detect the variant using a unique gene dropout detection pattern[36]. In addition to molecular diagnostics (*i.e.*, PCR), early evidence suggests that antigen tests can detect the SARS-CoV-2 Omicron form, although that sensitivity may be low[36].

There is much to learn about the reinfected population and effective treatment and management procedures with the Omicron variant, which has led many healthcare providers to doubt existing treatment modalities[38]. Mayer *et al*[38] conducted a recent case series investigation after a rise in people with mild respiratory symptoms of SARS-CoV-2 infections in the Western Cape province. After the patients received confirmation of their COVID-19 using molecular assays, they were placed in isolation and required a daily diary to record their symptoms[38]. A total of 7 patients were studied; of which, 6 of the 7 were fully vaccinated with a respective booster shot, and 5 of the 7 presented with the Omicron genome sequence[38]. Although the study reported breakthrough infections experienced by completely vaccinated patients and some who had also received a booster vaccine, all cases had increased levels of antibodies against the spike protein, a common finding in patients vaccinated with a booster dose[38,39]. Despite the inability to get accurate RNA viral loads, it is hypothesized that these individuals will have an increase in viral loads, suggesting that the Omicron variant could evade vaccine-induced immunity[38]. In another study on naive individuals following a booster shot (third dose), a 14-fold reduction in neutralizing activity against Omicron was observed; thus, the findings suggest the need for a third dose vaccination to provide robust neutralizing antibody responses against the Omicron variant[40].

Most COVID-19 vaccines have remained successful in preventing severe COVID-19, hospitalization, and death for all preceding variants, due to T-cell immune responses being more significant than antibodies[2]. In a matched study of more than 9000 Omicron cases in Ontario, the risk of hospitalization or death was lower for Omicron cases when compared with Delta cases[41]. Importantly, the implications of the remaining Omicron mutations are unknown, leaving a great deal of ambiguity about how the complete mix of deletions and mutations may affect viral behavior and vulnerability to natural and vaccine-mediated immunity[2]. Furthermore, a brief clinical course indicated that fully vaccinated patients who had received a booster dose retained sufficient protection against severe COVID-19 infections; thus, this supported the continued use of booster doses to help combat the spread of the Omicron variant[38,42].

COVID-19 has presented different lessons and challenges to various regions and countries of the world, and long-term data will be needed to assess vaccine efficacy in the face of the potential appearance of novel variants like Omicron[43]. Despite some evidence that vaccination alone may not be enough to prevent symptomatic infection, non-pharmaceutical practices such as continued use of face masks in the public despite vaccination and booster status of the vaccine, proper hygiene precautions, and social distancing, as well as genomic surveillance, are required to successfully combat this variant[38,44].

CONCLUSION

The emergence and global spread of Omicron, which may be antibody-resistant and appears to be

highly transmissible, emphasize the importance of genomic surveillance in conjunction with immune profiling. Reduced antibody titers may impair the ability of vaccines to prevent infection, but protection against severe disease is likely to be maintained. To avoid or minimize further spread and mutations, preventive measures such as adequate patient care management, early detection of suspicious cases, outbreak tracing, isolation protocols for the infected, continued adherence to social distancing, wearing a face mask, and vaccination must be accepted by the public and encouraged by public health professionals, government officials, and community leaders.

FOOTNOTES

Author contributions: Sanyaolu A, Marinkovic A, Prakash S, Haider N, Williams M, Okorie C, Badaru O and Smith S contributed to the design, writing and final approval of the manuscript.

Conflict-of-interest statement: The authors have no conflict of interest to this manuscript.

Country/Territory of origin: Nigeria

ORCID number: Adekunle Sanyaolu 0000-0002-6265-665X; Aleksandra Marinkovic 0000-0002-3672-0777; Stephanie Prakash 0000-0003-2664-9775; Nafees Haider 0000-0003-4449-0905; Martina Williams 0000-0001-5136-4179; Chuku Okorie 0000-0001-5483-0032; Olanrewaju Badaru 0000-0003-3035-2640; Stella Smith 0000-0003-2163-1189.

S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

REFERENCES

1 **World Health Organization**. Update on Omicron. [cited 17 December 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/news/item/28-11-2021-update-on-omicron
2 **Karim SSA**, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. *Lancet* 2021; **398**: 2126-2128 [PMID: 34871545 DOI: 10.1016/S0140-6736(21)02758-6]
3 **Centers for Disease Control and Prevention**. Science brief: Omicron (B.1.1.529) variant. [cited 10 January 2022]. In: Centers for Disease Control and Prevention [Internet]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html
4 **GISAID**. Tracking of variants. [cited 10 January 2022]. In: GISAID [Internet]. Available from: https://www.gisaid.org/hcov19-variants/
5 **Crist C**. Omicron may require fourth vaccine dose, Pfizer says. [cited 10 January 2022]. In: Medscape [Internet]. Available from: https://www.medscape.com/viewarticle/964505?spon=34&uac=289122PK&impID=3874271&sso=true&faf=1&src=WNL_mdpls_211214_mscpedit_fmed
6 **Roy M**. Most reported US Omicron cases have hit the fully vaccinated: CDC. [cited 10 January 2022]. In: Medscape [Internet]. Available from: https://www.medscape.com/viewarticle/964600?spon=34&uac=289122PK&impID=3874271&sso=true&faf=1&src=WNL_mdpls_211214_mscpedit_fmed
7 **World Health Organization**. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern. [cited 17 December 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern
8 **European Centre for Disease Prevention and Control**. Threat Assessment Brief: Implications of the emergence and spread of the SARS-CoV-2 B.1.1.529 variant of concern (Omicron), for the EU/EEA. [cited 10 January 2022]. In: European Centre for Disease Prevention and Control [Internet]. Available from: https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-emergence-sars-cov-2-variant-b.1.1.529
9 **Rodriguez A**. First known death from omicron variant reported in the UK. Everything to know about the latest COVID strain. [cited 17 December 2021]. In: USA Today [Internet]. Available from: https://www.usatoday.com/story/news/health/2021/11/29/omicron-variant-symptoms-mutations-vaccines/8791946002/
10 **Goodman B**. Vaccine protection drops against Omicron, making boosters crucial. [cited 17 December 2021]. In: Medscape [Internet]. Available from: https://www.medscape.com/viewarticle/964431?uac=289122PK&faf=1&sso=true&impID=3860584&src=mkm_covid_update_211208_MSCPEDIT
11 **Campbell M**. Omicron variant vs Pfizer vaccine - First data available. [cited 20 December 2021]. In: Biopharma [Internet]. Available from: https://www.technologynetworks.com/biopharma/news/omicron-variant-vs-pfizer-vaccine-first-data-available-356640

12 **Reuters Staff**. New data shows GSK-Vir drug works against all Omicron mutations. [cited 17 December 2021]. In: Medscape [Internet]. Available from: https://www.medscape.com/viewarticle/964276?uac=289122PK&faf=1&sso=true&impID=3860584&src=mkm_covid_update_211208_MSCPEDIT

13 **Torjesen I**. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. *BMJ* 2021; **375**: n2943 [PMID: 34845008 DOI: 10.1136/bmj.n2943]

14 **Dejnirattisai W**, Shaw RH, Supasa P, Liu C, Stuart AS, Pollard AJ, Liu X, Lambe T, Crook D, Stuart DI, Mongkolsapaya J, Nguyen-Van-Tam JS, Snape MD, Screaton GR; Com-COV2 study group. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. *Lancet* 2022; **399**: 234-236 [PMID: 34942101 DOI: 10.1016/S0140-6736(21)02844-0]

15 **Garcia-Vidal C**, Iglesias-Caballero M, Puerta-Alcalde P, Mas V, Cuesta-Chasco G, Garcia-Pouton N, Varona S, Pozo F, Vázquez-Morón S, Marcos MA, Soriano A, Casas I; HEMATOCOVID19-Researchers Group. Emergence of Progressive Mutations in SARS-CoV-2 From a Hematologic Patient With Prolonged Viral Replication. *Front Microbiol* 2022; **13**: 826883 [PMID: 35308337 DOI: 10.3389/fmicb.2022.826883]

16 **Tsanni A**. Covid-19: Africa scrambles to increase genomic testing capacity as variants spread. *BMJ* 2021; **373**: n1122 [PMID: 33962965 DOI: 10.1136/bmj.n1122]

17 **Sanyaolu A**, Okorie C, Marinkovic A, Haider N, Abbasi AF, Jaferi U, Prakash S, Balendra V. The emerging SARS-CoV-2 variants of concern. *Ther Adv Infect Dis* 2021; **8**: 20499361211024372 [PMID: 34211709 DOI: 10.1177/20499361211024372]

18 **Miller NL**, Clark T, Raman R, Sasisekharan R. Insights on the mutational landscape of the SARS-CoV-2 Omicron variant. 2021 Preprint. Available from: bioRxiv: 2021.12.06.471499 [DOI: 10.1101/2021.12.06.471499]

19 **Pulliam JRC**, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, Dushoff J, Mlisana K, Moultrie H. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* 2022; eabn4947 [PMID: 35289632 DOI: 10.1126/science.abn4947]

20 **AstraZeneca**. Vaxzevria is highly effective after one dose against severe disease or hospitalisation caused by Beta and Delta variants of concern. [cited 17 December 2021]. In: AstraZeneca [Internet]. Available from: https://www.astrazeneca.com/media-centre/press-%20releases/2021/vaxzevria-is-highly-effective-after-one-dose-against-severe-disease-or-hospitalisation-caused-by-beta-and-delta-variants-of-concern.html

21 **Liu Y**, Liu J, Xia H, Zhang X, Fontes-Garfias CR, Swanson KA, Cai H, Sarkar R, Chen W, Cutler M, Cooper D, Weaver SC, Muik A, Sahin U, Jansen KU, Xie X, Dormitzer PR, Shi PY. Neutralizing Activity of BNT162b2-Elicited Serum. *N Engl J Med* 2021; **384**: 1466-1468 [PMID: 33684280 DOI: 10.1056/NEJMc2102017]

22 **Kozlov M**. Waning COVID super-immunity raises questions about Omicron. *Nature* 2021 [PMID: 34907367 DOI: 10.1038/d41586-021-03674-1]

23 **Rossler A**, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 B.1.1.529 variant (Omicron) evades neutralization by sera from vaccinated and convalescent individuals. 2021 Preprint. Available from: medRxiv: 2021.12.08.21267491 [DOI: 10.1101/2021.12.08.21267491]

24 **Ford CT**, Machado DJ, Janies DA. Predictions of the SARS-CoV-2 Omicron variant (B.1.1.529) spike protein receptor-binding domain structure and neutralizing antibody interactions. 2021 Preprint. Available from: bioRxiv: 2021.12.03.471024 [DOI: 10.1101/2021.12.03.471024]

25 **Lewis RF**, Chen JIP, Mon Y, Ng BXY, Tan LML. Omicron (B.1.1.529) variant. [cited 17 December 2021]. In: National University of Singapore (NUS): Saw Swee Hock School of Public Health [Internet]. Available from: https://sph.nus.edu.sg/wp-content/uploads/2021/12/Omicron-Variant-Rapid-Review-3.0-21.12.17.pdf

26 **Kupferschmidt K**. Where did 'weird' Omicron come from? *Science* 2021; **374**: 1179 [PMID: 34855502 DOI: 10.1126/science.acx9738]

27 **Abbasi J**. Omicron Has Reached the US-Here's What Infectious Disease Experts Know About the Variant. *JAMA* 2021; **326**: 2460-2462 [PMID: 34870691 DOI: 10.1001/jama.2021.22619]

28 **Prasad U**, Soni R. How Omicron variant of COVID-19 may have arisen. [cited 17 December 2021]. In: Scientific European [Internet]. Available from: https://www.scientificeuropean.co.uk/covid-19/how-omicron-variant-of-covid-19-may-have-arisen/

29 **Callaway E**. Omicron likely to weaken COVID vaccine protection. *Nature* 2021; **600**: 367-368 [PMID: 34880488 DOI: 10.1038/d41586-021-03672-3]

30 **Wilhelm A**, Widera M, Grikscheit K, Toptan T, Schenk B, et al Reduced neutralization of SARS-CoV-2 Omicron variant by vaccine sera and monoclonal antibodies. 2021 Preprint. Available from: medRxiv: 2021.12.07.21267432 [DOI: 10.1101/2021.12.07.21267432]

31 **Callaway E**, Ledford H. How bad is Omicron? *Nature* 2021; **600**: 197-199 [PMID: 34857948 DOI: 10.1038/d41586-021-03614-z]

32 **Goldberg Y**, Mandel M, Bar-on YM, Bodenheimer O, Freedman L, Ash N, Alroy-Preis S, Huppert A, Milo R. Protection and waning of natural and hybrid COVID-19 immunity. 2021 Preprint. Available from: medRxiv: 2021.12.04.21267114 [DOI: 10.1101/2021.12.04.21267114]

33 **Wang LF**, Tan CW, Chia WN, Zhu F, Young B, Chantasrisawad N, Hwa SH, Yeoh AY, Lim BL, Yap WC, Pada SK, Tan SY, Jantarabenjakul W, Chen S, Zhang J, Mah YY, Chen V, Chen M, Wacharapluesadee S, Team CK, Putcharoen O, Lye D. Differential escape of neutralizing antibodies by SARS-CoV-2 Omicron and pre-emergent sarbecoviruses. *Res Sq* 2022; rs.3.rs-1362541 [PMID: 35233568 DOI: 10.21203/rs.3.rs-1362541/v1]

34 **Yamasoba D**, Kimura I, Nasser H, Morioka Y, Nao N, Ito J, Uriu K, Tsuda M, Zahradnik J, Shirakawa K, Suzuki R, Kishimoto M, Kosugi Y, Kobiyama K, Hara T, Toyoda M, Tanaka YL, Butlertanaka EP, Shimizu R, Ito H, Wang L, Oda Y, Orba Y, Sasaki M, Nagata K, Yoshimatsu K, Asakura H, Nagashima M, Sadamasu K, Yoshimura K, Kuramochi J, Seki M, Fujiki R, Kaneda A, Shimada T, Nakada T, Sakao S, Suzuki T, Ueno T, Takaori-Kondo A, Ishii KJ, Schreiber G; The Genotype to Phenotype Japan (G2P-Japan) Consortium, Sawa H, Saito A, Irie T, Tanaka S, Matsuno K, Fukuhara T, Ikeda T, Sato K. Virological characteristics of SARS-CoV-2 BA. 2 variant. 2021 Preprint. Available from: bioRxiv:2022.02.14.480335 [DOI: 10.1101/2022.02.14.480335]

35 **Desingu PA**, Nagarajan K, Dhama K. Emergence of Omicron third lineage BA.3 and its importance. *J Med Virol* 2022; **94**: 1808-1810 [PMID: 35043399 DOI: 10.1002/jmv.27601]

36 **U.S. Food and Drug Administration**. SARS-CoV-2 viral mutations: Impact on COVID-19 tests. [cited 10 January 2022]. In: U.S. Food and Drug Administration [Internet]. Available from: https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests

37 **Tahan S**, Parikh BA, Droit L, Wallace MA, Burnham CD, Wang D. SARS-CoV-2 E Gene Variant Alters Analytical Sensitivity Characteristics of Viral Detection Using a Commercial Reverse Transcription-PCR Assay. *J Clin Microbiol* 2021; **59**: e0007521 [PMID: 33903167 DOI: 10.1128/JCM.00075-21]

38 **Mayer CK**, Claassen M, Maponga T, Sutherland AD, Suliman T, Shaw M, Preiser W. Breakthrough infections with SARS-CoV-2 Omicron variant despite booster dose of mRNA vaccine. *SSRN* 2021 [DOI: 10.2139/ssrn.3981711]

39 **Centers for Disease Control and Prevention**. Omicron variant: What you need to know. [cited 10 January 2022]. In: Centers for Disease Control and Prevention [Internet]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html

40 **Edara VV**, Manning KE, Ellis M, Lai L, Moore KM, Foster SL, Floyd K, Davis-Gardner ME, Mantus G, Nyhoff LE, Bechnak S, Alaaeddine G, Naji A, Samaha H, Lee M, Bristow L, Gagne M, Roberts-Torres J, Henry AR, Godbole S, Grakoui A, Saxton M, Piantadosi A, Waggoner JJ, Douek DC, Rouphael N, Wrammert J, Suthar MS. mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant. *Cell Rep Med* 2022; **3**: 100529 [PMID: 35233550 DOI: 10.1016/j.xcrm.2022.100529]

41 **Ulloa AC**, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 Omicron Variant Severity in Ontario, Canada. *JAMA* 2022; **327**: 1286-1288 [PMID: 35175280 DOI: 10.1001/jama.2022.2274]

42 **Chenchula S**, Karunakaran P, Sharma S, Chavan M. Current evidence on efficacy of COVID-19 booster dose vaccination against the Omicron variant: A systematic review. *J Med Virol* 2022 [PMID: 35246846 DOI: 10.1002/jmv.27697]

43 **Godlee F**. Vaccines should not be the preserve of rich countries. *BMJ* 2021; **374**: n2044 [DOI: 10.1136/bmj.n2044]

44 **Centers for Disease Control and Prevention**. SARS-CoV-2 B.1.1.529 (Omicron) variant - United States, December 1-8, 2021. Morbidity and Mortality Weekly Report. [cited 10 January 2022]. In: Centers for Disease Control and Prevention [Internet]. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7050e1-H.pdf

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 May 25; 11(3): 144-149

DOI: 10.5501/wjv.v11.i3.144

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Basic Study

Omicron variant and change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 with the angiotensin-converting enzyme 2 receptor

Rujittika Mungmunpuntipantip, Viroj Wiwanitkit

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Casaca W, Brazil; Nazari N, Iran; Ren S, China

Received: December 16, 2021
Peer-review started: December 16, 2021
First decision: February 21, 2022
Revised: February 21, 2022
Accepted: April 26, 2022
Article in press: April 26, 2022
Published online: May 25, 2022

Rujittika Mungmunpuntipantip, Consultant, Private Consultant, Bangkok 102002022, Thailand

Viroj Wiwanitkit, Department of Community Medicine, Dr. DY Patil University, Pune 310330, India

Corresponding author: Rujittika Mungmunpuntipantip, PhD, Academic Research, Additional Professor, Consultant, Private Consultant, Bangkok 102002022, Thailand. rujittika@gmail.com

Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants are currently a new hazard. Since the first appearance of classical SARS-CoV-2 in late 2019, pathogen genetic alterations have continued to occur, and some new hazardous forms have already emerged. The underlying pathophysiological process leading to clinical issue is molecular change caused by genetic mutation.

AIM

To determine the change in the interaction between receptor binding domain of omicron variant SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2).

METHODS

The researchers investigated how alterations in the binding area of the SARS receptor CoV2 interacted electrostatically with the ACE2 receptor. In this report, three important coronavirus disease 2019 variants, beta, delta, and omicron, were investigated.

RESULTS

According to this study, there was a change of electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor due to each studied variant. The most change was detected in omicron variant followed by delta variant and beta variant.

CONCLUSION

Our results may support the clinical finding that the omicron variant is more transmissible than the wild type and other variants.

Key Words: Omicron; COVID-19; SARS-CoV-2; ACE2; Electrostatic

Core Tip: Change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 with the angiotensin-converting enzyme 2 receptor can support the clinical observation that the omicron variant has increased transmissibility compared to the wild type and other variants.

Citation: Mungmunpuntipantip R, Wiwanitkit V. Omicron variant and change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 with the angiotensin-converting enzyme 2 receptor. *World J Virol* 2022; 11(3): 144-149
URL: https://www.wjgnet.com/2220-3249/full/v11/i3/144.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i3.144

INTRODUCTION

In late 2019, a novel coronavirus epidemic emerged in Asia and quickly spread throughout the world [1]. A pandemic occurred, resulting in millions of cases of coronavirus disease 2019 (COVID-19) all across the world. The disease has already infected over 200 million individuals worldwide, resulting in millions of deaths. Since the initial appearance of classical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, scientists have been keeping a tight eye on the pathogen's genetic mutations all across the world[2]. Several pathogenic genetic mutations have been identified, and several variants have already proven to be troublesome novel variants[2,3].

The delta variant is one of the dangerous mutations that has spread globally[4,5]. Because transmission of the delta variation is higher than that of COVID-19, it can provide a concern in disease control. A newer form, the delta plus variant, has also been discovered, and it is now being considered in clinical practice[6,7]. The impact of novel variations on disease epidemiology and clinical characteristics is interesting. The newest troublesome variant of concern, the omicron variant, was discovered in Africa in November 2021[8]. There are various structural alterations in this new variant molecule. Omicron is spreading in a rapid manner, and many nations have already reported cases[9].

Clinically, the underlying pathophysiological mechanism that can result in a clinical disease is molecular change caused by genetic mutation. The impact of molecular changes is interesting, but it has received little research. The clinical impact of the omicron mutation is unknown. Pathogenesis may change as a result of molecular changes. A change in the interaction between receptor binding domain of SARS-CoV-2 with the ACE2 is an interesting issue. The authors conducted this study to see how mutations are associated with electrostatic interactions between the receptor binding domain of SARS-CoV-2 and the ACE2 receptor. In this report, three important COVID-19 variants, beta, delta, and omicron, are investigated.

MATERIALS AND METHODS

The current research is in the field of medical molecular bioinformatics. It is part of a series of experiments aimed at determining the effects of molecular changes in mutants of SARS-CoV-2. The goal of this research is to see how electrostatic interactions between SARS-CoV-2 and ACE2 receptor change according to the emerging variants. For the investigation of change of electrostatic interactions between receptor binding domain of SARS-CoV-2 with the ACE2 receptor, the authors applied a conventional informatics technique, as described in a recent publication[10].

Various protein-protein interactions are known to be dominated by electrostatic interactions[11]. Analysis was performed according to the published protocol[10]. Briefly, we examined the impact of electrostatic interactions on binding energetics. At the molecular level, both molecular mechanics and Monte Carlo simulations were used to assess the interaction between the receptor binding domain of spike viral protein and ACE2. The protein structure was obtained from the protein data bank and used in all computations (PDB ID: 6m17). To begin, the crystal structure was optimized using the python-based open technique[12]. Then, using multiconformation continuum electrostatics[13], rotamers were created, with each rotatable bond rotated by 60 degrees to sample precisely the sidechain conformations. Finally, the Poisson Boltzmann equation was utilized to calculate electrostatic interactions using optimized protein structures with the most occupied conformers[10]. When DELPHI was used to

calculate pairwise electrostatic interactions between conformers, it is referred to as DELPHI[10]. The Boltzmann distribution for all conformers was then estimated using Monte Carlo sampling for the WT and altered structures at pH 7 using multiconformation continuum electrostatics. For single and double mutant structures, as well as the wild type, the electrostatic and van der Waals contributions to the interaction energies of SARS-CoV-2/ACE2 were estimated[10].

The research type of SARS-CoV-2 included both wild type and mutation-free SARS-CoV-2. *In silico* mutation assignment was by PyMol (PyMol, version 2.4). The variants studied are: (1) Beta (K417N, E484K, and N501Y assigned mutations); (2) Delta (T478K, P681R, and L452R assigned mutations); and (3) Omicron (K417N, E484K, and N501Y assigned mutations) (A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F assigned mutations).

The overall electrostatic interactions value for wild type was derived from the previously mentioned bioinformatic procedure. The already described molecular changes were used for simulation to get the overall electrostatic interactions value for each specific variant. We then calculated the effects of the aforementioned mutations and compared our findings to those of the wild type (native) protein. In brief, the effect of variant on electrostatic interactions was calculated based on a direct comparison to the baseline electrostatic interactions value in wild type. For calculation, the derived overall electrostatic interactions for wild type and each SARS-CoV-2 variant were used as basic parameters. For each type, the change of electrostatic interactions compared to wild type was calculated by the formula "change of electrostatic interactions comparing to wild type = 100 x (electrostatic interactions in that type/ electrostatic interactions of wild type)" and presented in percentage.

RESULTS

The electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor for wild type, beta variant, delta variant, and omicron variant SARS-CoV-2 are presented in Figure 1. The values are equal to -39.38, -41.26, -163.82, and -643.71 kcal/mol, respectively.

There were differences in electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor among the variants studied. The most change was detected in the omicron variant, followed by delta variant and beta variant (Table 1).

DISCUSSION

In clinical genetics, a genetic change may occur, which may result in a new clinical condition. The clinical problem caused by the pathogen's genetic variation has already been noticed in COVID-19[4,5]. In clinical virology, a mutation in the SARS-CoV-2 virus could occur, and the new variety could be clinically significant. SARS-CoV-2 variations have been reported in a number of places. The changes occur at the receptor-binding region of the spike glycoprotein, which is critical for binding to the ACE2 receptor. The interaction between receptor and SARS-CoV-2 is a significant factor of sickness, according to pathophysiology.

Basically, several alterations have been discovered in the omicron variant's molecular structure. The mutations could lead to a shift in molecular pathogenesis. A key feature, electrostatic interaction with receptor, was evaluated in this study. The ability of SARS-CoV-2 to bind to a receptor is a critical factor in its transmission. There is no doubt that the new variant spreads quickly[7], which can be explained by the change in electrostatic interactions between receptor and SARS-CoV-2.

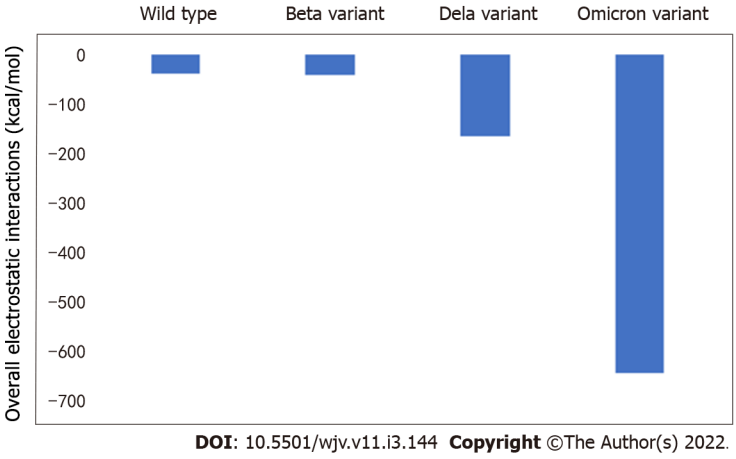
As a result, measuring changes in virus-receptor electrostatic interactions can help researchers better understand disease pathogenesis. According to this study, there has been a significant change in electrostatic interactions. The change of electrostatic interaction has been well described in the delta variant [10], and a change was also observed in the omicron variant. In delta variant, a replacement due to mutation resulted in electrostatic interaction change, and the increased magnitude of electrostatic interactions corresponded to the increased transmissibility of the virus[14].

According to this study, there is a different change of electrostatic interactions between receptor binding domain of SARS-CoV-2 and the ACE2 receptor due to different SARS-CoV-2 variants. The most change was detected in omicron variant, followed by delta variant and beta variant. According to Table 1, the greatest percentage of change compared to wild type was detected in omicron variant. The greatest degree of change indicates the most changes in electrostatic interactions, which can also indicate major changes in clinical features. When compared to wild type, the omicron variant poses around 16 times more electrostatic interactions, implying a significantly stronger connection between the virus and its receptor.

This finding can support the clinical observation that the omicron variant has an increased transmissibility compared to the wild type and other variants. The data from this preliminary study are useful for explaining the pathogenesis of the omicron variant. Further studies on the detailed flexibility of

Table 1 Change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 and the angiotensin-converting enzyme 2 receptor

Types	Mutations	Electrostatic interactions	
		Overall, kcal/mol	Change compared to wild type, %
Wild type	No	-39.38	0
Beta variant	T478K, P681R, and L452R	-41.26	104.8
Dela variant	T478K, P681R, L452R, and K417N	-163.82	416.0
Omicron variant	A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F	-634.71	1611.8



DOI: 10.5501/wjv.v11.i3.144

Figure 1 Graphical result showing electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 and the angiotensin-converting enzyme 2 receptor.

molecular binding, molecular mass change, and immunological epitope change will add to our understanding of the virological properties of the variant.

CONCLUSION

Each studied variant affects the electrostatic interactions between the SARS-CoV-2 receptor binding domain and the ACE2 receptor, according to this study. The omicron form demonstrated the greatest change, followed by the delta and beta variants. These results could support the clinical finding that the omicron variant is more contagious than the wild type and other SARS-CoV-2 variants.

ARTICLE HIGHLIGHTS

Research background

According to this study, each investigated variant altered the electrostatic interactions between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor binding domain and the angiotensin-converting enzyme 2 (ACE2) receptor. The omicron variant showed the biggest alteration, followed by the delta and beta variants. This finding could back up the clinical observation that the omicron variant is more transmissible than the wild type and other SARS-CoV-2 variants.

Research motivation

Each studied variant affected the electrostatic interactions between the SARS-CoV-2 receptor binding domain and the ACE2 receptor. The omicron form, followed by the delta and beta variants, displays the most change. This could support the clinical finding that the omicron variant is more contagious than

the wild type and other SARS-CoV-2 variants.

Research objectives

The authors conducted a study to see how mutations are associated with alterations of electrostatic interactions between receptor binding domain of SARS-CoV-2 with the ACE2 receptor.

Research methods

The researchers investigated how mutations affect electrostatic interactions between the SARS-CoV-2 receptor binding domain and the ACE2 receptor. In this report, three important coronavirus disease 2019 variants, beta, delta, and omicron, were investigated.

Research results

There was a change of electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor due to each studied variant compared to wild type. The most change was detected for the omicron variant, followed by delta variant and beta variant.

Research conclusions

Our findings can support the clinical observation that the omicron variant has an increased transmissibility comparable to the wild type and other variants.

Research perspectives

Our findings are consistent with the clinical observation that the omicron variation is more transmissible than the wild type and other variants.

FOOTNOTES

Author contributions: Mungmunpuntipantip R and Wiwanitkit V contributed to study conception and design, acquisition of data, and analysis and interpretation of data; Mungmunpuntipantip R drafted the article, revised it critically for important intellectual content, and approved the version of the article to be published

Conflict-of-interest statement: All authors declare that there are no conflicts of interest.

Country/Territory of origin: Thailand

ORCID number: Rujittika Mungmunpuntipantip 0000-0003-0078-7897; Viroj Wiwanitkit 0000-0003-1039-3728.

S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

REFERENCES

1 **Hsia W**. Emerging new coronavirus infection in Wuhan, China: situation in early 2020. *Case Study Case Rep* 2020; **10**: 8-9
2 **Callaway E**. Fast-spreading COVID variant can elude immune responses. *Nature* 2021; **589**: 500-501 [PMID: 33479534 DOI: 10.1038/d41586-021-00121-z]
3 **Lauring AS**, Hodcroft EB. Genetic Variants of SARS-CoV-2-What Do They Mean? *JAMA* 2021; **325**: 529-531 [PMID: 33404586 DOI: 10.1001/jama.2020.27124]
4 **Hendaus MA**, Jomha FA. Delta variant of COVID-19: A simple explanation. *Qatar Med J* 2021; **2021**: 49 [PMID: 34660217 DOI: 10.5339/qmj.2021.49]
5 **Torjesen I**. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. *BMJ* 2021; **373**: n1445 [PMID: 34088699 DOI: 10.1136/bmj.n1445]
6 **Callaway E**. Heavily mutated Omicron variant puts scientists on alert. *Nature* 2021; **600**: 21 [PMID: 34824381 DOI: 10.1038/d41586-021-03552-w]
7 **Torjesen I**. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. *BMJ* 2021; **375**: n2943 [PMID: 34845008 DOI: 10.1136/bmj.n2943]
8 **Rahman FI**, Ether SA, Islam MR. The "Delta Plus" COVID-19 variant has evolved to become the next potential variant of concern: mutation history and measures of prevention. *J Basic Clin Physiol Pharmacol* 2021; **33**: 109-112 [PMID:

34563102 DOI: 10.1515/jbcpp-2021-0251]

9 **Kannan SR**, Spratt AN, Cohen AR, Naqvi SH, Chand HS, Quinn TP, Lorson CL, Byrareddy SN, Singh K. Evolutionary analysis of the Delta and Delta Plus variants of the SARS-CoV-2 viruses. *J Autoimmun* 2021; **124**: 102715 [PMID: 34399188 DOI: 10.1016/j.jaut.2021.102715]

10 **Goher SS**, Ali F, Amin M. The Delta Variant Mutations in the Receptor Binding Domain of SARS-CoV-2 Show Enhanced Electrostatic Interactions with the ACE2. *Med Drug Discov* 2021; 100114 [PMID: 34901826 DOI: 10.1016/j.medidd.2021.100114]

11 **Li B**, Deng A, Li K, Hu Y, Li Z, Shi Y, Xiong Q, Liu Z, Guo Q, Zou L, Zhang H, Zhang M, Ouyang F, Su J, Su W, Xu J, Lin H, Sun J, Peng J, Jiang H, Zhou P, Hu T, Luo M, Zhang Y, Zheng H, Xiao J, Liu T, Tan M, Che R, Zeng H, Zheng Z, Huang Y, Yu J, Yi L, Wu J, Chen J, Zhong H, Deng X, Kang M, Pybus OG, Hall M, Lythgoe KA, Li Y, Yuan J, He J, Lu J. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant. *Nat Commun* 2022; **13**: 460 [PMID: 35075154 DOI: 10.1038/s41467-022-28089-y]

12 **Eastman P**, Swails J, Chodera JD, McGibbon RT, Zhao Y, Beauchamp KA, Wang LP, Simmonett AC, Harrigan MP, Stern CD, Wiewiora RP, Brooks BR, Pande VS. OpenMM 7: Rapid development of high performance algorithms for molecular dynamics. *PLoS Comput Biol* 2017; **13**: e1005659 [PMID: 28746339 DOI: 10.1371/journal.pcbi.1005659]

13 **Song Y**, Mao J, Gunner MR. MCCE2: improving protein pKa calculations with extensive side chain rotamer sampling. *J Comput Chem* 2009; **30**: 2231-2247 [PMID: 19274707 DOI: 10.1002/jcc.21222]

14 **Pascarella S**, Ciccozzi M, Zella D, Bianchi M, Benedetti F, Benvenuto D, Broccolo F, Cauda R, Caruso A, Angeletti S, Giovanetti M, Cassone A. SARS-CoV-2 B.1.617 Indian variants: Are electrostatic potential changes responsible for a higher transmission rate? *J Med Virol* 2021; **93**: 6551-6556 [PMID: 34260088 DOI: 10.1002/jmv.27210]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 May 25; 11(3): 150-169

DOI: 10.5501/wjv.v11.i3.150

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Observational Study

Educational, psychosocial, and clinical impact of SARS-CoV-2 (COVID-19) pandemic on medical students in the United States

Veronica Frank, Anjali Doshi, Natalie L Demirjian, Brandon K K Fields, Catherine Song, Xiaomeng Lei, Sravanthi Reddy, Bhushan Desai, Drayton C Harvey, Steven Cen, Ali Gholamrezanezhad

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Khosravi M, Iran; Liu XQ, China; Mohammadi S, Iran

Received: December 17, 2021
Peer-review started: December 17, 2021
First decision: February 21, 2022
Revised: March 10, 2022
Accepted: April 22, 2022
Article in press: April 22, 2022
Published online: May 25, 2022

Veronica Frank, Semmelweis University Faculty of Medicine, Semmelweis University Faculty of Medicine, Budapest 1085, Hungary

Anjali Doshi, Brandon K K Fields, Catherine Song, Drayton C Harvey, Keck School of Medicine of University of Southern California, Los Angeles, CA 90033, United States

Natalie L Demirjian, Department of Integrative Anatomical Sciences, Keck School of Medicine of University of Southern California, Los Angeles, CA 90033, United States

Xiaomeng Lei, Sravanthi Reddy, Bhushan Desai, Steven Cen, Ali Gholamrezanezhad, Department of Radiology, Keck School of Medicine of University of Southern California, Los Angeles, CA 90033, United States

Corresponding author: Ali Gholamrezanezhad, MD, Associate Professor, Department of Radiology, Keck School of Medicine of University of Southern California, 1500 San Pablo Street, Los Angeles, CA 90033, United States. a.gholamrezanezhad@yahoo.com

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic altered education, exams, and residency applications for United States medical students.

AIM

To determine the specific impact of the pandemic on US medical students and its correlation to their anxiety levels.

METHODS

An 81-question survey was distributed *via* email, Facebook and social media groups using REDCap™. To investigate risk factors associated with elevated anxiety level, we dichotomized the 1-10 anxiety score into low (≤ 5) and high (≥ 6). This cut point represents the 25th percentile. There were 90 (29%) shown as low anxiety and 219 (71%) as high anxiety. For descriptive analyses, we used contingency tables by anxiety categories for categorical measurements with chi square test, or mean ± STD for continuous measurements followed by *t*-test or Wilcoxson rank sum test depending on data normality. Least Absolute Shrinkage and Selection Operator was used to select important predictors for the final multivariate model. Hierarchical Poisson regression model was used to fit the

final multivariate model by considering the nested data structure of students clustered within State.

RESULTS

397 medical students from 29 states were analyzed. Approximately half of respondents reported feeling depressed since the pandemic onset. 62% of participants rated 7 or higher out of 10 when asked about anxiety levels. Stressors correlated with higher anxiety scores included "concern about being unable to complete exams or rotations if contracting COVID-19" (RR 1.34; 95%CI: 1.05-1.72, P = 0.02) and the use of mental health services such as a "psychiatrist" (RR 1.18; 95%CI: 1.01-1.3, P = 0.04). However, those students living in cities that limited restaurant operations to exclusively takeout or delivery as the only measure of implementing social distancing (RR 0.64; 95%CI: 0.49-0.82, P < 0.01) and those who selected "does not apply" for financial assistance available if needed (RR 0.83; 95%CI: 0.66-0.98, P = 0.03) were less likely to have a high anxiety.

CONCLUSION

COVID-19 significantly impacted medical students in numerous ways. Medical student education and clinical readiness were reduced, and anxiety levels increased. It is vital that medical students receive support as they become physicians. Further research should be conducted on training medical students in telemedicine to better prepare students in the future for pandemic planning and virtual healthcare.

Key Words: Medical student; SARS-CoV-2; Anxiety; Stress; Psychological; Impact clinical

Core Tip: The severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019) pandemic resulted in a significant impact on medical student education. Education was switched to on-line, examinations were changed, and students' faced dismissal from hospital wards. In this study we analyzed the unique stressors that resulted in higher anxiety levels in medical students. From the results, we can agree that the development of medical school curricula for public health and mass casualty planning as well as providing further mental health support for medical students is necessary and should be further studied.

Citation: Frank V, Doshi A, Demirjian NL, Fields BKK, Song C, Lei X, Reddy S, Desai B, Harvey DC, Cen S, Gholamrezanezhad A. Educational, psychosocial, and clinical impact of SARS-CoV-2 (COVID-19) pandemic on medical students in the United States. *World J Virol* 2022; 11(3): 150-169
URL: https://www.wjgnet.com/2220-3249/full/v11/i3/150.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i3.150

INTRODUCTION

In March 2020, the World Health Organization (WHO) declared the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a worldwide pandemic. Starting in China, SARS-CoV-2 [coronavirus disease 2019 (COVID-19)] went on to globally infect more than 426 million people and affect their community healthcare systems, calling on healthcare workers to work overtime to cover the exceeding demand for care[1]. American hospitals faced tremendous difficulty in not only providing enough hospital beds and ventilators for critically ill COVID-19 patients, but also in maintaining the care of existing critically ill patients recovering from a prolonged hospital course. Moreover, hospitals nationwide have faced a severe shortage of personal protective equipment (PPE) for front-line workers and healthcare workers in general[2]. These shortages with the necessity for slowing the rate of infection resulted in several isolation measures, including the temporary dismissal of many medical students from the hospital wards. Medical students amid their clinical training were placed in a particularly difficult spot; neither physicians, nurses, nor local public health departments were able to come to a consensus on whether or not medical students were to be considered "essential workers" amid the pandemic[3]. As a result, medical schools across the US varied in their placement of medical students during this time, either pulling medical students off the wards and away from progressing through their clinical training or fast-tracking their graduations to allow for additional assistance in hospitals and emergency departments with an overabundance of ill patients[4].

Classes were switched to online education to abide by local public health laws mandating stay-at-home orders. Students faced closures of their medical schools as well as postponements, cancellations,

or changes to their National Board of Medical Examiners (NBME) board and shelf exam[1] dates. In addition clinical rotation NBME shelf exams were switched from in-person proctored exams to online [5]. The United States Medical Licensing Examination (USMLE) Step series of board exams continued to be administered at Prometric and other official testing centers, but with far fewer available spots, causing many students to go without any test date. To address this problem, the USMLE had designated specific medical schools as eligible testing centers for board exam administration in late May[5]. Additionally, there had been modifications to the residency application cycle, calling for the suspension of all in-person interviews in favor of virtual interviews. This presents significant challenges in allowing institutions and students to get to know each other on the only personal, in person, level that was possible for a typical residency application cycle[6].

Clearly, COVID-19 has had a significant impact on medical students, perhaps with lasting consequences that may affect their future careers. We aim to understand the extent to which COVID-19 has affected medical students by focusing on educational impact and clinical outcome with corresponding levels of anxiety. More specifically, our goal is to qualitatively evaluate the cancellation of academic activities, USMLE exam planning and preparation, or change of school year end date due to COVID-19 as well as psychological and financial impacts of the pandemic on the medical students. By knowing how global health crises affect future physicians, healthcare systems, national organizations and medical institutions can take steps to best prepare medical students while ensuring a stable trajectory towards training as well as healthy personal well-being and morale.

MATERIALS AND METHODS

The online survey was designed to be anonymous to more accurately understand the impact of COVID-19 on medical students. A subset of questions were adapted from a survey studying the impact of COVID-19 on spine surgeons[7]. Only less than 30% of the questions were adopted from the survey on spine surgeons and the majority of questions were specifically designed for medical students. The questions went through several rounds of review and revision by the attendings of the medical school to verify they reliably assess the impact of COVID-19 on students. The Institutional Review Board of USC determined this study to be exempt from review (application number UP-20-00314).

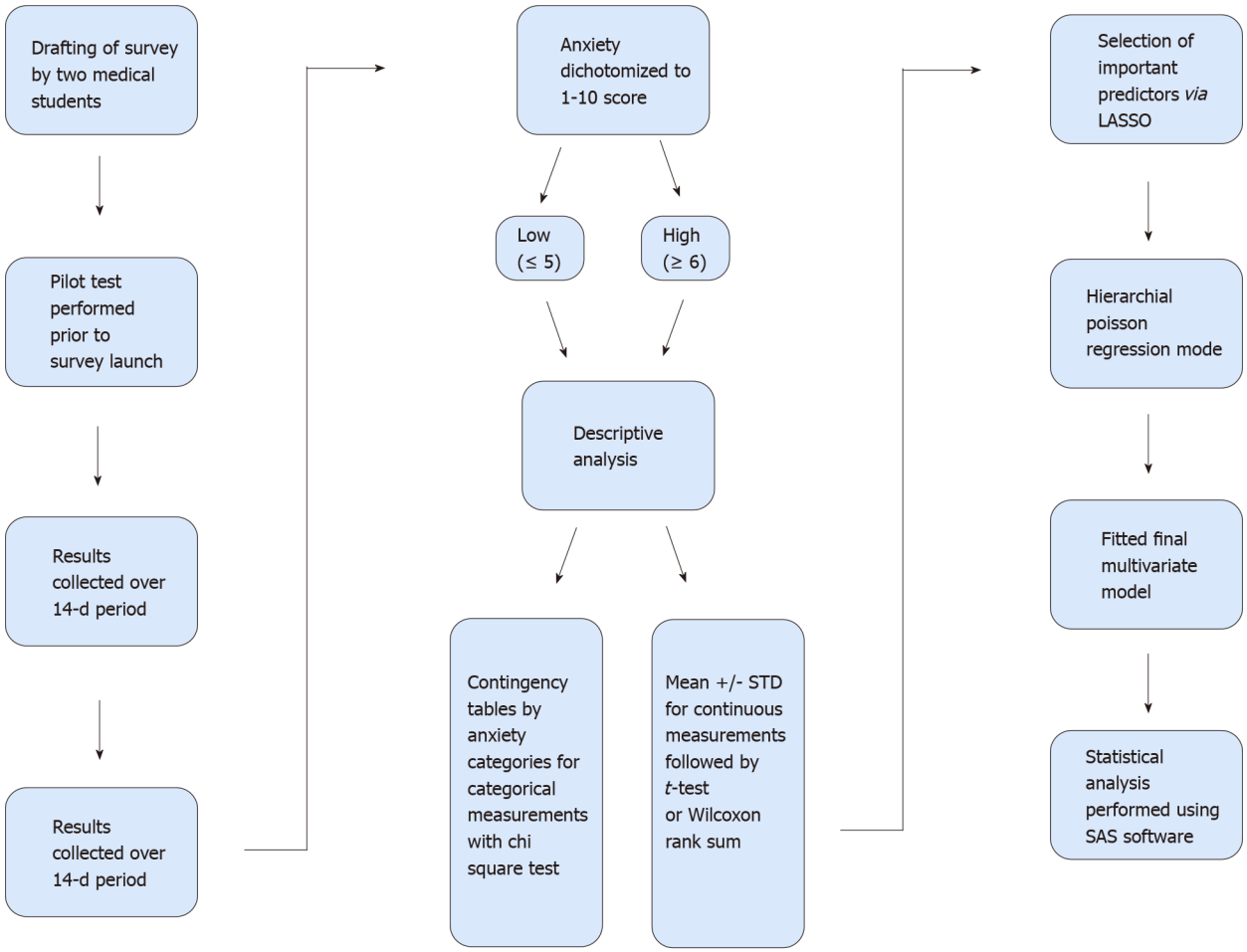
Study design and survey

A list of medical school contacts, including medical students and presidents from medical student associations, were compiled from 51 medical schools within the US through the students contributing to this survey. The survey was distributed using a secure web-based platform, REDCap™ (Research Electronic Data Capture), provided by our institution[8,9]. All invitations were sent *via* email or an online social networking platform with a short explanation of the study. Participants included medical students located in the United States in their pre-clinical, clinical, and research years. Participants were also encouraged to share the survey with their fellow medical students to expand the response rate. Due to the urgency of pandemic, we did not use any sampling strategy such as clustered sample or stratified sample. Instead, a broadcasting email went out to reach as many students as possible in a short period of time.

Two medical students drafted the survey questions, which were reviewed by a team that included medical students, research personnel, and physicians, and a pilot test was run prior to launch of the survey (Figure 1). A total of 81 questions were included in the survey with a 10-min estimated duration time. The survey analyzed the general demographics of participants including age, sex, medical school year, and the state in which medical school is located. The survey data included the following groupings on the impact of COVID-19: General impact, educational duties, medical school preparedness, exams and residency application impact, volunteering, working during the pandemic, financial, and psychological impact. For example, participants were asked about their local government restrictions, educational impact with closure of in-person medical schools, and how well their medical schools adapted. Further questions included changes made to exams, process of applying to residency changes, and levels of anxiety elicited by these changes and the uncertainty of the pandemic. The response options included: binary (yes/no), "non-applicable" and "I don't know"; use of Likert scales on rating participants agreement on provided statements, and selection of items from a list also including text boxes for further elaboration.

Data collection

The survey was distributed on May 6, 2020 *via* email and online social networking platforms using a secure web-based platform, REDCap™. To protect the identity of the participants, no personal identifiers were saved such as IP address tracking, browser activities, read receipts, email activity, or similar data. Participants were encouraged to complete the survey on their own time and in a private environment. Results were collected over a 14-d period and the survey was closed on May 20, 2020. After the survey closure, the collected results were downloaded from REDCap™ and data analysis was initiated.



DOI: 10.5501/wjv.v11.i3.150

Figure 1 Flowchart of the study process. LASSO: Least Absolute Shrinkage and Selection Operator.

Data analysis

Mean age, response distribution percentage, Chi-squared test for categorical data, and independent t-tests for continuous measurements were used for descriptive analysis. To investigate risk factors associated with elevated anxiety level, we dichotomized the 1-10 anxiety score into low (≤ 5) and high (≥ 6). This cut point represents the 25th percentile of the original scale. We dichotomized items in order to maximize the number of cases and improve statistical power based on a recent study[10].

For descriptive analyses, we used contingency tables by anxiety categories for categorical measurements with chi square test, or mean ± STD for continuous measurements followed by *t*-test or Wilcoxon rank sum test depending on data normality. Least Absolute Shrinkage and Selection Operator (LASSO) was used to select important predictors for the final multivariate model[11]. Hierarchical Poisson regression model was used to fit the final multivariate model by considering the nested data structure of students clustered within State. Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Participant characteristics

397 medical students (61.17% women, overall participant mean age = 26 ± 2.43 years) who responded to the survey from 29 states were included in the analysis. The distribution across the United States is shown in Table 1, and the demographics of the respondents is demonstrated in Table 2. Of the respondents, 33% were in their first year, 22% second years, 25% third years, and 18% in their fourth year. The remaining 2% were either MD/PhD track students or in their research year. The results of the survey are presented below.

Anxiety assessment

The anxiety scale (1-10) had a distribution of 6.8 ± 2.4, with median of 7, Q1-Q3 of 5-9. When

Table 1 Respondent distribution across the United States

State	N = 397 (%)
Missouri	139 (35.0)
California	68 (17.13)
Pennsylvania	39 (9.82)
Massachusetts	33 (8.31)
Washington	28 (7.05)
Florida	25 (6.3)
Texas	17 (4.28)
Nebraska	8 (2.02)
Illinois	5 (1.26)
New York	4 (1.01)
Wisconsin	4 (1.01)
New Jersey	3 (0.76)
Colorado	3 (0.76)
Ohio	3 (0.76)
Minnesota	2 (0.50)
Alabama	2 (0.50)
Nevada	2 (0.50)
Michigan	1 (0.25)
Arizona	1 (0.25)
North Carolina	1 (0.25)
Virginia	1 (0.25)
Maine	1 (0.25)
Georgia	1 (0.25)
Washington DC	1 (0.25)
Louisiana	1 (0.25)
South Carolina	1 (0.25)
North Dakota	1 (0.25)
Kansas	1 (0.25)
Idaho	1 (0.25)

dichotomized by Q1, there were 90 (29%) shown as low anxiety and 219 (71%) as high anxiety.

General impact of COVID-19

When asked in the survey about medical students' usual living situation during the school year, prior to the pandemic, 87% of participants selected "off-campus housing apartment-home" (Table 3). Approximately 39% of respondents noted a change in living situation due to the pandemic. Almost all participants (99%) selected "no" when asked if they currently feel sick with symptoms of COVID-19. The vast majority (95%) had not been tested for COVID-19. Notably, only 27% of respondents had a close relative or friend test positive for COVID-19. When asked to select all resources used to educate oneself about COVID-19 the top two were the World Health Organization (WHO)/the Center for Disease Control and Prevention (CDC) (86%) and reading publications (76%). It was important to understand which resources medical students utilized to receive information and how these sources affected their anxiety level. Medical students who educated themselves with reliable resources, such as WHO/CDC and medical publications, exhibited a lower anxiety level compared to those who relied on information seen on social media. Furthermore, more than half of respondents (75%) did not know what personal protective equipment their medical school or center provided, while 15% noted "none."

Table 2 Sample population characteristics

Characteristics	N = 309 (%)
Age (years)[1]	26 (2.43)
Gender	
Male	119 (38.51)
Female	189 (61.17)
Prefer not to say	1 (0.32)
Current year of medical school	
1	101 (32.79)
2	68 (22.08)
3	77 (25)
4	56 (18.18)
MD	3 (0.97)
Research year	2 (0.65)
Other	1 (0.32)

[1]Reported as mean ± SD. All data are presented as numerators and denominators with percentages in parentheses unless otherwise specified.

Educational impact

When asked if their current academic activity (clinical rotations, in-person class, *etc.*) was cancelled and had not moved online, 73% of participants responded with "no" (Table 4). This implies that students who were removed from campuses and hospitals continued their medical education and training through online supplementation. 44% of participants also reported cancellation of their future academic activities. For those who answered "yes" to cancellation of academic activities, 33% noted a 2-6-mo cancellation, while 30% answered with "I am not sure." Almost all participants (94%) had information being supplemented through distance or online learning. When asked how their overall workload was affected by the pandemic, more than half of the participants (54%) noted a decrease, while 14% had an increase in overall workload. 29% of participants also noted a decrease in research productivity. It is important to note that 45% of participants selected "does not apply," meaning they were not involved in research.

Out of the respondents, 80% agreed there was no change in the school year end date and 54% also noted no change in school exam dates. 41% of participants who stated they were taking the USMLE exams noted a postponement in the exam dates. Medical students spend months preparing for the USMLE exams, a requirement for applying to residency, and any uncertainty regarding the exam can cause an increased anxiety level. Half of the participants (51%) strongly agreed to being concerned how the pandemic would affect their continuing semesters or residency positions, if it were to extend past August.

Psychosocial impact

Respondents were asked using a Likert scale to rate their agreement with the statement "I am worried about the COVID-19 pandemic in general" (Table 5). 40% of participants strongly agreed and 43% agreed with the statement. Respondents were asked to rate their level of stress and anxiety using a scale from 1-10, with mean 6.7 ± 2.4 IQR (5, 8). The self-reported use of mental health resources compared to their previous experiences showed 59% remained unchanged, however there was an increase amongst some participants (17%). We asked to rate the accessibility to mental health services (psychologist, psychiatrist, 24-h emergency hotline, other) on a scale of 1 to 10. An average of 6.78 (SD = 2.33) was self-reported by the respondents. Half of the respondents (50%) reported experiencing an episode of depression during this time. The stressors which were most common amongst participants were waiting for campuses and clinical sites to reopen to students (51%), family well-being (46%), and personal well-being (41%). The self-care activities reported which were the most helpful to respondents were talking to friends (84%), television (81%), and exercise (77%).

Hierarchical Poisson regression model showed students who experienced episodes of depression during this time was a strong risk of high anxiety level (RR 1.6; 95%CI: 1.38–1.85, $P < 0.01$). However, those participants who selected "Participated in volunteer activities for child care for health care workers" (RR 0.68; 95%CI: 0.49–0.93, $P = 0.02$); "USMLE exams or equivalent state exams NOT postponed" (RR 0.87; 95%CI: 0.76–0.99, $P = 0.03$); "Experienced support from school administration and

Table 3 Univariate analysis on sample population general impact of coronavirus disease 2019

General impact	Low anxiety, N = 90 (%)	High anxiety, N = 219 (%)	Total, N = 309 (%)	Sig.
Usual living situation during the school year (*i.e.* before the pandemic)				0.97
Home with family	8 (30.77)	18 (69.23)	26 (8.41)	
Off-campus housing Apartment- House	78 (28.89)	192 (71.11)	270 (87.38)	
Campus housing – School dormitory or apartment	4 (30.77)	9 (69.23)	13 (4.21)	
Change in living situation during the pandemic				0.04
No	63 (33.33)	126 (66.67)	189 (61.17)	
Yes	27 (22.5)	93 (77.5)	120 (38.83)	
Currently living with				0.54
Alone	13 (28.89)	32 (71.11)	45 (14.56)	
With spouse partner	36 (34.29)	69 (65.71)	105 (33.98)	
With family	27 (25.47)	79 (74.53)	106 (34.3)	
With roommates	14 (29.17)	34 (70.83)	48 (15.53)	
Temporarily staying with friends or couch surfing	0 (0)	3 (100)	3 (0.97)	
Other	0 (0)	2 (100)	2(0.65)	
I have easy access to testing for COVID-19 through my medical school/center if needed				0.23
1 = Strongly disagree	9 (21.95)	32 (78.05)	41 (13.27)	
2 = Disagree	18 (22.5)	62 (77.5)	80 (25.89)	
3 = Neutral	26 (31.71)	56 (68.29)	82 (26.54)	
4 = Agree	22 (31.88)	47 (68.12)	69 (22.33)	
5 = Strongly agree	15 (40.54)	22 (59.46)	37 (11.97)	
Do you currently feel sick with symptoms of COVID-19?				0.36
No	90 (29.32)	217 (70.68)	307 (99.35)	
Yes	0 (0)	2 (100)	2 (0.65)	
Have you been tested for COVID-19				0.82
No	86 (29.35)	207 (70.65)	293 (95.13)	
Yes, awaiting test result	1 (25)	3 (75)	4 (1.3)	
Yes, result was negative	3 (33.33)	6 (66.67)	9 (2.92)	
Yes, result was positive	0 (0)	2 (100)	2 (0.65)	
Has a close relative or friend tested positive for COVID-19?				0.2
No	70 (31.25)	154 (68.75)	224 (72.73)	
Yes	20 (23.81)	64 (76.19)	84 (27.27)	
Resources used to educate about COVID-19-WHO CDC?				0.67
No	14 (31.82)	30 (68.18)	44 (14.24)	
Yes	76 (28.68)	189 (71.32)	265 (85.76)	
Resources used to educate about COVID-19-Reading publications?				0.9
No	22 (29.73)	52 (70.27)	74 (23.95)	
Yes	68 (28.94)	167 (71.06)	235 (76.05)	
Resources used to educate about COVID-19-Lectures educational resources from school?				0.52
No	27 (76.73)	74 (73.27)	101 (32.69)	

Yes	63 (30.29)	145 (69.71)	208 (67.31)	
Resources used to educate about COVID-19-Social media?				0.17
No	40 (33.61)	79 (66.39)	119 (38.51)	
Yes	50 (26.32)	140 (73.68)	190 (61.49)	
Medical school or center providing adequate access to PPE: Gowns				0.27
No	81 (28.32)	205 (71.68)	286 (92.56)	
Yes	9 (39.13)	14 (60.87)	23 (7.44)	
Medical school or center providing adequate access to PPE: Gloves				0.35
No	81 (28.42)	204 (71.58)	285 (92.23)	
Yes	9 (37.5)	15 (62.5)	24 (7.77)	
Medical school or center providing adequate access to PPE: Face shield or eye protection				0.21
No	81 (28.22)	206 (71.78)	287 (92.88)	
Yes	9 (40.91)	13 (59.09)	22 (7.12)	
Medical school or center providing adequate access to PPE: Surgical mask				0.35
No	81 (28.42)	204 (71.58)	285 (92.23)	
Yes	9 (37.5)	15 (62.5)	24 (7.77)	
Medical school or center providing adequate access to PPE: N95 or FF3 masks				0.14
No	82 (28.18)	209 (71.82)	291 (94.17)	
Yes	8 (44.44)	10 (55.56)	18 (5.83)	
Medical school or center providing adequate access to PPE: None				< 0.01
No	85 (32.2)	179 (67.8)	264 (85.44)	
Yes	5 (11.11)	40 (88.89)	45 (14.56)	
Medical school or center providing adequate access to PPE: I do not know				0.02
No	14 (18.42)	62 (81.58)	76 (24.6)	
Yes	76 (32.62)	157 (67.38)	233 (75.4)	

COVID-19: Coronavirus disease 2019; CDC: The Center for Disease Control and Prevention; PPE: Personal protective equipment; WHO: World Health Organization.

faculty regarding COVID-19" (RR 0.75; 95%CI: 0.65–0.87, $P < 0.01$); and "Less concerned about being unable to complete exams or rotations if I contract COVID-19" (RR 0.77; 95%CI: 0.62–0.96, $P = 0.02$) were less likely having high anxiety (Table 6). Therefore, these would propose a protective effect on the level of anxiety experienced.

Clinical impact

Respondents were asked to rate their level of agreement with the statement "COVID-19 has increased the community perception of physicians and healthcare workers as heroes" (Table 7). 23% strongly agreed with the statement and 19% were neutral regarding it. Most of the respondents (96%) were not assisting in the healthcare system at the time of the survey due to restraints caused by COVID-19. Respondents were asked to rate their level of preparedness working with COVID-19 patients on a scale of 1-5. It was important to know if medical students felt ready to care for patients, especially if they were required to volunteer. A lack of preparedness can further increase the anxiety and stress level medical students may already be experiencing. Approximately 45% felt not prepared at all, while 32% gave a rating of 2. When asked if they have the option to volunteer in the hospital for COVID-19, many students responded with no (78%). Out of the respondents, 49% would like to volunteer, however a portion were unable to volunteer due to external factors. The greatest external factor were respondents living or helping with family and/or friends and they did not want to risk exposure. It should be noted that medical students in their pre-clinical years are more likely to feel less prepared to volunteer in the hospital, compared to those students in their clinical and post-graduate years who have more experience on the hospital wards.

Table 4 Univariate analysis on sample population educational impact of coronavirus disease 2019

Educational impact	Low anxiety, N = 90 (%)	High anxiety, N = 219 (%)	Total, N = 309 (%)	Sig.
Was your current academic activity (for example clinical rotations, in-personal class, *etc.*) cancelled, and not moved online?				0.29
Yes	20 (24.39)	62 (75.61)	82 (26.62)	
No	69 (30.53)	157 (69.47)	226 (73.38)	
Were your future academic activities cancelled?				0.02
Yes	31 (22.63)	106 (77.37)	137 (44.34)	
No	59 (34.3)	113 (65.7)	172 (55.66)	
Is information being supplemented through distance/online learning?				< 0.01
No	0 (0)	17 (100)	17 (5.52)	
Yes	89 (30.58)	202 (69.42)	291 (94.48)	
How has your overall workload been affected?				< 0.01
Increased	5 (11.36)	39 (88.64)	44 (14.24)	
Decreased	60 (36.14)	106 (63.86)	166 (53.72)	
Unchanged	25 (26.6)	69 (73.4)	94 (30.42)	
Does not apply	0 (0)	5 (100)	5 (1.62)	
How has your research productivity been affected?				< 0.01
Increased	15 (38.46)	24 (61.54)	39 (12.62)	
Decreased	23 (25.56)	67 (74.44)	90 (29.13)	
Unchanged	20 (50)	20 (50)	40 (12.94)	
Does not apply	32 (22.86)	108 (77.14)	140 (45.31)	
Has the school year end date been:				0.04
Cancelled	1 (14.29)	6 (85.71)	7 (2.27)	
Postponed	0 (0)	8 (100)	8 (2.59)	
Unchanged	76 (30.89)	170 (69.11)	246 (79.61)	
Moved forward	2 (16.67)	10 (83.33)	12 (3.88)	
Does not apply	8 (53.33)	7 (46.67)	15 (4.85)	
I don't know	3 (14.29)	18 (85.71)	21 (6.8)	
Has graduation been:				0.24
Cancelled	15 (23.08)	50 (76.92)	65 (21.1)	
Postponed	3 (60)	2 (40)	5 (1.62)	
Unchanged	44 (32.59)	91 (67.41)	135 (43.83)	
Moved forward	0 (0)	5 (100)	5 (1.62)	
Does not apply	21 (30.43)	48 (69.57)	69 (22.4)	
I don't know	7 (24.14)	22 (75.86)	29 (9.42)	
If applicable have your USMLE exams or equivalent state exams been postponed?				< 0.01
Yes	25 (19.84)	101 (80.16)	126 (40.78)	
No	11 (36.67)	19 (63.33)	30 (9.71)	
Does not apply	53 (38.41)	85 (61.59)	138 (44.66)	

Not sure	1 (6.67)	14 (93.33)	15 (4.85)	
If the COVID-19 pandemic extends until or past August, I am concerned it will have a major effect on my continuing semesters or residency position				< 0.01
1 = Strongly disagree	3 (100)	0 (0)	3 (0.97)	
2 = Disagree	12 (70.59)	5 (29.41)	17 (5.5)	
3 = Neutral	6 (26.09)	17 (73.91)	23 (7.44)	
4 = Agree	34 (41.98)	47 (58.02)	81 (26.21)	
5 = Strongly agree	27 (17.2)	130 (82.8)	157 (50.81)	
Does not apply	8 (28.57)	20 (71.43)	28 (9.06)	
How effectively have your medical school leadership been managing this outbreak?				< 0.01
Inadequate	11 (13.58)	70 (86.42)	81 (26.47)	
Appropriate	79 (36.07)	140 (63.93)	219 (71.57)	
Excessive	0 (0)	6 (100)	6 (1.96)	
Which of the following best describes your medical school communication efforts to students?				< 0.01
Overly frequent updates	8 (33.33)	16 (66.67)	24 (7.79)	
Adequately frequent updates	69 (35.38)	126 (64.62)	195 (63.31)	
Infrequent updates	11 (14.47)	65 (85.53)	76 (24.68)	
No regular updates	2 (15.38)	11 (84.62)	13 (4.22)	

COVID-19: Coronavirus disease 2019; USMLE: The United States Medical Licensing Examination.

Financial impact

When presented with the statement "has the pandemic affected you financially," participants were asked to respond in a Likert scale format (Table 8) in which 21% agreed with the statement. Financial assistance availability was present for 34% of respondents, and 41% did not know if any was present. When asked which available emergency funds were accessible the highest response rate (19.2%) was through the school financial aid office.

Future impact

The anticipation of having similar outbreaks in the future was presented with a Likert scale and respondents were asked to rate the statement in which 51% agreed with the statement (Table 9). Respondents were asked to rate on a scale of 1-5 their fear of how future public health crises will be handled. 48% of participants agreed, and 22% strongly agreed, that the lessons learned from this outbreak will help us cope with future crises. The need for medical school curricula in local mass casualty planning was addressed in a Likert scale, in which 50% of respondents agreed and 22% strongly agreed with the statement.

DISCUSSION

Currently, there is minimal literature on medical students experiencing a pandemic and how a public health crisis may affect medical education. In our study, we have used a 1-10 scale to quality anxiety level, then dichotomized base one Q1 value of 5 into "At least some anxiety (≥ 6) " or "low to no anxiety (≤ 5)". By treating the anxiety measurements as a continuous scale, it is more likely to dilute important information. The difference between a scoring of 1 *vs* 3, 4 *vs* 6, or 7 *vs* 9 is the same, however a scoring of 1 and 3 or 7 and 9 will belong to the same level of anxiety. Dichotomizing a continuous anxiety/stress scale has been used in literature. In most cases, studies would like to detect high risk populations who had higher anxiety/stress level and the risk factors associated with the elevated anxiety level. The benefit of dichotomizing includes providing more clinical meaningful result and better statistical power compared to the modeling approach using outcome with multiple categories[12,13].

Our study was designed to rapidly respond to a worldwide pandemic. To maintain data accuracy, we used the QC procedure to examine any missing data. 19.6% of our survey results were returned with some missing data. Among those, only four participants with more than four missing items were found, from a total of 308 survey questions. The sensitivity analysis was conducted with and without the

Table 5 Univariate analysis on sample population psychosocial impact of coronavirus disease 2019

Psychosocial impact	Low anxiety, N = 90 (%)	High anxiety, N = 219 (%)	Total, N = 309 (%)	Sig.
I am worried about COVID-19 pandemic in general				< 0.01
1 = Strongly disagree	3 (75)	1 (25)	4 (1.29)	
2 = Disagree	11 (68.75)	5 (31.25)	16 (5.18)	
3 = Neutral	15 (48.39)	16 (51.61)	31 (10.03)	
4 = Agree	46 (34.59)	87 (65.41)	133 (43.04)	
5 = Strongly Agree	15 (12)	110 (88)	125 (40.45)	
I am worried about contracting COVID-19				< 0.01
1 = Strongly disagree	11 (55)	9 (45)	20 (6.47)	
2 = Disagree	25 (39.06)	39 (60.94)	64 (20.71)	
3 = Neutral	31 (34.44)	59 (65.56)	90 (29.13)	
4 = Agree	21 (18.92)	90 (81.08)	111 (35.92)	
5 = Strongly agree	2 (8.33)	22 (91.67)	24 (7.77)	
If applicable, how has your utilization of mental health resources changed?				< 0.01
Increased	9 (17.31)	43 (82.69)	52 (16.83)	
Decreased	2 (7.41)	25 (92.59)	27 (8.74)	
Unchanged	59 (32.07)	125 (67.93)	184 (59.55)	
Does not apply	20 (43.48)	26 (56.52)	46 (14.89)	
Mental health services the university provides: Psychologist				0.29
No	31 (33.33)	62 (66.67)	93 (30.1)	
Yes	59 (27.31)	157 (72.69)	216 (69.9)	
Mental health services the university provides: Psychiatrist				0.84
No	59 (29.5)	141 (70.5)	200 (64.72)	
Yes	31 (28.44)	78 (71.56)	109 (35.28)	
Mental health services the university provides: 24 hour emergency hotline				0.7
No	41 (28.08)	105 (71.92)	146 (47.25)	
Yes	49 (30.06)	114 (69.94)	163 (52.75)	
Mental health services the university provides: Does not apply				0.02
No	73 (26.84)	199 (73.16)	272 (88.03)	
Yes	17 (45.95)	20 (54.05)	37 (11.97)	
On a scale of 1-10, how accessible do you find mental health services?				0.21
1	3 (33.33)	6 (66.67)	9 (2.95)	
2	0 (0)	5 (100)	5 (1.64)	
3	4 (21.05)	15 (78.95)	19 (6.23)	
4	1 (11.11)	8 (88.89)	9 (2.95)	
5	10 (19.23)	42 (80.77)	52 (17.05)	
6	8 (25.81)	23 (74.19)	31 (10.16)	
7	17 (32.08)	36 (67.92)	53 (17.38)	
8	20 (36.36)	35 (63.64)	55 (18.03)	

9	4 (19.05)	17 (80.95)	21 (6.89)	
10	20 (39.22)	31 (60.78)	51 (16.72)	
Most Stress: Residency applications				0.03
No	68 (33.01)	138 (66.99)	206 (66.67)	
Yes	22 (21.36)	81 (78.64)	103 (33.33)	
Most Stress: Community well-being				0.12
No	56 (26.42)	156 (73.58)	212 (68.61)	
Yes	34 (35.05)	63 (64.95)	97 (31.39)	
Most Stress: Personal well-being				0.31
No	57 (31.32)	125 (68.68)	182 (58.9)	
Yes	33 (25.98)	94 (74.02)	127 (51.1)	
Most Stress: Family well-being				0.08
No	56 (33.33)	112 (66.67)	168 (54.37)	
Yes	34 (24.11)	107 (75.89)	141 (45.63)	
Most Stress: Clinical education related to COVID-19				0.05
No	70 (32.41)	146 (67.59)	216 (69.9)	
Yes	20 (21.51)	73 (78.49)	93 (30.1)	
Most Stress: Limited to only essential activities				0.04
No	47 (24.87)	142 (75.13)	189 (61.17)	
Yes	43 (35.83)	77 (64.17)	120 (38.83)	

COVID-19: Coronavirus disease 2019.

missing data. The findings between the two data sets were consistent. Therefore, we have concluded that this minimal amount of missing data did not influence our findings from the study.

From our study, we have found that COVID-19 has significantly impacted medical students across the United States. 54.87% of respondents were first- and second-year medical students and 43.18% were third-year medical students, most of whom were suddenly disrupted during the peak of their clinical education. Regardless of their progress through medical school, nearly all students have faced abrupt changes in medical education and clinical training, resulting in concern and uncertainty with regard to their paths towards residency programs. Most students noted restrictions in their cities, including medical school closure, shelter or safer-at-home measures, social distancing, limited restaurant operations, and mandates to keep only essential businesses open. The majority of respondents reported that their current academic activities had been cancelled and moved online to a distance learning curriculum, predominantly *via* Zoom, and approximately half felt it was not beneficial to them. Of these respondents, decreased motivation with online learning and an inadequate quality of virtual curriculum were cited as the biggest issues. Due to the unforeseen nature of the pandemic, schools were not prepared to teach medical students remotely. This consequentially resulted in decreased medical student workloads. Restrictions from going on campus and to corresponding medical centers may have contributed to a decrease in students' research productivity as well.

Of those facing postponements in their USMLE or equivalent state exams, almost half of respondents felt very or extremely concerned about the impact of COVID-19 on the residency application process. With this year's residency application deadline looming at the end of October 2020, it is worrisome for students to consider submitting an incomplete application to a system that is already extremely competitive. In an effort to reduce unnecessary exposure and further viral spread, virtual residency interviews will be held for the 2021 Match. It is expected to cause many difficulties in the application process and perhaps negatively impact the applicant even further. It is anticipated that applicants will accept more interviews because of the reduced cost and time needed to travel to each institution, adding to the already growing hyperinflation in the application process. With these changes, programs will ultimately spend less money and time on each applicant. This begs the question if there will be an increase in the number of interview invites. Medical students may anticipate saving money with these adjustments as well, thus being more likely to apply to an increased number of residency programs. While this may seem like a positive result of the pandemic, with more competitive medical students overapplying, less competitive students may consequentially have more difficulty securing a virtual

Table 6 Multivariate analyses of anxiety association factors after Least Absolute Shrinkage and Selection Operator

Survey questions	Rate ratio	Confidence interval	Sig.
I feel disenchanted with the healthcare system due to inadequate response, lack of PPE, lack of testing, *etc.*			
Disagree (2) *vs* Strongly disagree (1)	0.93	0.5-1.72	0.81
Neutral (3) *vs* Strongly disagree (1)	1.39	0.85-2.27	0.19
Agree (4) *vs* Strongly disagree (1)	1.48	0.95-2.31	0.09
Strongly agree (5) *vs* Strongly disagree(1)	1.39	0.86-2.25	0.18
Does not apply *vs* Strongly disagree (1)	0.93	0.5-1.72	0.81
Volunteer Activities - Child care for health care workers: Yes *vs* No	0.68	0.49-0.93	0.02
Is the distance learning beneficial to you?			
Agree *vs* Strongly agree	0.87	0.6-1.27	0.47
Neutral *vs* Strongly agree	0.93	0.62-1.37	0.7
Disagree *vs* Strongly agree	0.98	0.66-1.46	0.93
Strongly disagree *vs* Strongly agree	0.84	0.57-1.23	0.36
If applicable, have your USMLE exams or equivalent state exams been postponed?			
No *vs* Yes	0.87	0.76-0.99	0.03
Does not apply *vs* Yes	1.01	0.87-1.18	0.85
Not sure *vs* Yes	1.19	0.96-1.48	0.12
How concerned are you that COVID-19 will affect the residency application process?			
Slightly concerned (2) *vs* Not concerned (1)	1.3	0.79-2.13	0.3
Moderately concerned (3) *vs* Not concerned (1)	1.22	0.79-1.88	0.36
Very concerned (4) *vs* Not concerned (1)	0.86	0.58-1.26	0.43
Extremely concerned (5) *vs* Not concerned (1)	1	0.6-1.68	1
Does not apply *vs* Not concerned (1)	1.3	0.79-2.13	0.3
On a scale of 1-5 how supportive have school administration and faculty been regarding COVID-19?			
2 *vs* Not supportive	0.81	0.63-1.04	0.1
Moderately supportive *vs* Not supportive	0.75	0.65-0.87	< 0.01[1]
4 *vs* Not supportive	0.79	0.6-1.03	0.09
Extremely supportive *vs* Not supportive	0.89	0.78-1.02	0.11
Have you experienced episodes of depression during this time?	1.6	1.38-1.85	< 0.01[1]
I am concerned about being unable to complete exams or rotations if I contract COVID-19			
Strongly disagree (1) *vs* Strongly agree (5)	0.66	0.26-1.7	0.39
Disagree (2) *vs* Strongly agree (5)	0.77	0.62-0.96	0.02
Neutral (3) *vs* Strongly agree (5)	1.11	0.95-1.3	0.2
Agree (4) *vs* Strongly agree (5)	1.05	0.84-1.31	0.68
Does not apply *vs* Strongly agree (5)	0.88	0.69-1.14	0.34

[1]These covariates were significant using a cut-off *P* value of < 0.01. COVID-19: Coronavirus disease 2019.

interview. To avoid this issue, a fifteen-interview limit per applicant, per specialty, could allow below-average applicants an equal opportunity, but there is no guarantee that AAMC will implement such a regulation[6].

Less than half of medical student respondents indicated wanting to volunteer during the pandemic, perhaps because none reported previous or current infection. Based on survey respondent comments, many based this on their attempt to preserve their own health and the health of family members and friends. Additionally, this finding may emphasize that medical students feel vastly ill-prepared to work

Table 7 Univariate analysis on sample population clinical impact of coronavirus disease 2019

Clinical, future, and financial impact	Low anxiety, N = 90 (%)	High anxiety, N = 219 (%)	Total, N = 309 (%)	Sig.
COVID-19 has increased the community perception of physicians and healthcare workers				0.1
1 = Strongly disagree	1 (25)	3 (75)	4 (1.29)	
2 = Disagree	7 (26.92)	19 (73.08)	26 (8.41)	
3 = Neutral	11 (18.64)	48 (81.36)	59 (19.09)	
4 = Agree	44 (30.14)	102 (69.86)	146 (47.25)	
5 = Strongly agree	25 (34.72)	47 (65.28)	72 (23.3)	
Does not apply	2 (100)	0 (0)	2 (0.65)	
Are you required to assist in the healthcare system currently due to COVID-19?				0.06
Yes I am being put to work wherever I a needed	0 (0)	3 (100)	3 (0.97)	
Yes I am continuing to work in the same clinical role that I was in pre-pandemic	0 (0)	10 (100)	10 (3.24)	
No	90 (30.41)	206 (69.59)	296 (95.79)	
Do you have the option to volunteer to work in the hospital for COVID-19?				0.31
No	66 (27.5)	174 (72.5)	240 (77.92)	
Yes	23 (33.82)	45 (66.18)	68 (22.08)	
Would you like to volunteer?				0.34
Yes	46 (30.26)	106 (69.74)	152 (49.35)	
No	28 (32.94)	57 (67.06)	85 (27.6)	
Cannot due to external factors	16 (22.54)	55 (77.46)	71 (23.05)	
Cannot volunteer due to external factors: I live or help out with family and or friends who I do not want to risk exposure				0.1
No	81 (30.92)	181 (69.08)	262 (84.79)	
Yes	9 (19.15)	38 (80.85)	47 (15.21)	
Cannot volunteer due to external factors: I am concerned about my own safety				0.56
No	88 (29.63)	209 (70.37)	297 (96.12)	
Yes	2 (16.67)	10 (83.33)	12 (3.88)	
Cannot volunteer due to external factors: I have to work elsewhere for financial reasons				0.11
No	90 (29.7)	213 (70.3)	303 (98.06)	
Yes	0 (0)	6 (100)	6 (1.94)	
Volunteer activities: Fundraising or obtaining PPE for hospitals				0.52
No	81 (29.89)	190 (70.11)	271 (87.7)	
Yes	3 (21.43)	29 (76.32)	38 (12.3)	
Volunteer Activities: Helping answer COVID-19 phone lines				0.41
No	84 (29.79)	198 (70.21)	282 (91.26)	
Yes	6 (22.22)	21 (77.78)	27 (8.74)	
Volunteer Activities: Child care for healthcare workers				0.02
No	78 (27.37)	207 (72.63)	285 (92.33)	
Yes	12 (50)	12 (50)	24 (7.77)	
On a scale of 1-5, how prepared to you feel to work with COVID-19 patients?				0.38
1 = Not at all prepared	37 (72.79)	99 (72.79)	136 (44.16)	
2	26 (26.26)	73 (73.74)	99 (32.14)	

3 = Adequately prepared	14 (42.42)	19 (57.58)	33 (10.71)	
4	5 (27.78)	13 (72.22)	18 (5.84)	
5 = Extremely well prepared	0 (0)	3 (100)	3 (0.97)	
Does not apply	7 (36.84)	12 (63.16)	19 (6.17)	
On a scale of 1-5, how prepared to you feel to work in the general healthcare system (caring for internal medicine patients, surgical patients, *etc.*)?				0.5
1 = Not at all prepared	17 (34)	33 (66)	50 (16.18)	
2	25 (28.74)	62 (71.26)	87 (28.16)	
3 = Adequately prepared	23 (25.27)	68 (74.73)	91 (29.46)	
4	17 (33.33)	34 (66.67)	51 (16.5)	
5 = Extremely well prepared	2 (13.33)	13 (86.67)	15 (4.85)	
Does not apply	6 (40)	9 (60)	15 (4.85)	

COVID-19: Coronavirus disease 2019; PPE: Personal protective equipment.

Table 8 Univariate analysis on sample population financial impact of coronavirus disease 2019

Financial impact	Low anxiety, N = 90 (%)	High anxiety, N = 219 (%)	Total, N = 309 (%)	Sig.
Has the pandemic affected you financially?				< 0.01
Strongly Agree	1 (5.56)	17 (94.44)	18 (5.83)	
Agree	13 (20.31)	51 (79.69)	64 (20.71)	
Neutral	25 (22.73)	85 (77.27)	110 (35.6)	
Disagree	36 (39.56)	55 (60.44)	91 (29.45)	
Is financial assistance available to you if needed?				0.3
Yes	37 (35.24)	68 (64.76)	105 (33.98)	
No	10 (20.83)	38 (79.17)	48 (15.53)	
I do not know	35 (27.34)	93 (72.66)	128 (41.42)	
Does not apply	8 (28.57)	20 (71.43)	28 (9.06)	

in a pandemic environment. It is difficult for medical students to feel prepared and secure if they do not see this reflected in their own institution. A majority of students did not have adequate or any access to PPE gowns, N-95 or FF3 masks during this time. In light of the lack of preparative measures to protect healthcare workers, and by extension medical students, in a pandemic or public health crisis, it is no surprise that more than half of respondents believe their medical school should offer curricula in national mass casualty planning[14]. In order for medical schools to be prepared for future public health crises, we now know that measures must be in place to allow for the continuation of quality medical school education regardless of outbreak or mass casualty status. In addition to the evident need for better PPE preparation across the US, a preparation that should include all students working in a clinical setting, there is concern over how the COVID-19 pandemic, and possible future public health crises, will affect medical students' ability to work clinically and prevent early burnout. Based on our results, medical students already feel disenchanted with the US healthcare system with an overarching sense of worry for the current state of affairs and what is to come with future health crises. In a career path previously touted as stable, nothing seems predictable now. Almost half of respondents have been most stressed by their inability to go to campus or clinical sites. These destinations are not only a source of education for students, but also a source of community. As our data shows, this disruption has caused a predictable increase in anxiety. The additional stress of being limited to essential activities and worrying about residency applications also does not bode well for mental health outcomes in these future physicians. This crisis has exacerbated existing medical student mental health issues in addition to instilling fear for the future, which an overwhelming majority of respondents indicated experiencing.

Clearly, medical students and residency program applications care about hands-on education. However, given the current situation, an effort to teach future physicians how to practice non-traditionally is needed, which may include telemedicine and tele-education. Recent research into remote and virtual medical education may prove to be a solution for future needs. Some studies have even

Table 9 Univariate analysis on sample population future impact of coronavirus disease 2019

Future impact	Low anxiety, N = 90 (%)	High anxiety, N = 219 (%)	Total, N = 309 (%)	Sig.
I anticipate having similar outbreaks in the future				0.35
1 = Strongly disagree	1 (100)	0 (0)	1 (0.32)	
2 = Disagree	6 (46.15)	7 (53.85)	13 (4.22)	
3 = Neutral	11 (31.43)	24 (68.57)	35 (11.36)	
4 = Agree	46 (29.3)	111 (70.7)	157 (50.97)	
5 = Strongly agree	25 (25)	75 (75)	100 (32.47)	
Does not apply	1 (50)	1 (50)	2 (0.65)	
I am fearful of how future public health crises will be handled?				< 0.01
1 = Strongly disagree	2 (100)	0 (0)	2 (0.65)	
2 = Disagree	15 (65.22)	8 (34.78)	23 (7.52)	
3 = Neutral	16 (43.24)	21 (56.76)	37 (12.09)	
4 = Agree	31 (24.8)	94 (75.2)	125 (40.85)	
5 = Strongly agree	25 (21.19)	93 (78.81)	118 (38.56)	
Does not apply	1 (100)	0 (0)	1 (0.33)	
I think the lessons we learn from this outbreak will help us cope with future crises?				0.04
1 = Strongly disagree	3 (37.5)	5 (62.5)	8 (2.59)	
2 = Disagree	11 (34.38)	21 (65.63)	32 (10.36)	
3 = Neutral	9 (17.65)	42 (82.35)	51 (16.5)	
4 = Agree	38 (25.68)	110 (74.32)	148 (47.9)	
5 = Strongly agree	28 (40.58)	41 (59.42)	69 (22.33)	
Does not apply	1 (100)	0 (0)	1 (0.32)	
I think we need medical school curricula in national mass casualty planning?				0.13
1 = Strongly disagree	0 (0)	4 (100)	4 (1.3)	
2 = Disagree	7 (41.18)	10 (58.82)	17 (5.52)	
3 = Neutral	22 (28.21)	56 (71.79)	78 (25.32)	
4 = Agree	49 (33.56)	97 (66.44)	146 (47.4)	
5 = Strongly agree	11 (17.74)	51 (82.26)	62 (20.13)	
Does not apply	0 (0)	1 (100)	1 (0.32)	

shown virtual reality to be a useful tool for both learning motivation and learning competency in medical students[15]. With the AAMC recommendation to remove students from the wards to conserve PPE, new modalities of clinical education have already been put into place, such as remote grand rounds *via* Zoom, virtual reality cadaver dissections, and case discussions through online curriculum platforms such as Aquifer[16]. We recommend more research into these methods, as well as medical student exposure to participating in clinical care *via* telemedicine. These changes, understandably, bring feelings of uncertainty and instability to not only educators, but also medical students. In addition to the changes brought about by the pandemic, medical students face uncertainty with what to expect this school year and perhaps beyond graduation. We found that 74.6% feel concerned about the pandemic affecting continuing semesters or their residency position were the pandemic to extend past August 2020. 55.6% indicated concern over being unable to complete rotations and/or exams were they to be infected with COVID-19. Medical students make an immense investment by committing to medical school, both financially and mentally, and many cite the job's stability and satisfaction as primary factors for choosing to go into medicine in the first place. It is understandable that lacking the clear path towards a career so often cited as a stable and predictable journey has stirred up discomfort for the

entire medical community. For medical students in particular, anxiety had already been on the rise, and now further exacerbated by the pandemic[17].

We conducted our multivariate analysis to specifically look at the effect of these educational and clinical changes on the anxiety of medical students. The level of anxiety of the participant, or lack of, may impact the response rate to those survey questions dealing with anxiety. It is not uncommon to have a high percentage of "no response" rate. The missing data is not necessarily problematic in every instance. Participants may not report on one variable because of the anxiety exhibited from it or because of it. For example, a study which examined the tobacco use of adolescent smokers who smoked heavily found that the number of cigarettes smoked per day was not reported. It is assumed that due to the illegality of smoking for these individuals, many participants may have experienced fear of repercussions, thus limiting their response rate[18]. This concept seen in adolescent smokers can provide a valuable explanation on the "no response" rate seen on those questions using anxiety as its variable in this study. Thus, we grouped non-respondents and high-level of anxiety respondents *vs* low-level of anxiety respondents in the multivariate analysis, which looked at educational impact and clinical outcome as the main variables causing an effect on anxiety.

Uncertainty has been one of the main drivers of anxiety among medical students. We found that those who were unsure whether their USMLE or equivalent state exams would be postponed were more likely to have a higher level of anxiety. Those who primarily used the WHO and CDC websites as a source of their education regarding COVID-19 were less likely to have high levels of anxiety. Those who reported experiencing episodes of depression during this time were more likely to have high levels of anxiety. Those who indicated being worried about contracting COVID-19 were more likely to have high levels of anxiety as well. Medical schools have made attempts to better wellness programs for their students and to make mental health resources more available, and perhaps the accessibility of these resources is indeed reaching students in need. We found that those who selected or knew their school offered a psychiatrist were more likely to have high levels of anxiety. We can interpret that because of their anxiety, they have contemplated seeking or have sought the aid of a psychiatrist, and thus were knowledgeable about their school having this resource available.

The need for mental health resource accessibility for medical students remains clear; approximately 33% of medical students worldwide have anxiety, a significantly greater prevalence than the general population[19]. This anxiety does not stop after medical school graduation. The anxiety, stress, and susceptibility to depression continues throughout residency and into attending life if help-seeking behaviors are not encouraged early on in the work environment[20]. Availability of mental health resources for medical students has a lasting effect, helping future physicians develop healthy stress-reducing habits early on in their careers. Adequate mental health should not only be a concern for physicians-in-training and physicians, but also for patients. Studies have found that physicians are less likely to make medical errors when less stressed[20]. Now more than ever, there need to be adequate mental health programs in place. The pandemic has only further exacerbated psychosocial issues that were already problems for student doctors and physicians[21]. Undeniably, the best way to improve health outcomes and patient care is to support our doctors and doctors-in training, and this includes doctors supporting each other. Without this, we risk a devastating mental health crisis that would affect all[21].

There is minimal information regarding the effects of the COVID-19 pandemic on medical students. The study of Harries *et al*[22] shows that more than two third of medical students believe the pandemic has significantly disrupted their education. More than half of the students expressed desire to return to their normal clinical rotations, accepting the risk of infection with COVID-19. In another study by Alsoufi *et al*[23] more than 85% of the participating medical students reported suspended educational programs, lectures, and clinical rotations during the pandemic. However, the reported studies suffer from significant limitations, such as limited survey response rate (although the students were directly contacted from their medical school leadership), and therefore, further studies in this field were recommended.

Perhaps this surreal time in our lives has indicated we need to conduct medical education differently. The pandemic has revealed the flaws in medical education when curriculum is devoted entirely or predominantly towards in-person learning. We need to incorporate nontraditional learning into medical education. This may include educating and preparing medical students for practicing in nontraditional ways, such as *via* telemedicine. We have found that clinic visits can be conducted successfully over a remote interface, posing the question if follow-up in-person visits are actually essential to quality medical care. In fact, the pandemic has highlighted much of what is truly essential in healthcare, and a closer look at what has been emphasized and successfully conducted during this time can guide medical school curriculum committees on where to emphasize their medical education efforts.

There are several limitations to this study. The sample population was largely composed of medical students with access to social media, neglecting those who may limit their social media presence. Furthermore, survey responses were dependent upon the point in time in which respondents filled out the survey, as responses would surely vary at different times during the pandemic. Most of the studied subjects were from California, Florida, Massachusetts, Missouri, Pennsylvania, and Washington. However, we may say that those six states with the highest participants are from West, Central, and East of the USA, which somehow can represent a sample of the entire nation's students. These states are

also very popular to receive students from other states, which again helps in generalizability of the results to the entire country. Additionally, our survey may not ask all pertinent questions assessing the holistic impact of COVID-19 on medical students. The majority of students participating in the survey were in their beginning four years of their studies. This highlights an additional limitation as the final two years are the clinical training years and students faced dismissal from the hospital wards. Lastly, our survey was voluntary, potentially biasing our results to respondents who may have felt strongly about sharing their experiences. Although our study has some limitations, it focuses on some aspects of the medical student education, such as preparation and planning for USMLE exams and school year end date, that have not been assessed in the published reports. More importantly, respondent distribution across the United States in our study is geographically different from the limited available reports, which is another important advantage of our study. Given the fact that the geographic distribution of COVID-19 is not uniform, its psychosocial effects on the population is also not homogeneous. More specifically, different medical schools have implemented different strategies to respond to the pandemic, which certainly result in different effects on their medical students. As research on the impact of pandemics on medical students is limited, adding to the pool of these reports and data could positively improve our understanding about how pandemics affect medical schools, which areas of educational programs are more vulnerable, and which supporting strategies are important to employ to subdue the effects of pandemics effectively and safely on the education.

CONCLUSION

This study provides insight and important information about how medical students have experienced and been affected by the pandemic. Ultimately, we found that medical students have been significantly impacted in numerous ways. From our results, we now know that amid a public health crisis, medical student education and clinical readiness were reduced, with predictably negative outcomes on medical student anxiety and presumably, residency applications. As no prior research has been done on the effect of a global pandemic on medical students and medical education, we recommend that efforts be placed in healthcare system readiness for public health crises[24], the development of medical school curricula for public health and mass casualty planning, and further mental health support that starts with changing physician culture and stigma and encouraging mental health resource utilization. Furthermore, we encourage research on medical student education that is focused on what has been found to be critically essential. This includes training students in telemedicine and virtual care where applicable. We hope that the results of this study will initiate a restructuring of medical education that will consider medical students' experiences and the potential consequences of future challenges as well as training in non-traditional ways.

ARTICLE HIGHLIGHTS

Research background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic prompted abrupt closures of medical schools affecting education, exams, and residency applications for United States medical students.

Research motivation

The survey was drafted by two medical students who faced on-campus closure's of their medical schools and the uncertainty of it's impact on medical education. We wanted to determine potential outcomes caused by the SARS-CoV-2 pandemic on medical students and examine what measures should be taken in the future to better prepare students for pandemics.

Research objectives

The aim of the study was to determine what specific factors impacted medical students, their anxiety, and the effect on medical education. It is important to examine these factors and determine what can be done in the future to prevent similar outcomes.

Research methods

The survey was drafted by two medical students, revised by multiple attending physicians, and a pilot test was performed prior to the survey launch. Anxiety scores were dichotomized to a 1-10 score and for descriptive analysis contingency tables by anxiety categories for categorical measurements and mean ± STD for continuous measurements followed by t-test or Wilcoxson rank were performed. Least Absolute Shrinkage and Selection Operator was utilized to select important predictors for the final multivariate model. The final model was fitted by Hierarchical Poisson regression model.

Research results

The SARS-CoV-2 pandemic greatly impacted medical students' anxiety levels. There was a strong educational and clinical impact and students were faced with many uncertainties, driving up their anxiety levels. It has become evident the need for mental health resource accessibility for medical students is crucial. We still need to better understand the long term effects the pandemic will have on these students as they transition into becoming doctors and how medical schools can better prepare students for future pandemics or global health crises.

Research conclusions

This study provides insight on important information about how medical students have experienced and been affected by the pandemic. We recommend that efforts be placed in the healthcare system readiness for public health crisis, the development of medical school curricular for public health and mass casualty planning, along with further mental health support. We encourage research on medical education that is focused on what has been found to be critically essential: training students in tele-medicine and virtual care.

Research perspectives

Further research should be focused on the long-term effects of the pandemic on medical students, especially as they transition into residency. Research should also be conducted on training students in virtual care and preparedness for future public health crises.

FOOTNOTES

Author contributions: Doshi A and Frank V drafted the survey for the present study; Doshi A managed the survey edits, coding the survey, and submission; Desai B obtained IRB approval; Demirjian NL, Fields BKK, and Song C assisted in survey question editing rephrasing; Desai B, Reddy S, and Gholamrezanezhad A reviewed study documents, survey modifications, and provided input; Doshi A, Frank V, Demirjian NL, Fields BKK, Harvey DC facilitated network outreach; Lei X and Cen S performed statistical analysis on the data; Doshi A and Frank V drafted the manuscript. Prior to submission all authors provided edits; Doshi A and Frank V equally contributed to the work.

Institutional review board statement: The Institutional Review Board of USC determined this study to be exempt from review (application number UP-20-00314).

Informed consent statement: The study was a survey, for which informed consent was waived by IRB, as no clinical or identifying information from the participants were recorded.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: United States

ORCID number: Veronica Frank 0000-0001-7096-8138; Anjali Doshi 0000-0001-9486-7657; Natalie L Demirjian 0000-0002-1368-1568; Brandon K K Fields 0000-0002-1727-2091; Catherine Song 0000-0003-3096-1251; Xiaomeng Lei 0000-0001-8899-5177; Sravanthi Reddy 0000-0002-6007-4429; Bhushan Desai 0000-0001-9998-0536; Drayton C Harvey 0000-0002-6571-312X; Steven Cen 0000-0002-7859-8909; Ali Gholamrezanezhad 0000-0001-6930-4246.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 Coronavirus disease (COVID-19). World Health Organization 2020. (accessed February 23, 2022). Available from:

https://www.who.int/emergencies/diseases/novel-coronavirus-2019

2 **Ranney ML**, Griffeth V, Jha AK. Critical Supply Shortages - The Need for Ventilators and Personal Protective Equipment during the Covid-19 Pandemic. *N Engl J Med* 2020; **382**: e41 [PMID: 32212516 DOI: 10.1056/NEJMp2006141]

3 **Whelan A**, Prescott J, Young G, Catanese VM, McKinney R. Guidance on Medical Students' Participation in Direct Patient Contact Activities. AAMC 2020. (accessed May 28, 2020). Available from: www.aamc.org/system/files/2020-04/meded-April-14-Guidance-on-Medical-Students-Participation-in-Direct-Patient-Contact-Activities.pdf

4 Thousands of medical students are being fast-tracked into doctors to help fight the coronavirus. CNN 2020. (accessed June 12, 2020). https://edition.cnn.com/2020/03/19/europe/medical-students-coronavirus-intl/index.html

5 United States Medical Licensing Examination | Announcements 2020. (accessed June 8, 2020). Available from: https://www.usmle.org/announcements/

6 **Rajesh A**, Asaad M. Alternative Strategies for Evaluating General Surgery Residency Applicants and an Interview Limit for MATCH 2021: An Impending Necessity. *Ann Surg* 2021; **273**: 109-111 [PMID: 32941286 DOI: 10.1097/SLA.0000000000004501]

7 **Louie PK**, Harada GK, McCarthy MH, Germscheid N, Cheung JPY, Neva MH, El-Sharkawi M, Valacco M, Sciubba DM, Chutkan NB, An HS, Samartzis D. The Impact of COVID-19 Pandemic on Spine Surgeons Worldwide. *Global Spine J* 2020; **10**: 534-552 [PMID: 32677575 DOI: 10.1177/2192568220925783]

8 **Harris PA**, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; **95**: 103208 [PMID: 31078660 DOI: 10.1016/j.jbi.2019.103208]

9 **Harris PA**, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377-381 [PMID: 18929686 DOI: 10.1016/j.jbi.2008.08.010]

10 **Drachev SN**, Brenn T, Trovik TA. Prevalence of and factors associated with dental anxiety among medical and dental students of the Northern State Medical University, Arkhangelsk, North-West Russia. *Int J Circumpolar Health* 2018; **77**: 1454786 [PMID: 29564967 DOI: 10.1080/22423982.2018.1454786]

11 **Frank E HJ**. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. 2015 [DOI: 10.1007/978-3-319-19425-7_13]

12 **Kim SY**, Shin YC, Oh KS, Shin DW, Lim WJ, Kim EJ, Cho SJ, Jeon SW. The association of occupational stress and sleep duration with anxiety symptoms among healthy employees: A cohort study. *Stress Health* 2020; **36**: 675-685 [PMID: 32314860 DOI: 10.1002/smi.2948]

13 **Stockbridge EL**, Wilson FA, Pagán JA. Psychological distress and emergency department utilization in the United States: evidence from the Medical Expenditure Panel Survey. *Acad Emerg Med* 2014; **21**: 510-519 [PMID: 24842501 DOI: 10.1111/acem.12369]

14 **Myers L**, Balakrishnan S, Reddy S, Gholamrezanezhad A. Coronavirus Outbreak: Is Radiology Ready? *J Am Coll Radiol* 2020; **17**: 724-729 [PMID: 32304643 DOI: 10.1016/j.jacr.2020.03.025]

15 **Sattar MU**, Palaniappan S, Lokman A, Hassan A, Shah N, Riaz Z. Effects of Virtual Reality training on medical students' learning motivation and competency. *Pak J Med Sci* 2019; **35**: 852-857 [PMID: 31258607 DOI: 10.12669/pjms.35.3.44]

16 **Weiner S**. No classrooms, no clinics: Medical education during a pandemic. AAMC 2020. (accessed May 30, 2020). Available from: https://www.aamc.org/news-insights/no-classrooms-no-clinics-medical-education-during-pandemic

17 **Gallagher TH**, Schleyer AM. "We Signed Up for This! *N Engl J Med* 2020; **382**: e96 [PMID: 32268020 DOI: 10.1056/NEJMp2005234]

18 **Little TD**, Jorgensen TD, Lang KM, Moore EW. On the joys of missing data. *J Pediatr Psychol* 2014; **39**: 151-162 [PMID: 23836191 DOI: 10.1093/jpepsy/jst048]

19 **Quek TT**, Tam WW, Tran BX, Zhang M, Zhang Z, Ho CS, Ho RC. The Global Prevalence of Anxiety Among Medical Students: A Meta-Analysis. *Int J Environ Res Public Health* 2019; **16** [PMID: 31370266 DOI: 10.3390/ijerph16152735]

20 **Nielsen KJ**, Pedersen AH, Rasmussen K, Pape L, Mikkelsen KL. Work-related stressors and occurrence of adverse events in an ED. *Am J Emerg Med* 2013; **31**: 504-508 [PMID: 23347716 DOI: 10.1016/j.ajem.2012.10.002]

21 **Bowman J**, MD, L A, ry, June 11 M| C|, 2020. We need improved mental health care for physicians. KevinMDCom 2020. (accessed June 20, 2020). Available from: https://www.kevinmd.com/blog/2020/06/we-need-improved-mental-health-care-for-physicians.html

22 **Harries AJ**, Lee C, Jones L, Rodriguez RM, Davis JA, Boysen-Osborn M, Kashima KJ, Krane NK, Rae G, Kman N, Langsfeld JM, Juarez M. Effects of the COVID-19 pandemic on medical students: a multicenter quantitative study. *BMC Med Educ* 2021; **21**: 14 [PMID: 33407422 DOI: 10.1186/s12909-020-02462-1]

23 **Alsoufi A**, Alsuyihili A, Msherghi A, Elhadi A, Atiyah H, Ashini A, Ashwieb A, Ghula M, Ben Hasan H, Abudabuos S, Alameen H, Abokhdhir T, Anaiba M, Nagib T, Shuwayyah A, Benothman R, Arrefae G, Alkhwayildi A, Alhadi A, Zaid A, Elhadi M. Impact of the COVID-19 pandemic on medical education: Medical students' knowledge, attitudes, and practices regarding electronic learning. *PLoS One* 2020; **15**: e0242905 [PMID: 33237962 DOI: 10.1371/journal.pone.0242905]

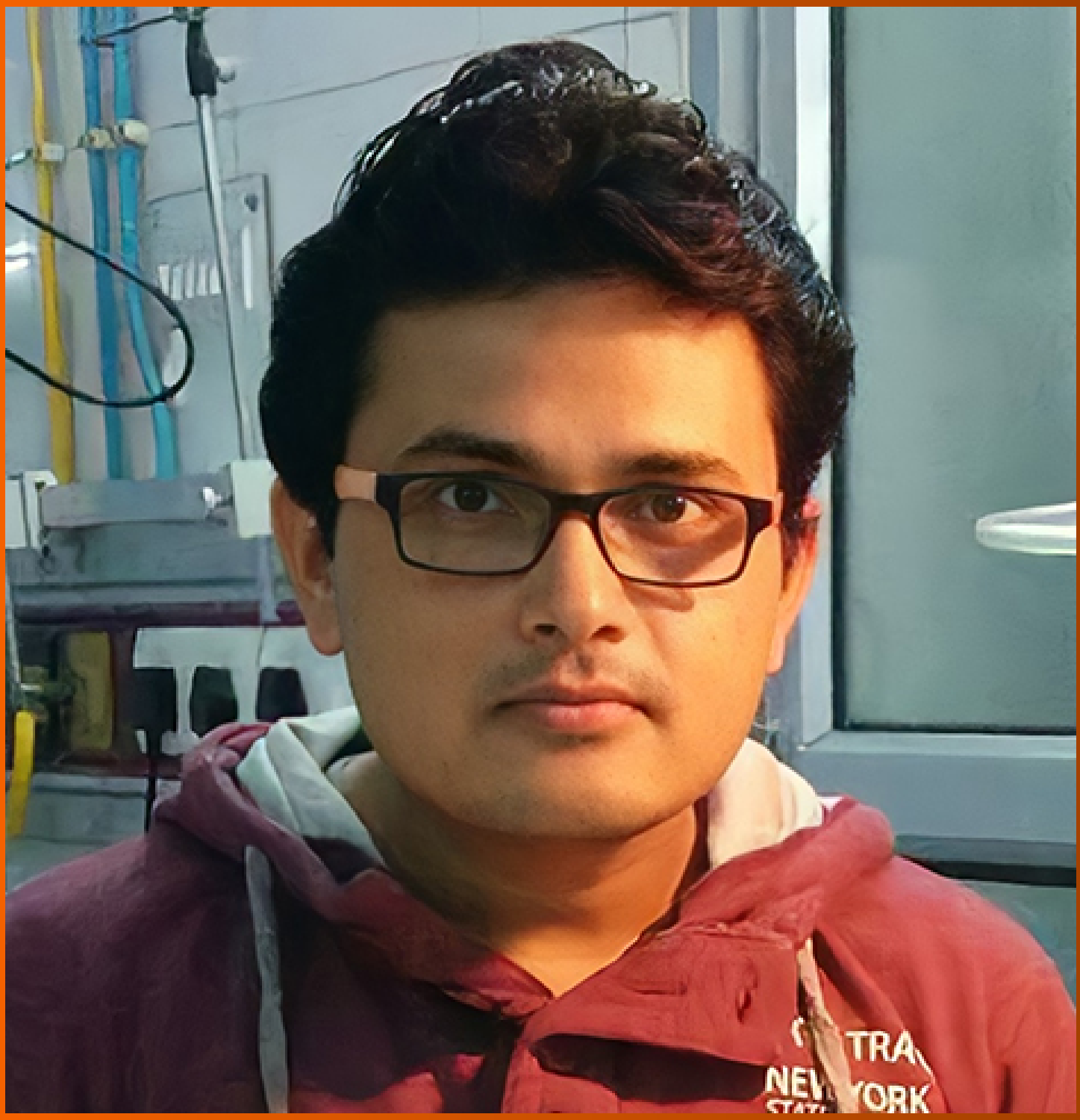
24 **Demirjian NL**, Fields BKK, Song C, Reddy S, Desai B, Cen SY, Salehi S, Gholamrezanezhad A. Impacts of the Coronavirus Disease 2019 (COVID-19) pandemic on healthcare workers: A nationwide survey of United States radiologists. *Clin Imaging* 2020; **68**: 218-225 [PMID: 32892107 DOI: 10.1016/j.clinimag.2020.08.027]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2022 July 25; 11(4): 170-220



Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents **Bimonthly Volume 11 Number 4 July 25, 2022**

World Journal of Virology

Bimonthly Volume 11 Number 4 July 25, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Virology*, Shahid Akhtar Siddiqui, MBBS, MD, Assistant Professor, Doctor, Department of Pediatrics, MLN Medical College, King George Medical University, Lucknow, Allahabad 211002, Uttar Pradesh, India. sha.akht@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
En-Qiang Chen, Mahmoud El-Bendary

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
July 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 170-175

DOI: 10.5501/wjv.v11.i4.170

ISSN 2220-3249 (online)

MINIREVIEWS

COVID-19 vaccination and myocarditis: A review of current literature

Kartik Dhaduk, Jagjit Khosla, Muzna Hussain, Vrunda Mangaroliya, Shaylika Chauhan, Kumar Ashish, Rahul Gupta, Suman Pal

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Freij BJ, United States; Odhar HA, Iraq
A-Editor: Liu X, China

Received: December 24, 2021
Peer-review started: December 24, 2021
First decision: March 7, 2022
Revised: March 25, 2022
Accepted: May 22, 2022
Article in press: May 22, 2022
Published online: July 25, 2022

Kartik Dhaduk, Muzna Hussain, Vrunda Mangaroliya, Shaylika Chauhan, Department of Internal Medicine, Geisinger Wyoming Valley Medical Center, Wilkes-Barre, PA 18702, United States

Jagjit Khosla, Department of Cardiology, University of Oklahoma, Oklahoma, OK 73019, United States

Kumar Ashish, Department of Internal Medicine, Carolina East Medical Center, North Carolina, NC 28560, United States

Rahul Gupta, Department of Medicine, Westchester Medical Center, Valhalla, NY 10595, United States

Suman Pal, Department of Internal Medicine, University of New Mexico, New Mexico, NM 87106, United States

Corresponding author: Kartik Dhaduk, MD, Staff Physician, Department of Internal Medicine, Geisinger Wyoming Valley Medical Center, 1000 E Mountain Dr, Wilkes-Barre, PA 18702, United States. kartikdhaduk@gmail.com

Abstract

Vaccination for coronavirus disease 2019 (COVID-19) is a critical strategy in controlling the current pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). After widespread COVID-19 vaccine implementation, isolated case reports about myocarditis as a potential adverse reaction started coming. As of November 12, 2021, Centers for Disease Control and Prevention (CDC) has reported 1793 cases of myocarditis or pericarditis among young people with age 12-29 years, most cases have been reported in the male adolescent age group after the second dose of mRNA COVID-19 vaccines. It is very important to monitor the safety standards and adverse reactions of vaccines to effectively implement the vaccination policies. The CDC and the United States Food and Drug Administration actively monitor vaccine-associated adverse reactions a well-known platform such as Vaccine Adverse Event Reporting System. CDC continues to recommend COVID-19 vaccines and booster doses for eligible individuals (age limit according to the type of vaccine) after careful consideration from risk-benefit assessment and favorable outcomes from vaccination. Mechanisms behind COVID-19 vaccine-induced myocarditis are not clear yet but several possibilities such as molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens, immune response to mRNA, and activation of host immunological system, trigger of the pre-existing dysregulated immunological system have been documented in the literature. Overall, data

suggests a good prognosis, especially in young patients. In this review article, we cover currently available data on COVID-19 vaccine-related myocarditis incidence, concerns, possible mechanisms of myocarditis, current treatment, and outcome trends, risk *vs* benefit assessment of COVID-19 vaccination in this current pandemic.

Key Words: Coronavirus disease 2019 vaccine; Myocarditis; mRNA vaccine; Severe acute respiratory syndrome coronavirus-2; Vaccine complications; Risk assessment

Core Tip: Coronavirus disease 2019 (COVID-19) vaccination campaign is progressing successfully, and more than 400 million vaccine doses have been administered in the United States. We support the COVID-19 vaccination drive given positive data on preventing significant morbidities from COVID-19 disease in fully vaccinated people and relatively rare occurrences of serious side effects. Many questions remain open such as: whether patients with a history of vaccine-associated myocarditis should receive the subsequent vaccines or booster doses, the long-term effect of vaccine-associated myocarditis, how to identify the high-risk individuals for such adverse reactions to selectively save vulnerable populations, *etc.* There is still substantial research to be done in this direction to answer unsolved questions.

Citation: Dhaduk K, Khosla J, Hussain M, Mangaroliya V, Chauhan S, Ashish K, Gupta R, Pal S. COVID-19 vaccination and myocarditis: A review of current literature. *World J Virol* 2022; 11(4): 170-175
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/170.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.170

INTRODUCTION

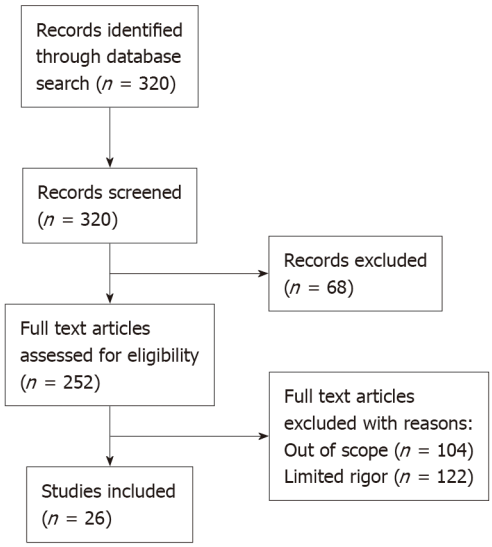
Coronavirus disease 2019 (COVID-19), a disease that originated from a viral infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a global pandemic on March 11, 2020, by the World Health Organization. Since the declaration of the pandemic, tremendous efforts have been made towards the development of safe and effective COVID-19 mitigation, specifically through the administering of vaccines. Three of the COVID-19 vaccines were approved by the United States Food and Drug Administration (FDA) for emergency use: the first approval was for Pfizer-BioNTech COVID-19 Vaccine on August 23, 2020[1], the second approval was for Moderna COVID-19 vaccine on December 18, 2020[2] and the third approval was for Janssen COVID-19 vaccine on February 27, 2021[3].

Viral infections are known to cause acute myocarditis by a direct effect on cardiac myocytes causing myonecrosis[4]. Additionally, other mechanisms have also been described including autoimmune response and vasculitis leading to injury. Post-immunization myocarditis as a rare adverse reaction after vaccination has been reported historically after the administering of the smallpox, anthrax, Haemophilus type B, influenza type B, BCG, typhoid fever, influenza and hepatitis B vaccines[5]. The Centers for Disease Control and Prevention (CDC) and the FDA monitor vaccine-associated adverse reactions through the use of a system known as the Vaccine Adverse Event Reporting System (VAERS) [6]. The CDC and FDA use extensive data and statistical methods to generate recommendations relative to vaccine safety and continue to recommend COVID-19 vaccination among everyone ages 5 and older [7]. VAERS is also contingent upon reporting bias, including underreporting (mild adverse events) and overreporting (especially with intense media attention and public awareness)[6].

The data and literature continue to accumulate each day regarding COVID-19 vaccine-related adverse events. Myocarditis, in general, has been reported as a rare adverse reaction after the 2nd dose of the COVID-19 vaccine, especially in young males. Within the contents of this review article, we intend to expound upon COVID-19 vaccine-related myocarditis incidence, available data and statistics, possible mechanisms of vaccine-related myocarditis, current treatment trends, outcomes of such events, and risk *vs* benefit assessments of COVID-19 vaccination in the current pandemic. PRISMA flow diagram for article review is shown in Figure 1.

COVID-19 VACCINE-RELATED MYOCARDITIS INCIDENCE AND CLINICAL PRESENTATION

The CDC reported that more than 448 million doses of the COVID-19 vaccine had been administered in



DOI: 10.5501/wjv.v11.i4.170

Figure 1 PRISMA flow diagram.

the United States as of November 19, 2021. Furthermore, upwards of 195 million people have been fully vaccinated, and 33.5 million people have received the COVID-19 booster vaccine[8]. The CDC has reported 1793 cases of myocarditis or pericarditis among young individuals (age 12-29 years) vaccinated for COVID-19, predominantly in adolescent males after the second dose of mRNA COVID-19 vaccines [9].

The estimated incidence rate appears to be very low; a comprehensive cohort study from Israel reported 2.13 cases per 100000 vaccinated persons with an incidence rate per 100000 persons for disease severity as 1.62 for mild myocarditis, 0.47 for intermediate myocarditis, and 0.04 for fulminant myocarditis[10]. Another study observed an incidence of 0.8 cases per 1 million doses of first dose COVID-19 vaccine and 5.8 cases per 1 million doses of second dose in 10-d observation window[11]. There is substantial heterogeneity in the incidence rate of vaccine-associated myocarditis, in respect to age and sex of the population as well. Numerous case series and case reports have reported findings consistent with post-COVID-19 immunization myocarditis. Such association was not found in clinical trials for these vaccines. One of the explanations could be a rarity of such adverse reactions, which gained clinical attention after the beginning of the global scale vaccine administration program.

Data from the available literature suggest patients experienced the symptoms within 12 h to 5 d and primarily after the second dose of COVID-19 vaccine administration; the majority were young male individuals and had good clinical outcomes[12-14]. A study from Israel reported 54 cases of postimmunization myocarditis within approximately 3 to 5 d after the second dose of the vaccine; only one case was fulminant and required extracorporeal membrane oxygenation, 83% of patients did not have co-existing medical conditions, 69% of patients developed myocarditis after the second dose of COVID-19 vaccine[10].

The key to identifying such cases is a high index of suspicion in young patients presenting with chest pain or cardiac symptoms within a few days of COVID-19 immunization. A review of the literature suggests patients with acute myocarditis typically present with chest pain (100% cases); myalgia, fatigue, fever (33%-86% cases); palpitations, dyspnoea, fatigue[15]. Blood work shows elevated troponin, C-reactive protein, brain natriuretic peptide; common electrocardiography (EKG) findings are ST-segment elevation, diffuse ST-T changes, ventricular and supraventricular tachycardias, but no EKG changes have also been reported. Echocardiogram findings varied from being normal to reduced systolic heart function, but a review article has reported primarily normal cardiac function in patients ages 18 years and younger, and more systolic dysfunction in patients ages 30 years and older. Cardiac magnetic resonance imaging was only available in a selective number of patients; late gadolinium enhancement in anterolateral and inferolateral cardiac walls was consistently noticed, few patients had myocardial edema on T2 mapping. Cardiac biopsy is a confirmatory test for acute myocarditis, it was noted very infrequently in available literature[10,15,16].

POSSIBLE MECHANISM OF MYOCARDITIS

The Pfizer-BioNTech and Moderna COVID-19 vaccines are mRNA vaccines, which contain nucleoside modified mRNA encoding the SARS-COV-2 viral spike protein. Once administered, mRNA particles induce viral spike protein synthesis in the host cells which then stimulates adaptive immune response to

produce IgG antibodies to this spike proteins. Such vaccine induced IgG antibodies help neutralising the virus by preventing the attachment of SARS-COV-2 virus to host cell receptors *via* spike protein[15].

The generation of heart reactive autoantibodies against multiple antigens can have a functional effect on cardiac cells[17]. Autoantibodies develop more frequently in first degree relatives of patients with cardiomyopathy, raising possibility of genetically susceptible subgroup of patients. The role of molecular mimicry between the spike protein in the SARS-COV-2 virus and self-antigens has been extensively studied. A study has demonstrated possible cross-reactions between viral spike protein and many tissue proteins including alfa-myosin[18] which may potentially play a role in molecular mimicry mechanism affecting cardiomyocytes. Nucleoside modification plays a critical role in effective and safe mRNA vaccine development as it selectively activates the innate immune system to appropriate target cells and regulates the immune response which is essential in vaccine development[19]. The innate immune system can recognize genetic materials of pathogen that usually lack RNA modifications[19]. A potential immune mediated adverse event such as triggering of the pre-existing dysregulated immune pathways in susceptible individuals leading to exaggerated immune response could be a potential mechanism of myocarditis after mRNA vaccination, such hypothesis have already been generated for COVID-19 viral infection[20]. The overresponse and overproduction of the innate immune system with adaptive mechanisms leads to pathological response. The overexpression of interferon-gamma that drives innate and viral responses to the vaccine booster leads to cardiac events which involve MAPK and JAK-STAT pathways[21]. A report demonstrated no significant elevation of IgM and IgG antibody levels in patients with myocarditis compared to patients without myocarditis after mRNA vaccination [22], provided an evidence against a hyperimmune response as a potential mechanism in general population. Young male predominance for myocarditis cases have been reported in the literature but there is no clear understanding of it. One possibility may be that gender differences in the stimulation of neutrophils and release of cytokines such as TNF-α and IFN-γ with predisposition in males and higher hormonal stimulation at puberty may explain propensity of males to get higher rate of vaccine associated myocarditis, but this needs to be validated[23]. Significant research is still required to better understand the molecular and genetic aspects of such potential mechanisms and vaccine complications.

MANAGEMENT AND OUTCOMES OF COVID-19 VACCINE RELATED MYOCARDITIS

Fortunately, most cases of myocarditis after COVID-19 vaccination had favorable outcomes. Those patients responded well to medical therapy and recovered from their symptoms within a short period. All patients presenting with chest pain within a week after receiving the COVID-19 vaccination should undergo complete evaluation for broad differentials of diagnoses. Initial evaluation includes EKG, troponin levels, and inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein. Further workups including echocardiography, cardiac catheterization, and cardiac magnetic resonance imaging should be considered to establish the diagnosis of myocarditis/pericarditis. Besides cardiology, infectious diseases and rheumatology should also be consulted to rule out other causes of myocarditis/pericarditis[15]. All these cases should be reported to VAERS. Further management of these patients is based on their clinical presentation, hemodynamic and rhythmic stability, and disease progression. Patients with acute chest pain, up-trending troponins, EKG changes, or signs of hemodynamic/rhythm instability need to be hospitalized and closely monitored. Many patients responded well with supportive care, nonsteroidal anti-inflammatory drugs, colchicine, and steroids. In patients with left ventricular systolic failure, it may be reasonable to consider additional treatments such as beta-blockers, aspirin, and angiotensin-converting enzyme inhibitors. The average duration of hospital stay is found to be less than a week in the cases reported so far[15,24]. Recently, a case report was published mentioning fulminant myocarditis after COVID-19 vaccination, which unfortunately proved to be fatal for one patient in particular[25]. While such an outcome is certainly alarming, the CDC has not confirmed any death that could be directly attributed to myocarditis related to COVID-19 vaccination.

RISK ASSESSMENT OF VACCINATION

Despite reports of myocarditis, COVID-19 vaccination data is reassuring in terms of safety standards. The CDC reports a significantly higher rate of hospitalization for unvaccinated adults compared to vaccinated adults; risk is 10 times higher for unvaccinated adolescents ages 12 to 17 years, 9 times higher for unvaccinated adults more than 18 years of age, 14 times higher for unvaccinated adults 18 to 49 years of age, 13 times higher for unvaccinated adults 50 to 64 years of age, and around 6 times higher in unvaccinated adults older than 65 years of age[26]. In terms of mortality risk, CDC data from August 2021 reported unvaccinated individuals had a risk of death from COVID-19 related complications around 11 times higher compared to vaccinated individuals[27]. Infection rate and mortality rate were lower in vaccinated individuals irrespective of vaccine brand (Pfizer, Moderna, or Janssen). As of November 19, 2021, more than 448 million doses of the COVID-19 vaccine have been administered in

the United States[8] and during this time, VAERS has received 9810 reports of death (0.0022%) related to the COVID-19 vaccine[9]. Reports of adverse events including mortality reports do not necessarily mean a vaccine-related complication. Total deaths from COVID-19 disease as of November 20, 2021 are more than 770461 in United States alone[28]. Considering the risks and benefits of COVID-19 vaccines, it is evident that vaccines have a positive impact on COVID-19 related morbidity and mortality. Therefore, the CDC continues to recommend COVID-19 immunisation to all eligible individuals and continues to monitor upcoming data very closely.

CONCLUSION

In conclusion, the COVID-19 vaccination campaign is progressing successfully, and more than 400 million vaccine doses have been administered in the United States. The CDC and other organizations are actively monitoring the safety standards and adverse reactions related to COVID-19 vaccination. After a thorough evaluation of risk *vs* benefit, the CDC continues to recommend COVID-19 vaccination in everyone ages 5 or older[7]. We support the COVID-19 vaccination drive given positive data on preventing significant morbidities from COVID-19 disease in fully vaccinated people and relatively rare occurrences of serious side effects. Many questions remain open such as: whether patients with a history of vaccine-associated myocarditis should receive the subsequent vaccines or booster doses, the long-term effect of vaccine-associated myocarditis, how to identify the high-risk individuals for such adverse reactions to selectively save vulnerable populations, *etc*. There is still substantial research to be done in this direction to answer unsolved questions.

FOOTNOTES

Author contributions: Dhaduk K conceptualized the manuscript; Dhaduk K, Khosla J, Hussain M and Mangaroliya V wrote the manuscript; Chauhan S, Kumar A and Gupta R performed the literature review, concept modification; Pal S provided expert review of the manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: No conflict-of-interest to declare.

Country/Territory of origin: United States

ORCID number: Kartik Dhaduk 0000-0002-2324-0301; Jagjit Khosla 0000-0001-5342-9781; Muzna Hussain 0000-0003-1533-6634; Vrunda Mangaroliya 0000-0002-3901-6646; Shaylika Chauhan 0000-0002-0253-3973; Kumar Ashish 0000-0002-2225-3936; Rahul Gupta 0000-0002-2511-2119; Suman Pal 0000-0002-2051-9788.

S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

REFERENCES

1 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine. [cited 19 November 2021]. In: Food and Drug Administration. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine
2 Moderna COVID-19 Vaccine. [cited 19 November 2021]. In: Food and Drug Administration. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine
3 Janssen COVID-19 Vaccine. [cited 19 November 2021]. In: Food and Drug Administration. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine
4 **Leonard EG**. Viral myocarditis. *Pediatr Infect Dis J* 2004; **23**: 665-666 [PMID: 15247607 DOI: 10.1097/01.INF.0000132280.36984.A9]
5 **Su JR**, McNeil MM, Welsh KJ, Marquez PL, Ng C, Yan M, Cano MV. Myopericarditis after vaccination, Vaccine Adverse Event Reporting System (VAERS), 1990-2018. *Vaccine* 2021; **39**: 839-845 [PMID: 33422381 DOI: 10.1016/j.vaccine.2020.12.046]
6 **Shimabukuro TT**, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2015; **33**: 4398-4405 [PMID: 26209838 DOI: 10.1016/j.vaccine.2015.07.035]

7 Clinical Considerations: Myocarditis after mRNA COVID-19 Vaccines. [cited 14 November 2021]. In: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html

8 **CDC COVID-19 Response Team**, Food and Drug Administration. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70**: 125-129 [PMID: 33507892 DOI: 10.15585/mmwr.mm7004e1]

9 Selected Adverse Events Reported after COVID-19 Vaccination. [cited 19 November 2021]. In: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.

10 **Witberg G**, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD, Kornowski R. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. *N Engl J Med* 2021; **385**: 2132-2139 [PMID: 34614329 DOI: 10.1056/NEJMoa2110737]

11 **Simone A**, Herald J, Chen A, Gulati N, Shen AY, Lewin B, Lee MS. Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older. *JAMA Intern Med* 2021; **181**: 1668-1670 [PMID: 34605853 DOI: 10.1001/jamainternmed.2021.5511]

12 **Montgomery J**, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, Loran D, Hrncir D, Herring K, Platzer M, Adams N, Sanou A, Cooper LT Jr. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. *JAMA Cardiol* 2021; **6**: 1202-1206 [PMID: 34185045 DOI: 10.1001/jamacardio.2021.2833]

13 **Marshall M**, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, Shaughnessy R, Caron R, Fuss C, Corbin KJE, Emuren L, Faherty E, Hall EK, Di Pentima C, Oster ME, Paintsil E, Siddiqui S, Timchak DM, Guzman-Cottrill JA. Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination. *Pediatrics* 2021; **148**: e2021052478 [PMID: 34088762 DOI: 10.1542/peds.2021-052478]

14 **Schauer J**, Buddhe S, Colyer J, Sagiv E, Law Y, Mallenahalli Chikkabyrappa S, Portman MA. Myopericarditis After the Pfizer Messenger Ribonucleic Acid Coronavirus Disease Vaccine in Adolescents. *J Pediatr* 2021; **238**: 317-320 [PMID: 34228985 DOI: 10.1016/j.jpeds.2021.06.083]

15 **Bozkurt B**, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. *Circulation* 2021; **144**: 471-484 [PMID: 34281357 DOI: 10.1161/CIRCULATIONAHA.121.056135]

16 **Das BB**, Moskowitz WB, Taylor MB, Palmer A. Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far? *Children (Basel)* 2021; **8** [PMID: 34356586 DOI: 10.3390/CHILDREN8070607]

17 **Caforio AL**, Mahon NJ, Tona F, McKenna WJ. Circulating cardiac autoantibodies in dilated cardiomyopathy and myocarditis: pathogenetic and clinical significance. *Eur J Heart Fail* 2002; **4**: 411-417 [PMID: 12167378 DOI: 10.1016/S1388-9842(02)00010-7]

18 **Vojdani A**, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol* 2020; **217**: 108480 [PMID: 32461193 DOI: 10.1016/j.clim.2020.108480]

19 **Karikó K**, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* 2005; **23**: 165-175 [PMID: 16111635 DOI: 10.1016/j.immuni.2005.06.008]

20 **Caso F**, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, Scarpa R. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? *Autoimmun Rev* 2020; **19**: 102524 [PMID: 32220633 DOI: 10.1016/j.autrev.2020.102524]

21 **Hajjo R**, Sabbah DA, Bardaweel SK, Tropsha A. Shedding the Light on Post-Vaccine Myocarditis and Pericarditis in COVID-19 and Non-COVID-19 Vaccine Recipients. *Vaccines (Basel)* 2021; **9** [PMID: 34696294 DOI: 10.3390/VACCINES9101186]

22 **Muthukumar A**, Narasimhan M, Li QZ, Mahimainathan L, Hitto I, Fuda F, Batra K, Jiang X, Zhu C, Schoggins J, Cutrell JB, Croft CL, Khera A, Drazner MH, Grodin JL, Greenberg BM, Mammen PPA, Morrison SJ, de Lemos JA. In-Depth Evaluation of a Case of Presumed Myocarditis After the Second Dose of COVID-19 mRNA Vaccine. *Circulation* 2021; **144**: 487-498 [PMID: 34133883 DOI: 10.1161/CIRCULATIONAHA.121.056038]

23 **Aomatsu M**, Kato T, Kasahara E, Kitagawa S. Gender difference in tumor necrosis factor-α production in human neutrophils stimulated by lipopolysaccharide and interferon-γ. *Biochem Biophys Res Commun* 2013; **441**: 220-225 [PMID: 24140406 DOI: 10.1016/j.bbrc.2013.10.042]

24 **Rosner CM**, Genovese L, Tehrani BN, Atkins M, Bakhshi H, Chaudhri S, Damluji AA, de Lemos JA, Desai SS, Emaminia A, Flanagan MC, Khera A, Maghsoudi A, Mekonnen G, Muthukumar A, Saeed IM, Sherwood MW, Sinha SS, O'Connor CM, deFilippi CR. Myocarditis Temporally Associated With COVID-19 Vaccination. *Circulation* 2021; **144**: 502-505 [PMID: 34133885 DOI: 10.1161/CIRCULATIONAHA.121.055891]

25 **Verma AK**, Lavine KJ, Lin CY. Myocarditis after Covid-19 mRNA Vaccination. *N Engl J Med* 2021; **385**: 1332-1334 [PMID: 34407340 DOI: 10.1056/NEJMc2109975]

26 Rates of laboratory-confirmed COVID-19 hospitalizations by vaccination status. [cited 19 November 2021]. In: Centers for Disease Control and Prevention. Available from: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination

27 Rates of COVID-19 Cases and Deaths by Vaccination Status. [cited 21 November 2021]. In: Centers for Disease Control and Prevention. Available from: https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status

28 United States COVID-19 Cases, Deaths, and Laboratory Testing (NAATs) by State, Territory, and Jurisdiction. [cited 21 November 2021]. In: Centers for Disease Control and Prevention. Available from: https://covid.cdc.gov/covid-data-tracker/#cases_totalcases

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 176-185

DOI: 10.5501/wjv.v11.i4.176

ISSN 2220-3249 (online)

MINIREVIEWS

Air leaks in COVID-19

Deven Juneja, Sahil Kataria, Omender Singh

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Munteanu C, Romania; Santulli G, United States
A-Editor: Yao QG

Received: February 2, 2022
Peer-review started: February 2, 2022
First decision: April 8, 2022
Revised: April 11, 2022
Accepted: June 27, 2022
Article in press: June 27, 2022
Published online: July 25, 2022

Deven Juneja, Sahil Kataria, Omender Singh, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Corresponding author: Deven Juneja, DNB, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, 1, Press Enclave Road, New Delhi 110017, India.
devenjuneja@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) continues to create havoc and may present with myriad complications involving many organ systems. However, the respiratory system bears the maximum brunt of the disease and continues to be most commonly affected. There is a high incidence of air leaks in patients with COVID-19, leading to acute worsening of clinical condition. The air leaks may develop independently of the severity of disease or positive pressure ventilation and even in the absence of any traditional risk factors like smoking and underlying lung disease. The exact pathophysiology of air leaks with COVID-19 remains unclear, but multiple factors may play a role in their development. A significant proportion of air leaks may be asymptomatic; hence, a high index of suspicion should be exercised for enabling early diagnosis to prevent further deterioration as it is associated with high morbidity and mortality. These air leaks may even develop weeks to months after the disease onset, leading to acute deterioration in the post-COVID period. Conservative management with close monitoring may suffice for many patients but most of the patients with pneumothorax may require intercostal drainage with only a few requiring surgical interventions for persistent air leaks.

Key Words: Air leak; COVID-19; Pneumothorax; Pneumomediastinum; SARS-CoV-2; Subcutaneous emphysema

Core Tip: Air leaks are an under-recognized and under-reported complication of coronavirus disease 2019 (COVID-19). Air leaks may also develop in spontaneously breathing patients without any underlying risk factors. Because these leaks may be asymptomatic and may even develop weeks to months after the onset of disease, a high index of suspicion is warranted to ensure early diagnosis and timely intervention. Still, patients with air leaks have poorer overall outcomes with greater need for ventilatory support, longer length of hospitalizations, and higher mortality rates. A better understanding of its pathophysiology may help in preventing the development of air leaks and improve outcomes.

Citation: Juneja D, Kataria S, Singh O. Air leaks in COVID-19. *World J Virol* 2022; 11(4): 176-185
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/176.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.176

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a multisystem disorder that can lead to a myriad of complications. The pathogenesis of respiratory failure is complex and covers different clinical scenarios such as pneumonia, acute respiratory distress syndrome (ARDS) with normal to low lung compliance, pulmonary embolism, and heart failure. Air leak (AL) injury is a well-documented but rare complication of COVID-19, leading to increased morbidity and mortality, particularly in the intensive care unit (ICU) setting[1]. AL is a clinical phenomenon associated with the leakage of air from a cavity that contains air into spaces that usually, under normal circumstances, do not have air[2]. The AL syndrome (ALS) is the presence of AL with associated symptoms of respiratory distress[2]. The AL may be classified as pneumothorax (air within the pleural cavity), pneumomediastinum (air in the mediastinum), pneumopericardium (air within the pericardial sac), pneumoperitoneum (air within the peritoneal cavity), subcutaneous emphysema (air within the subcutaneous tissue), pneumorrhachis (air within the spinal canal), and retroperitoneal emphysema (air within the retroperitoneum area).

Because of the possible inherent component of COVID-19, the patients are more prone to develop AL than other ICU patients. It can be spontaneous, occurring without any precipitating event, or iatrogenic due to invasive or non-invasive mechanical ventilation[1]. Pneumothorax has been reported as the most common cause of AL, followed by pneumomediastinum, and subcutaneous emphysema, with a few case reports of pneumopericardium and pneumoperitoneum[1,3]. However, pneumomediastinum may be under-recognized and under-reported as most patients are asymptomatic, and pneumomediastinum may be easily missed in chest X-rays. Some case series have reported that pneumomediastinum may be the commonest form of AL and may also be a predictive factor for pneumothorax[4,5].

The literature on AL in COVID-19 patients is limited to case reports, case series, and meta-summaries. The data on the guidelines and management of AL does not explicitly address the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients. This review aims to examine the breadth of the available literature on this challenging clinical entity concerning the ongoing pandemic, its clinical effects, and its management strategies.

EPIDEMIOLOGY

The exact incidence of AL remains uncertain in COVID-19 patients, as most studies on the subject did not have a specific imaging protocol for the diagnosis. The reported incidence of AL in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome is 12%-30% and 15%-30%, respectively[6-8]. However, the incidence is lower (0.6%-1%) among COVID-19 patients, but a higher incidence (12.8%-28.6%) has been reported in critically ill patients[1,9]. Compared with non-COVID-19 acute respiratory distress syndrome (ARDS), the patients with COVID-19 related ARDS (CARDS) requiring invasive mechanical ventilation (IMV) had a seven times higher incidence of AL, despite using lung-protective mechanical ventilation[10,11].

A retrospective analysis of the SARS-CoV database identified the mean presentation of AL at 19.6 ± 4.6 d from the onset of symptoms[12]. While most of the data show variability in the onset of AL from 9 to 19.6 d from the time of COVID-19 admission[9], it has been seen up to 60 d in some case reports[13]. In patients requiring IMV, it is generally detected after 4-14 d of its initiation[9].

Risk factors

ALs have been shown to occur more commonly in the older population with COVID-19, and there is a higher incidence in males (M:F = 4:1)[3,14,15]. Nevertheless, this age difference could result from the selection bias of elderly patients who tend to run a more severe course of COVID-19.

While pulmonary diseases like asthma, chronic obstructive airway disease (COPD), interstitial lung disease, lung bulla, and a history of smoking are known risk factors for pneumothorax in the general patient population, no such correlation has been observed in COVID-19 patients[3,9,13-15]. In fact, studies have shown that non-smoking COVID-19 patients have a 5.5 times increased risk of developing pneumothorax[15]. Several other risk factors have been reported in different studies, as enumerated in Table 1.

PATHOGENESIS

The pathogenesis of SARS-CoV-2 causing AL injuries is complex and not entirely comprehended. Whether CARDS represents a typical or atypical form of ARDS remains a matter of debate. The primary target site of SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE-2) receptors. The higher affinity of ACE-2 receptors for SARS-CoV-2 than that for the SARS coronavirus-1 (SARS-CoV1) may be responsible for the high infectivity of the former[16]. ACE-2 receptors are mainly expressed in type II pneumocytes, besides the vascular endothelium, myocardium, proximal tubules of the kidneys, and intestines[16]. Down-regulation of ACE-2 receptors by SARS-CoV-2 leads to the loss of ACE2 protective function in the local renin-angiotensin system of the lung on inflammation, fibrosis, and pulmonary arterial hypertension. Endothelial dysfunction plays a pivot role in the pathogenesis of SARS-CoV-2 infection by: (1) Unopposed angiotensin II upregulation causing vasoconstriction, increasing the dead space, and producing arterial hypoxemia; (2) coagulation and complement system activation, leading to a thrombotic macro- and micro-angiopathy; and (3) maladaptive immune response and exaggerated inflammatory response[17]. Eventually, these elements cause a lung injury characterized by interstitial inflammatory infiltrates, interstitial alveolar edema, hyaline membrane formation, airway inflammation, and microvascular thrombosis[1,16,17,18]. These factors increase the frailty of airways and alveoli, with early cyst or bullae formation and extensive alveolar destruction, forming cavitary lesions over time, mainly in the non-dependent and caudal region. The peripherally located cysts can either rupture spontaneously or during positive pressure ventilation (PPV) due to increased alveolar pressures, especially in the advanced stages when the lung has undergone fibrotic changes. While PPV may be a contributing factor, data suggest that 30-40% of the patients with COVID-19 who developed ALs were never on invasive ventilation, suggesting that mechanisms apart from barotrauma may play a significant role in the development of AL[3,14].

AL in spontaneously breathing patients

Macklin phenomenon: The marginal alveoli have bases in the bronchi, bronchioles, blood vessels, and pleura separated by a connective tissue layer or interstitium. Increased intrathoracic pressure, by coughing, vomiting, sneezing, defecation, or in cases of asthma or COPD exacerbation, results in increased intra-alveolar pressure and overinflation of the alveoli creating a large pressure gradient between the damaged marginal alveoli and lung interstitium. A pressure gradient may also develop during the Valsalva maneuver by reducing the calibration of pulmonary vasculature without affecting alveolar pressure. This can rupture the marginal alveoli causing the air to leak with centripetal dissection along the bronchovesicular sheath towards the lung's hilum and follow to the low-pressure mediastinum causing spontaneous pneumomediastinum. Pressure in the mediastinum is relieved by the escape of the air into the subcutaneous tissue resulting in subcutaneous emphysema, mainly at the root of the neck, as the cervical fascia is continuous with the mediastinum. Air can then further tract to various cavities causing pneumothorax, pneumopericardium, and retroperitoneal emphysema (Figure 1)[19].

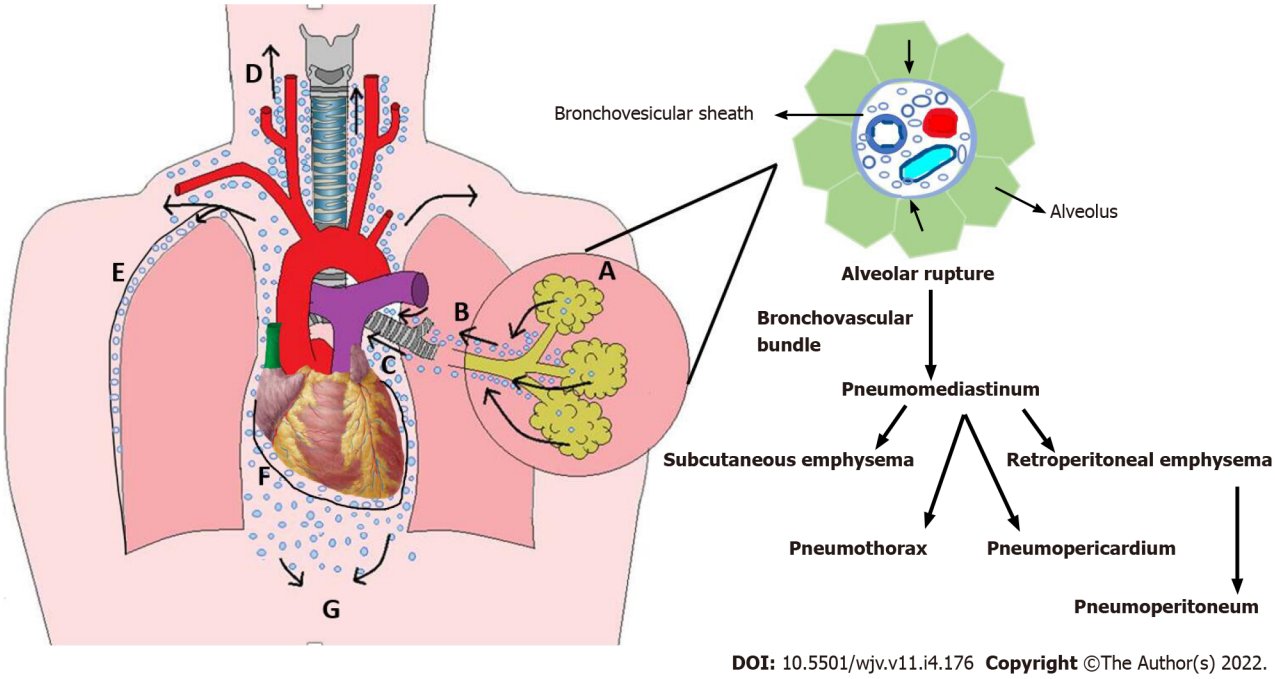
Patient self-inflicted lung injury: Patient self-inflicted lung injury (P-SILI) signifies the possibility of lung injury induced by or worsened by the patient's intense inspiratory effort. P-SILI is a vicious cycle as worsening lung injury increases the respiratory drive, resulting in further strong respiratory efforts. A strong inspiratory effort in a previously injured lung can lead to the following changes[20]: (1) Swings in transpulmonary pressure causing the inflation of large volumes, *i.e.*, excessive strain; (2) abnormal decrease in the alveolar pressure below the positive end-expiratory pressure (PEEP) during assisted ventilation increasing the transvascular hydrostatic pressure, favoring the aggravation of negative-pressure pulmonary edema; (3) significant regional transpulmonary pressure differences in the dependent (posterior) regions than non-dependent (anterior) ones are accompanied by a pendelluft phenomenon, an intrapulmonary shift of gas from non-dependent to dependent lung regions at the very onset of inspiratory effort, even before the start of ventilator insufflation. These effects lead to regional volutrauma and increased cyclic inflation of the dependent regions that were collapsed during expiration (atelectrauma); and (4) diaphragm injury caused by injurious eccentric contractions.

Early intubation was recommended earlier during the pandemic; however, with the increasing incidence of morbidity and mortality associated with IMV, a trial of high-frequency nasal cannula (HFNC) or non-invasive ventilation (NIV) is generally recommended for respiratory support at the outset. Although these strategies might delay IMV, they can still contribute to AL injury by increasing P-SILI. In addition, NIV and HFNC may be associated with a higher incidence of barotrauma than

Table 1 Risk factors for air leaks in coronavirus disease 2019

Risk factors	Probable mechanism
Comorbidities like hypertension, diabetes mellitus, and morbid obesity	By increasing the risk of diffuse alveolar damage
Persistent cough	Significant strain by causing sudden alveolar distension
Time from symptom onset	Increased risk of P-SILI
Mode of ventilation	
Non-invasive: HFNC and NIV	Increasing the risk of P-SILI
Invasive mechanical ventilation	Ventilation associated lung injury
Corticosteroids	Weakening the interstitial tissue, lowering immunity, and impairing healing

HFNC: High frequency nasal cannula; P-SILI: Patient self-induced lung injury; NIV: Non-invasive ventilation.



DOI: 10.5501/wjv.v11.i4.176

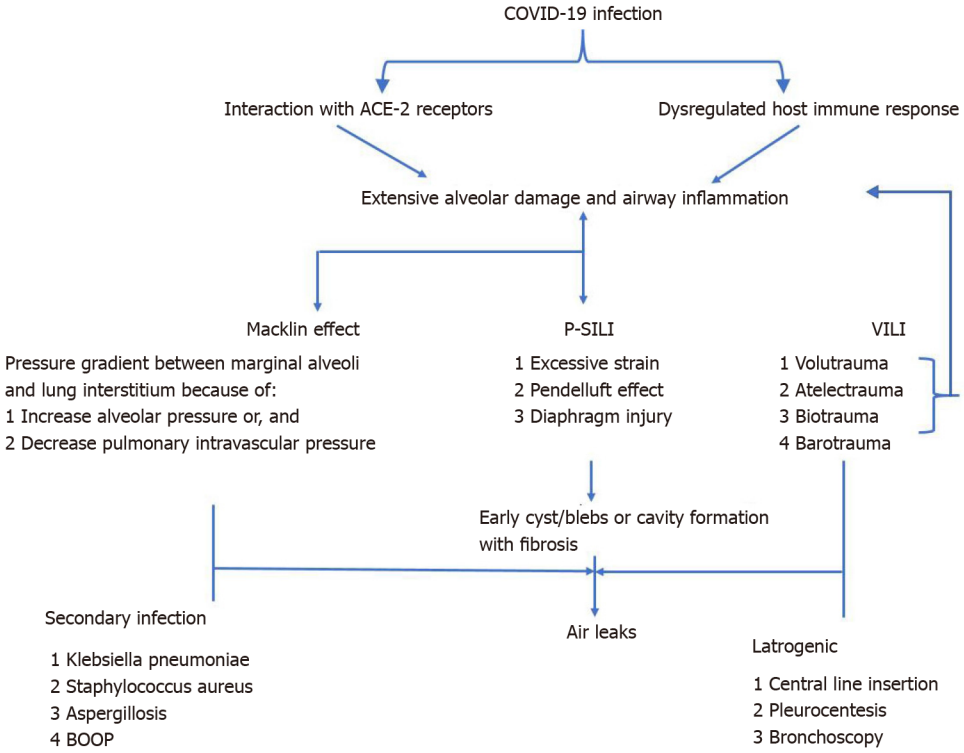
Figure 1 Macklin effect. A: Macklin effect - Increase in pressure gradient between the damaged marginal alveoli and lung interstitium due to increase in intrathoracic pressure and or decrease pulmonary intravascular pressure, leads to alveoli rupture and development of interstitial emphysema; B: Air disseminates in the peribronchovascular space up to the pulmonary hila; C: Pnemomediastinum; D: Subcutaneous emphysema; E: Pneumothorax; F: Pneumopericardium; G: Retroperitoneal emphysema.

standard low-flow oxygen therapies[21]. Hence, delaying intubation and initiation of IMV may also increase the chances of AL. Therefore, the time from symptom onset to intubation is an independent predictor of AL development[11].

Secondary bacterial infections may enhance the inflammatory mechanism of lung injury triggered by SARS-CoV-2 infection, thus increasing the susceptibility to persistent ALs (PALs). Necrotizing lung infections caused by *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Aspergillus spp.* may also increase the susceptibility to AL (Figure 2).

CLINICAL FEATURES

As already stated, ALs generally develop later in the disease course, but a minority of patients (less than 1%) have been shown to have AL at the initial presentation[15]. Clinical manifestations can vary from being asymptomatic to having life-threatening conditions. AL may be an incidental finding in 50% of the patients as they may be asymptomatic or have symptoms that might be attributed to disease progression rather than AL[3].



DOI: 10.5501/wjv.v11.i4.176

Figure 2 Pathogenesis of air leaks in coronavirus disease 2019. COVID-19: Coronavirus disease 2019; ACE-2: Angiotensin-converting enzyme-2; P-SILI: Patient self-inflicted lung injury; VILI: Ventilator-induced lung injury.

In some studies, pneumothorax in COVID-19 is primarily unilateral and predominately on the right side[1,3]. The most common symptoms of pneumothorax include chest pain and dyspnoea, causing respiratory distress and requiring hospital admission, or worsening of pre-existing respiratory symptoms with increased oxygen requirement. Chest pain is of sudden onset, often sharp, and stabbing type of pleuritic pain, which radiates to the ipsilateral shoulder or arm. The patient might be tachypnoeic and tachycardic, with reduced chest movements and absent breath sounds on examination.

Pneumomediastinum is generally benign; however, retroperitoneal chest pain, dyspnoea, coughing spells, neck pain, or dysphagia can be present[22]. Mediastinal crunching over the cardiac apex and the left sternal border, synchronous with the heartbeat, known as the Hamman's sign, can be heard on auscultation. Subcutaneous emphysema causes painless swelling over the neck and chest, which on palpation gives a feeling of tissue paper in the hands, known as crepitus. This may be the first sign suggestive of an AL. On physical examination, pneumopericardium can be detected by water wheel sound ("bruit de Moulin").

Malignant pneumomediastinum, pneumopericardium, or tension pneumothorax can result in mechanical obstruction, causing a decrease in venous return, hemodynamic instability, and circulatory collapse. This compels a prompt diagnosis and intervention.

CLINICAL EVALUATION

Thorough clinical history and physical assessment remains the key to diagnosing ALs. Apart from pulmonary embolism and acute coronary syndrome, a high index of suspicion for ALS is advised in COVID-19 patients with acute onset of hemodynamic instability, worsening hypoxemia, and or hypercapnia.

Laboratory parameters

As such, there is no single laboratory parameter that may assist in making the diagnosis or confirming AL. In patients with SARS-CoV AL, high lactate dehydrogenase (LDH) levels were associated; however, in COVID-19 patients, LDH levels are not significantly high, and mixed results are observed[21,23,24]. Other laboratory parameters associated with increased incidence of AL are increased serum bilirubin and C-reactive protein levels[11]. Arterial blood gases may be helpful to document hypoxemia and sometimes hypercapnia. The resultant respiratory distress or shock may lead to hyperlactatemia.

Imaging

Chest radiography: Chest radiography is the first investigation performed as it is simple, inexpensive, and rapid. Chest X-ray has a pooled sensitivity of 52-60% and specificity of 88-95% for diagnosing pneumothorax and pneumomediastinum[25]. The best diagnostic film for pneumomediastinum or pneumothorax is a lateral chest X-ray, with the affected side up for the latter. However, the lateral view is challenging to achieve in the ICU setting. Pneumomediastinum can be differentiated from pneumopericardium on chest X-ray as the former shows air around the heart anteriorly (behind the sternum) and superiorly lifting the thymus but not below (diaphragmatic border). In contrast, air surrounds all the heart's borders in pneumopericardium.

Chest ultrasonography: Ultrasonography is a readily available bedside tool in evaluating critically ill patients and is the only imaging modality that allows scouring for reversible causes of non-arrhythmogenic cardiac arrest during ongoing resuscitation. Ultrasound has a pooled sensitivity of 88%-95% and specificity of 100% for diagnosing pneumothorax. However, the presence of subcutaneous emphysema can affect the accuracy of ultrasound[26]. Features of lung ultrasound for the diagnosis of pneumothorax include: Absence of lung sliding (high sensitivity and specificity), absence of comet-tail artifact (high sensitivity and low specificity), and presence of lung point (high specificity and low sensitivity).

Pneumopericardium and pneumomediastinum are arduously diagnosed by ultrasound. In the case of a large pneumopericardium, an echocardiogram shows "no heart" or absent cardiac images, especially during systole as the heart is pushed further away from the transducer by the air and then returns with diastole. This finding is also known as an "air gap sign" found in pneumomediastinum and pneumopericardium, seen using M-mode[27]. One distinguishing factor between the two is the inability to see the heart in the subxiphoid view in the case of pneumopericardium. In contrast, the heart is usually well visualized in pneumomediastinum due to its direct contact with the diaphragm without an obstructing air artifact[28]. However, similar findings are often seen with respiratory interference, which may develop if the patient is tachypnoeic. Spontaneous or swirling bubbles may be seen in the pericardial space in patients with pneumopericardium. Ultrasonography is heavily operator-dependent, and its sensitivity further drops in patients with ARDS. In addition, it cannot be used to discriminate between a COPD-associated bleb and pneumothorax.

Computed tomography: Computed tomography (CT) is the gold standard in diagnosing ALs and differentiating bullous disease from pneumothorax. Nevertheless, transporting a critically ill patient on mechanical ventilation and vasopressors to the imaging facility could be perilous. Also, the risk-benefit should be contemplated owing to radiation risk with CT. In addition, the risk of spread of infection should also be kept in mind in patients with active COVID-19 disease.

The Macklin effect on lung parenchyma in CT images is a linear collection of air contiguous to the broncho-vascular sheath. CT has a sensitivity of 89.2% (95% confidence interval [CI]: 74.6–96.9), specificity of 95.6% (95%CI: 90.6–98.4), and accuracy of 94.2% (95%CI: 89.6-97.2) to detect the Macklin effect. Macklin's effect on CT can accurately predict AL development in CARDS patients 8.5 d in advance[29].

CLASSIFICATION OF SEVERITY

The most straightforward and widely used technique to quantify AL is asking the patient to cough while observing the water column and the water seal column in the chest tube drainage system. During this maneuver, no air bubbles in the water seal suggest that pleural space is devoid of air. If the intensity of bubbles remains the same on repeated coughs, it is likely to be an active leak. The AL is deemed significant if bubbling is even present during normal breathing or while the patient is talking. However, this method lacks standardization and validation among observers.

The other most commonly used classification is the Cerfolio system[30], which is also based on observation but is less subjective and is a validated classification. It is based on the degree of the leak (measured with an AL meter) and the phase of respiration in which it appears (Table 2). However, there is no specific classification for AL in COVID-19 patients.

PERSISTENT AIR LEAK

Persistent AL (PAL) refers to the continued airflow from the endobronchial tree to the pleural space, which can occur due to an abnormal connection between the pleural space and airways (bronchopleural fistula, BPF) or alveolus. An AL is referred to as a PAL when it persists longer than 5–7 d. This typically used 5-d cut-off to define PAL was initially derived from the expected length of stay following pulmonary resection, where an AL for several days was not uncommon[31,32]. However, some authors suggest that an AL in the setting of secondary spontaneous pneumothorax should be considered

Table 2 Cerfolio classification of air leaks

Grade	Description
Grade 1, FE	During forced expiration only, typically when asking the patient to cough
Grade 2, E	During expiration only
Grade 3, I	During inspiration only
Grade 4, C	Continuous bubbling both during expiration and inspiration

persistent after 48 h[31]. Although the exact incidence of PAL is unknown, it may be prevalent in patients with COVID-19. Before diagnosing PAL, one must inspect the chest tube drainage circuit, as a leak in the circuit or malfunctioning three-way stop cock may masquerade as BPF.

MANAGEMENT

The treatment option for COVID-19 associated ALs depends on their type and severity. Currently, there are no guidelines for managing ALs in COVID-19 patients. Many patients with ALs may be managed conservatively, gradually absorbing the air in the following days. The patient should be closely monitored for any clinical deterioration. If possible, PPV should be avoided in such patients, and low-flow oxygen delivery devices for oxygen supplementation or, if required, an HFNC might be preferable over NIV. No independent lung ventilation strategies are consistently effective in expediting the resolution of ALs in a patient on PPV. Although reducing the tidal volume, PEEP, and inspiratory time, if feasible, can promote closure of the pleural defect[33].

Even though most of the COVID-19 patients with pneumomediastinum and around 30% of patients with pneumothorax may be managed conservatively, the remaining patients will require intercostal drainage (ICD), and a few will require further surgical intervention[34]. Tension pneumothorax, pneumomediastinum, or pneumopericardium can be fatal and require immediate decompression. For tension pneumothorax, needle drainage may be performed through the second intercostal space anteriorly in the mid-clavicular line, followed by chest tube drainage. For tension pneumomediastinum drains on the anterior thoracic wall, and for tension pneumopericardium pericardiocentesis may be performed for decompression.

As per British Thoracic Society guidelines, in bubbling chest drains in patients with COVID-19, viral filters should be installed onto the suction port of a chest drain bottle. An alternative approach to reducing the risk of spread of infection through droplets is the use of digital drain circuits (for example, Thopaz+, Medela), though they do not contain a viral filter[35].

Management of PAL

The management of PAL can prove to be a challenging task, with the first step being localization of AL. The lack of predictive models to identify patients in whom a resolution of AL is likely to occur conservatively leads to incertitude. As a result, management strategies have been highly variable among different centres. There are reports of 80% of cases having been treated conservatively for 14 d with success; however, a delay in surgery may detrimentally affect surgical outcomes and prolong hospital stay. Therefore, an individualized approach to PAL is suggested to improve patient outcomes[31]. As per the two guidelines on the management of PAL, based on the consensus of expert panels, one should consider early surgery in case that the AL persists beyond 4 d, followed by pleurodesis to prevent recurrence[36,37]. However, surgical repair may not be feasible in critically ill patients with CARDS due to a further increase in morbidity or mortality. In the case of an expected conservative resolution, ICD for a prolonged duration may be preferred[3]. The other promising option is the bronchoscopic placement of a one-way endobronchial valve, which appears to be a reasonable minimally invasive therapeutic option with a high success rate. Again, the risk of spread of infection while performing bronchoscopy should be considered in patients with active COVID-19. Autologous blood pleurodesis, Heimlich valve positioning, and albumin-glutaraldehyde tissue adhesives are additional less invasive options for recurrent and refractory cases[38].

Negative pressure suction

It is common to apply negative suction to chest tubes to enhance pleural apposition. There is no unanimity on whether or not applying suction to the chest tube is beneficial or hazardous. A water seal is usually not helpful or even contraindicated in patients with severe restrictive lung disease and a substantial risk of bleeding. An "alternate suction" protocol with suction pressure of –10 cm H_2O during the night and water seal only during daytime appears to be a safe option in such patients. It may decrease AL or chest tube duration in patients without a relevant pneumothorax, progressive

subcutaneous emphysema, or cardiorespiratory deterioration[39]. There is no data regarding the use of suction in COVID-19 patients. While managing COVID-19 patients, if no viral filter is attached to the suction port, the drainage system can be placed on suction with a suction canister, and the medical gas vacuum lines exhaust providing negative pressure.

PREVENTION OF AIR LEAK SYNDROME

As the development of AL is associated with substantial morbidity and mortality, every measure should be taken to prevent AL. If the CT scan demonstrates the Macklin effect, such patients should take extra care to avoid further damage, *e.g.*, avoiding PPV, avoiding high airway pressure, and favoring extracorporeal technologies instead.

Conceptually, HFNC could limit P-SILI risks compared to NIV, but the tidal volume in the former is difficult to monitor. Also, clinicians should be aware that HFNC may be associated with a higher incidence of barotrauma than the standard, low-flow oxygen therapies, which should be preferred if the patient's condition allows.

In patients on IMV, using a lung-protective ventilation strategy by reducing the alveolar pressure and distension reduces the risk of developing pneumothorax. Judicious use of neuromuscular blockers in patients with high airway pressures or those with patient-ventilator dyssynchrony may also reduce the chances of AL by reducing the negative pressure and shear stress in the pleural cavity.

An excessive and insufficient respiratory effort may result in deleterious anatomical and functional modifications of the diaphragm. Thus, if feasible, using lung and diaphragm protective ventilation simulates a normal inspiratory effort, which also benefits early weaning by reducing the sedation requirement. Transposing this notion into clinical practice needs assessment of the patient's inspiratory effort and potentially perilous patient-ventilator interactions, which may be significantly facilitated by oesophageal pressure (Pes) monitoring. If Pes is unavailable, meticulous clinical assessment and analysis of tidal volume, flow, and airway pressure waveforms from the ventilator can help detect situations at risk of P-SILI. Nonetheless, no clinical study has demonstrated improved patient outcomes by limiting P-SILI risk[20,40].

Lastly, timely application of extracorporeal carbon dioxide removal and extracorporeal membrane oxygenation with lung-protective ventilation strategy may play a key role in preventing pneumothorax in critically ill patients with severe ARDS and refractory hypoxemia.

OUTCOME

The overall prognosis of patients with AL is guarded. The development of AL has been associated with a higher need for IMV, prolonged hospitalization, and higher in-hospital mortality[1,9,13]. High mortality rates ranging from 40% to 74% have been reported. Patients with pneumothorax have been reported to have higher mortality than patients with pneumomediastinum. Also, patients developing AL while on PPV may have higher mortality rates[1,3,9,33].

CONCLUSION

As our clinical knowledge of COVID-19 expands, we must recognize that AL is not an uncommon complication of COVID-19. It is likely a sequela of COVID-19 progression resulting from an inflammatory insult and increase in respiratory effort that may foist changes within the lung parenchyma. A high level of clinical suspicion is merited for an early diagnosis as most patients are asymptomatic, and it should be suspected when there is sudden respiratory or hemodynamic deterioration. One should be vigilant when choosing to continue oxygen therapy *via* various oxygen delivery devices in patients with a high respiratory drive, as P-SILI can aggravate the disease progression, especially in patients who have evidence of Macklin effect on CT. Patients with AL may be managed conservatively but under strict observation. ALS is associated with increased morbidity and mortality, especially in the elderly and patients on IMV despite lung-protective ventilation.

FOOTNOTES

Author contributions: Juneja D and Kataria S performed the majority of the writing, prepared the figures and tables, and performed data accusation; Singh O provided the input in writing the paper and reviewed the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

Country/Territory of origin: India

ORCID number: Deven Juneja 0000-0002-8841-5678; Sahil Kataria 0000-0002-0756-4154; Omender Singh 0000-0002-3847-4645.

S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Liu JH

REFERENCES

1 **Nasa P**, Juneja D, Jain R. Air leak with COVID-19 - A meta-summary. *Asian Cardiovasc Thorac Ann* 2022; **30**: 237-244 [PMID: 34247490 DOI: 10.1177/02184923211031134]
2 **Adeyinka A**, Pierre L. Air Leak. 2022 May 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan [PMID: 30020594]
3 **Martinelli AW**, Ingle T, Newman J, Nadeem I, Jackson K, Lane ND, Melhorn J, Davies HE, Rostron AJ, Adeni A, Conroy K, Woznitza N, Matson M, Brill SE, Murray J, Shah A, Naran R, Hare SS, Collas O, Bigham S, Spiro M, Huang MM, Iqbal B, Trenfield S, Ledot S, Desai S, Standing L, Babar J, Mahroof R, Smith I, Lee K, Tchrakian N, Uys S, Ricketts W, Patel ARC, Aujayeb A, Kokosi M, Wilkinson AJK, Marciniak SJ. COVID-19 and pneumothorax: a multicentre retrospective case series. *Eur Respir J* 2020; **56** [PMID: 32907891 DOI: 10.1183/13993003.02697-2020]
4 **Eperjesiova B**, Hart E, Shokr M, Sinha P, Ferguson GT. Spontaneous Pneumomediastinum/Pneumothorax in Patients With COVID-19. *Cureus* 2020; **12**: e8996 [PMID: 32642391 DOI: 10.7759/cureus.8996]
5 **Wadhawa R**, Thakkar A, Chhanwal HS, Bhalotra A, Rana Y, Wadhawa V. Spontaneous pneumomediastinum and subcutaneous emphysema in patients with COVID-19. *Saudi J Anaesth* 2021; **15**: 93-96 [PMID: 34188623 DOI: 10.4103/sja.sja_939_20]
6 **Lew TW**, Kwek TK, Tai D, Earnest A, Loo S, Singh K, Kwan KM, Chan Y, Yim CF, Bek SL, Kor AC, Yap WS, Chelliah YR, Lai YC, Goh SK. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; **290**: 374-380 [PMID: 12865379 DOI: 10.1001/jama.290.3.374]
7 **Peiris JS**, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; **361**: 1767-1772 [PMID: 12781535 DOI: 10.1016/s0140-6736(03)13412-5]
8 **Das KM**, Lee EY, Al Jawder SE, Enani MA, Singh R, Skakni L, Al-Nakshabandi N, AlDossari K, Larsson SG. Acute Middle East Respiratory Syndrome Coronavirus: Temporal Lung Changes Observed on the Chest Radiographs of 55 Patients. *AJR Am J Roentgenol* 2015; **205**: W267-W274 [PMID: 26102309 DOI: 10.2214/AJR.15.14445]
9 **Chong WH**, Saha BK, Hu K, Chopra A. The incidence, clinical characteristics, and outcomes of pneumothorax in hospitalized COVID-19 patients: A systematic review. *Heart Lung* 2021; **50**: 599-608 [PMID: 34087677 DOI: 10.1016/j.hrtlng.2021.04.005]
10 **Lemmers DHL**, Abu Hilal M, Bnà C, Prezioso C, Cavallo E, Nencini N, Crisci S, Fusina F, Natalini G. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? *ERJ Open Res* 2020; **6** [PMID: 33257914 DOI: 10.1183/23120541.00385-2020]
11 **Belletti A**, Palumbo D, Zangrillo A, Fominskiy EV, Franchini S, Dell'Acqua A, Marinosci A, Monti G, Vitali G, Colombo S, Guazzarotti G, Lembo R, Maimeri N, Faustini C, Pennella R, Mushtaq J, Landoni G, Scandroglio AM, Dagna L, De Cobelli F; COVID-BioB Study Group. Predictors of Pneumothorax/Pneumomediastinum in Mechanically Ventilated COVID-19 Patients. *J Cardiothorac Vasc Anesth* 2021; **35**: 3642-3651 [PMID: 33678544 DOI: 10.1053/j.jvca.2021.02.008]
12 **Chu CM**, Leung YY, Hui JY, Hung IF, Chan VL, Leung WS, Law KI, Chan CS, Chan KS, Yuen KY. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. *Eur Respir J* 2004; **23**: 802-804 [PMID: 15218989 DOI: 10.1183/09031936.04.00096404]
13 **Juneja D**, Goel A, Singh O, Kataria S, Gupta A, Singh A. Air Leak In Post COVID-19 Patients: Incidence, ICU Course And Outcomes. *Med Intensiva* 2022 [PMID: 35017767 DOI: 10.1016/j.medin.2021.12.012]
14 **Udwadia ZF**, Toraskar KK, Pinto L, Mullerpatan J, Wagh HD, Mascarenhas JM, Gandhi BM, Tripathi A, Sunavala A, Agrawal U, Nanda V, Abraham N, Francis B, Zore RR, Pundpal G, Gondse B, Gupta GA. Increased frequency of pneumothorax and pneumomediastinum in COVID-19 patients admitted in the ICU: A multicentre study from Mumbai, India. *Clin Med (Lond)* 2021; **21**: e615-e619 [PMID: 34862221 DOI: 10.7861/clinmed.2021-0220]
15 **Miró Ò**, Llorens P, Jiménez S, Piñera P, Burillo-Putze G, Martín A, Martín-Sánchez FJ, García-Lamberetchs EJ, Jacob J, Alquézar-Arbé A, Mòdol JM, López-Díez MP, Guardiola JM, Cardozo C, Lucas Imbernón FJ, Aguirre Tejedo A, García García Á, Ruiz Grinspan M, Llopis Roca F, González Del Castillo J; Spanish Investigators on Emergency Situations Team (SIESTA) Network. Frequency, Risk Factors, Clinical Characteristics, and Outcomes of Spontaneous Pneumothorax in Patients With Coronavirus Disease 2019: A Case-Control, Emergency Medicine-Based Multicenter Study. *Chest* 2021;

159: 1241-1255 [PMID: 33227276 DOI: 10.1016/j.chest.2020.11.013]
16 **Sardu C**, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? *J Clin Med* 2020; **9** [PMID: 32403217 DOI: 10.3390/jcm9051417]
17 **Quinaglia T**, Shabani M, Breder I, Silber HA, Lima JAC, Sposito AC. Coronavirus disease-19: The multi-level, multi-faceted vasculopathy. *Atherosclerosis* 2021; **322**: 39-50 [PMID: 33706082 DOI: 10.1016/j.atherosclerosis.2021.02.009]
18 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]
19 **Iqbal N**, Malik A, Chaudhry M. The Macklin Effect in COVID-19. *Cureus* 2021; **13**: e16949 [PMID: 34513517 DOI: 10.7759/cureus.16949]
20 **Carteaux G**, Parfait M, Combet M, Haudebourg AF, Tuffet S, Mekontso Dessap A. Patient-Self Inflicted Lung Injury: A Practical Review. *J Clin Med* 2021; **10** [PMID: 34205783 DOI: 10.3390/jcm10122738]
21 **Nalewajska M**, Feret W, Wojczyński Ł, Witkiewicz W, Wiśniewska M, Kotfis K. Spontaneous Pneumothorax in COVID-19 Patients Treated with High-Flow Nasal Cannula outside the ICU: A Case Series. *Int J Environ Res Public Health* 2021; **18** [PMID: 33672281 DOI: 10.3390/ijerph18042191]
22 **Adhikary AB**, R U, Patel NB, S VP, Boruah P, Chandrakar S. Spectrum of pneumothorax/pneumomediastinum in patients with coronavirus disease 2019. *Qatar Med J* 2021; **2021**: 41 [PMID: 34604018 DOI: 10.5339/qmj.2021.41]
23 **Shan S**, Guangming L, Wei L, Xuedong Y. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19: case report and literature review. *Rev Inst Med Trop Sao Paulo* 2020; **62**: e76 [PMID: 33053145 DOI: 10.1590/S1678-9946202062076]
24 **Chowdhary A**, Nirwan L, Abi-Ghanem AS, Arif U, Lahori S, Kassab MB, Karout S, Itani RM, Abdalla R, Naffaa L, Karout L. Spontaneous Pneumomediastinum in Patients Diagnosed with COVID-19: A Case Series with Review of Literature. *Acad Radiol* 2021; **28**: 1586-1598 [PMID: 34391638 DOI: 10.1016/j.acra.2021.07.013]
25 **Iyer VN**, Joshi AY, Ryu JH. Spontaneous pneumomediastinum: analysis of 62 consecutive adult patients. *Mayo Clin Proc* 2009; **84**: 417-421 [PMID: 19411438 DOI: 10.1016/S0025-6196(11)60560-0]
26 **Elnaem WH**, Tammam HM, Zidan MA, Mahmoud MI. The relative efficacy of chest ultrasonography in comparison to other diagnostic modalities in the evaluation of dyspneic patient. *Egyptian J Chest Dis Tuber* 2017; 66: 165-168 [DOI: 10.1016/j.ejcdt.2016.12.005]
27 **Reid CL**, Chandraratna AN, Kawanishi D, Bezdek WD, Schatz R, Nanna M, Rahimtoola SH. Echocardiographic detection of pneumomediastinum and pneumopericardium: the air gap sign. *J Am Coll Cardiol* 1983; **1**: 916-921 [PMID: 6826980 DOI: 10.1016/s0735-1097(83)80209-5]
28 **Allgood NL**, Brownlee JR, Green GA. Inability to view the heart through the subxiphoid echocardiographic window: a harbinger of disaster. *Pediatr Cardiol* 1994; **15**: 27-29 [PMID: 8115268 DOI: 10.1007/BF00797002]
29 **Palumbo D**, Zangrillo A, Belletti A, Guazzarotti G, Calvi MR, Guzzo F, Pennella R, Monti G, Gritti C, Marmiere M, Rocchi M, Colombo S, Valsecchi D, Scandroglio AM, Dagna L, Rovere-Querini P, Tresoldi M, Landoni G, De Cobelli F; COVID-BioB Study Group. A radiological predictor for pneumomediastinum/pneumothorax in COVID-19 ARDS patients. *J Crit Care* 2021; **66**: 14-19 [PMID: 34392131 DOI: 10.1016/j.jcrc.2021.07.022]
30 **Cerfolio RJ**, Bryant AS. The quantification of postoperative air leaks. *Multimed Man Cardiothorac Surg* 2009; **2009**: mmcts.2007.003129 [PMID: 24412989 DOI: 10.1510/mmcts.2007.003129]
31 **Lazarus DR**, Casal RF. Persistent air leaks: a review with an emphasis on bronchoscopic management. *J Thorac Dis* 2017; **9**: 4660-4670 [PMID: 29268535 DOI: 10.21037/jtd.2017.10.122]
32 **Kurman JS**. Persistent air leak management in critically ill patients. *J Thorac Dis* 2021; **13**: 5223-5231 [PMID: 34527361 DOI: 10.21037/jtd-2021-32]
33 **Singh A**, Singh Y, Pangasa N, Khanna P, Trikha A. Risk Factors, Clinical Characteristics, and Outcome of Air Leak Syndrome in COVID-19: A Systematic Review. *Indian J Crit Care Med* 2021; **25**: 1434-1445 [PMID: 35027806 DOI: 10.5005/jp-journals-10071-24053]
34 **Kangas-Dick A**, Gazivoda V, Ibrahim M, Sun A, Shaw JP, Brichkov I, Wiesel O. Clinical Characteristics and Outcome of Pneumomediastinum in Patients with COVID-19 Pneumonia. *J Laparoendosc Adv Surg Tech A* 2021; **31**: 273-278 [PMID: 32936034 DOI: 10.1089/lap.2020.0692]
35 **Hallifax R**, Evison M, Wrightson JM, Bibby A, Walker S, Stanton A, Bedawi E, Clive A, Latham J, Blyth K, Jackson S, Marshall K, Maskell N, Bhatnagar R, Corcoran J, Belcher E, Rahman N, Munavvar M. Pleural services during the "COVID-19" Pandemic – Revised. V4.0 13 December 2021. Pleural services during COVID-19 pandemic.pdf. Assessed on 2nd February 2022
36 **Baumann MH**, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, Luketich JD, Panacek EA, Sahn SA; AACP Pneumothorax Consensus Group. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. *Chest* 2001; **119**: 590-602 [PMID: 11171742 DOI: 10.1378/chest.119.2.590]
37 **Havelock T**, Teoh R, Laws D, Gleeson F; BTS Pleural Disease Guideline Group. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010; **65** Suppl 2: ii61-ii76 [PMID: 20696688 DOI: 10.1136/thx.2010.137026]
38 **Saha BK**, Bonnier A, Chong WH, Chenna P. Successful use of endobronchial valve for persistent air leak in a patient with COVID-19 and bullous emphysema. *BMJ Case Rep* 2021; **14** [PMID: 34799393 DOI: 10.1136/bcr-2021-246671]
39 **Porcel JM**. Chest Tube Drainage of the Pleural Space: A Concise Review for Pulmonologists. *Tuberc Respir Dis (Seoul)* 2018; **81**: 106-115 [PMID: 29372629 DOI: 10.4046/trd.2017.0107]
40 **Goligher EC**, Jonkman AH, Dianti J, Vaporidi K, Beitler JR, Patel BK, Yoshida T, Jaber S, Dres M, Mauri T, Bellani G, Demoule A, Brochard L, Heunks L. Clinical strategies for implementing lung and diaphragm-protective ventilation: avoiding insufficient and excessive effort. *Intensive Care Med* 2020; **46**: 2314-2326 [PMID: 33140181 DOI: 10.1007/s00134-020-06288-9]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 186-197

DOI: 10.5501/wjv.v11.i4.186

ISSN 2220-3249 (online)

SYSTEMATIC REVIEWS

COVID-19 pandemic effects on the distribution of healthcare services in India: A systematic review

Nirav Nimavat, Mohammad Mehedi Hasan, Sundip Charmode, Gowthamm Mandala, Ghanshyam R Parmar, Ranvir Bhangu, Israr Khan, Shruti Singh, Amit Agrawal, Ashish Shah, Vishi Sachdeva

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Munteanu C, Romania; Papadopoulos K, Thailand; Wang TJ, China; Wang TJ, China

A-Editor: Wang MK, China

Received: December 28, 2021
Peer-review started: December 28, 2021
First decision: February 8, 2022
Revised: February 19, 2022
Accepted: June 26, 2022
Article in press: June 26, 2022
Published online: July 25, 2022

Nirav Nimavat, Department of Community Medicine, Dr. Kiran C Patel Medical College and Research Institute, Bharuch 392001, India

Mohammad Mehedi Hasan, Department of Biochemistry and Molecular Biology, Mawlana Bhashani Science and Technology University, Tangail 1902, Bangladesh

Sundip Charmode, Department of Anatomy, All India Institute of Medical Sciences, Rajkot 360006, Gujarat, India

Gowthamm Mandala, Independent Researcher, Centre Groove High School, Greenwood, IN 46143, United States

Ghanshyam R Parmar, Ashish Shah, Department of Pharmacy, Sumandeep Vidyapeeth, Vadodara 391760, India

Ranvir Bhangu, Department of Medical, Caribbean Medical University, Des Plaines, IL 60018, United States

Israr Khan, Shifa International Hospital, Islamabad 999010, Pakistan

Shruti Singh, Department of Pharmacology, All India Institute of Medical Sciences, Patna 801507, India

Amit Agrawal, Department of Paediatrics, Gandhi Medical College, Bhopal 462001, India

Vishi Sachdeva, Department of Medical, Adesh Institute of Medical Sciences and Research, Bathinda 151009, India

Corresponding author: Nirav Nimavat, MD, Assistant Professor, Department of Community Medicine, Dr. Kiran C Patel Medical College and Research Institute, New Civil Hospital Campus, Bharuch 392001, India. nkniraj1529@gmail.com

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has brought fundamental changes to our problems and priorities, especially those related to the healthcare sector. India was one of the countries severely affected by the harsh consequences of the COVID-19 pandemic.

AIM
To understand the challenges faced by the healthcare system during a pandemic.

METHODS
The literature search for this review was conducted using PubMed, EMBASE, Scopus, Web of Science, and Google Scholar. We also used Reference Citation Analysis (RCA) to search and improve the results. We focused on the published scientific articles concerned with two major vital areas: (1) The Indian healthcare system; and (2) COVID-19 pandemic effects on the Indian healthcare system.

RESULTS
The Indian healthcare system was suffering even before the pandemic. The pandemic has further stretched the healthcare services in India. The main obstacle in the healthcare system was to combat the rising number of communicable as well as noncommunicable diseases. Besides the pandemic measures, there was a diversion of focus of the already established healthcare services away from the chronic conditions and vaccinations. The disruption of the vaccination services may have more severe short and long-term consequences than the pandemic's adverse effects.

CONCLUSION
Severely restricted resources limited the interaction of the Indian healthcare system with the COVID-19 pandemic. Re-establishment of primary healthcare services, maternal and child health services, noncommunicable diseases programs, National Tuberculosis Elimination Program, *etc.* are important to prevent serious long-term consequences of this pandemic.

Key Words: COVID-19; Healthcare system; Pandemic; India; Healthcare services

Core Tip: The interaction of the Indian healthcare system with the coronavirus disease 2019 pandemic was limited by restricted resources. Lack of infrastructure, low percentage of gross domestic product expenditure on health, and deficiency of skilled manpower play a critical role in the healthcare system to manage infectious diseases, noncommunicable diseases and maternal and child health services.

Citation: Nimavat N, Hasan MM, Charmode S, Mandala G, Parmar GR, Bhangu R, Khan I, Singh S, Agrawal A, Shah A, Sachdeva V. COVID-19 pandemic effects on the distribution of healthcare services in India: A systematic review. *World J Virol* 2022; 11(4): 186-197
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/186.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.186

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, since its start at the end of 2019 in Wuhan, China, has changed the face of our planet. The pandemic affects almost every detail in our daily life, from dietary consumption to education and obviously to healthcare utilization, the primary sector affected by the pandemic[1]. The evolution of the pandemic has created extra challenges to the different healthcare sectors across the world, either those dealing with patients directly or those responsible for logistic supplies to the healthcare facilities[2]. The healthcare sectors in the developing countries were especially affected, suffering from the limited public health infrastructure and medical supplies even before the pandemic[3-5]. In India alone, COVID-19 infected > 10 million citizens, and > 45000 had died by the end of September 2021, and the number is increasing every day[6].

The strain and fast changes created by the pandemic have put the Indian healthcare services in an impending collapse due to the destructive waves of the pandemic[7]. Before the pandemic, the Indian healthcare services were struggling to meet the primary healthcare (PHC) demands of the public affected by a variety of communicable diseases and noncommunicable diseases (NCDs)[8]. Besides COVID-19, other medical conditions with a public health concern like acquired immune deficiency syndrome, tuberculosis (TB), and malaria outbreaks continue to pose a strain on the healthcare services and continuous monitoring is required to detect and manage these conditions at an early stage[9]. Also, NCDs are now the leading cause of death in India, accounting for about 60% of all deaths across the country[10]. The emergence of the COVID-19 pandemic at the end of 2019 has forced many secondary and tertiary healthcare centers designated to receive millions of daily patients to be dedicated only for

COVID-19 presumptive cases. These effects have created a huge gap in the provision of healthcare services in managing chronic cases[11].

A recent multicenter survey conducted by Raman *et al*[12] has demonstrated that the COVID-19 pandemic has a significant negative effect on healthcare providers with an exaggerated feeling of inadequacy: [odds ratio (OR) = 3.015], inappropriateness: (OR = 2.225), and discontinuity of care: (OR = 6.756) together with associated depression and social loneliness. India, which was already suffering from an unacceptably high maternal mortality rate of 41.4 per 1000 live births in 2013, developed a significant interruption in the maternal and child health services during the pandemic[13,14]. This negative effect has extended to almost all established maternal/child healthcare services, including antenatal care and immunization services. For instance, some regions have demonstrated a decrease in institutional deliveries by about 2.26%. Antenatal health services were badly affected, with a decline estimated to be 22.9%[15]. Prenatal care visits in China have dropped, healthcare infrastructure has been stretched, and possibly damaging practices have been introduced with insufficient proof[16]. Garg *et al* [15] has demonstrated that PHC services were severely disrupted. They have also surveyed the readiness of PHCs across India and demonstrated a severe shortage in infection control measures, *i.e.*, infection prevention and control. Twenty-nine of 51 participating PHCs had inadequate ventilation in the workplace, while NK95 masks were available only in half of the centers[15,17]. During the pandemic in Australia, healthcare utilization fell by roughly a third, with significant variance, and with more considerable decreases among persons with less severe disease[18].

This narrative review discusses the different factors associated with the unavailability of resources in healthcare facilities during the COVID-19 pandemic in India. We also highlight how the deficiency of PHC services may contribute to the sustainability of the COVID-19 pandemic in India.

MATERIALS AND METHODS

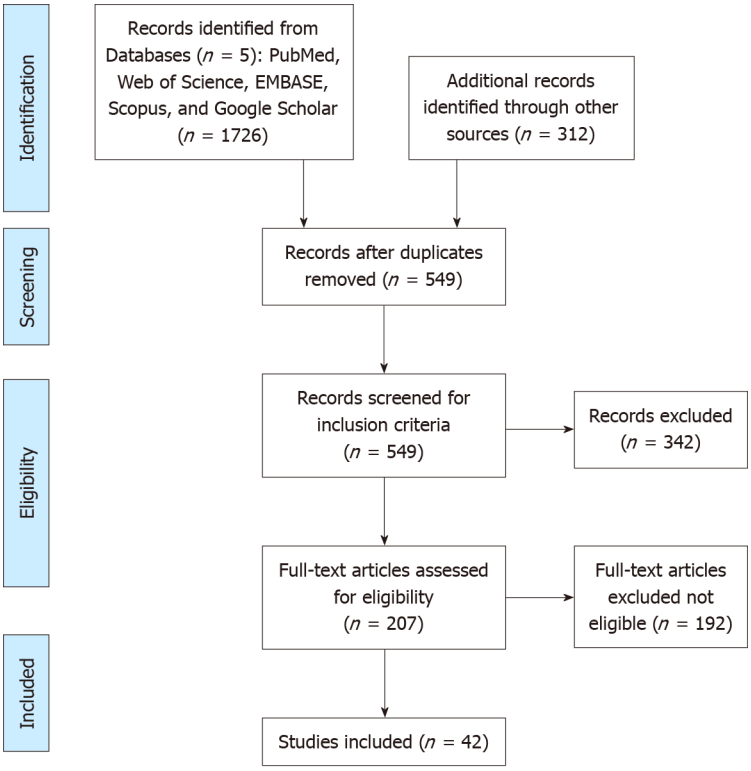
The review was carried out through the following methodological steps (Figure 1). Different search terms related to the Indian healthcare system formulated two health strategies. The first health strategy was used to target the characteristics of the Indian healthcare system before the pandemic together with its associated challenges, which include: ((((("India"[Mesh]) AND "Delivery of Health Care"[Mesh]) OR "Community Health Planning"[Mesh]) OR "Health Services"[Mesh]) AND "Epidemiology"[Mesh]. The second health strategy was centered on the Indian healthcare system and health situation during the pandemic using the following terms ((("India"[Mesh]) OR ("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh])) AND "Delivery of Health Care"[Mesh]) OR "Delivery of Health Care, Integrated"[Mesh]. PubMed, EMBASE, Scopus, Reference Citation Analysis (RCA), Web of Science, and Google Scholar were used to search the related literature. We also employed Reference Citation Analysis, an open multiple disciplines citation analysis database powered by artificial intelligence technologies. All of the papers were stacked and screened initially by title to categorize the papers into eligible or noneligible. Eligible literature was further screened using full text to exclude any irrelevant information. References of the relevant studies were also screened to track any missed helpful literature. The above methodology was consistent with the previously reported methodology of narrative reviews studies.

RESULTS

The healthcare situation in India before the pandemic

India has a large and diverse healthcare system that suits the cultural diversity of the community[5]. The healthcare system in India was initially built to ensure that all citizens have access to essential healthcare services regardless of their socioeconomic status[19]. However, the ambitious healthcare system plans were not associated with considerable funds from the governmental agencies. In 2015, India spent only 1.2% of its gross domestic product (GDP) on health, considered among the lowest in the world[20]. The inadequacy of government healthcare services has resulted in the simultaneous evolution of the private health sector[21]. Subsequently, India has one of the highest proportions of household out-of-pocket expenditures on health globally, estimated at 71.1% in 2008-2009[22]. In addition, India has the lowest doctor-patient ratios as it has one doctor for 1000 and a specialist for every 1445 people[23]. The low healthcare expenditure in India had a severe negative impact on health status even before the COVID-19 pandemic. The pandemic further stretched the fragile nonimmune Indian healthcare system, leading to a collapse in providing healthcare services in order to contain COVID-19.

Among its 1.3 billion citizens, NCDs are responsible for 5.78 million (60%) of all deaths in India each year. The significant NCD-related deaths are usually attributed to cardiovascular disease, cancer and diabetes[24]. The rising NCD trend is a common phenomenon seen in developing countries where rapid urbanization leads to an overall economic improvement and has considerable adverse effects on public health[25]. The Indian health system has adopted multiple changes aiming to bring down NCD-related



DOI: 10.5501/wjv.v11.i4.186

Figure 1 PRISMA flowchart.

mortality by < 25% by 2025[26]. Although some progress has been achieved in decreasing tobacco and alcohol consumption, an increasing trend was found for overweight and obesity among Indian adults aged 15-49 years[24]. Reddy and Kar[26] have demonstrated that the Indian Government's efforts were insufficient to achieve its ambitious targets by 2025, even before the pandemic.

Since the start of the epidemiological transition in 1970, there have been significant changes in the pattern of different diseases across every state in India[27]. Omran's theory[28,29] describes the epidemiological transition as a shift in the causes of morbidity and mortality, primarily from infectious diseases to NCDs. However, the situation was different in India, where the burden of NCDs has been added to the burden of infectious disease, resulting in a double burden on the undeveloped Indian healthcare system[27,30]. In India, the epidemiological transition has led to the development of a new theory based on the concept of the double burden of both infectious diseases and NCDs[31]. The burden of communicable diseases has declined from 47.7% to only 22.1% between 1970 to the mid-1990s[31].

Even after 40 years from the start of the epidemiological transition in 2011, infectious diseases still pose a challenge to the Indian health system and account for about 30% of the disease burden[32]. It was estimated that an Indian citizen had a 15 times greater burden of infectious diseases than United Kingdom citizens in 2004 and that about 30% of the disease burden in India is attributable to infections [32]. The lack of strong staple public healthcare infrastructure has contributed largely to stagnation of the infectious disease burden in addition to the burden of NCDs[30,32]. For instance, in 2009, India recorded about 2 million new cases of TB, which is considered one of the highest incidences globally [32]. After 10 years in 2019, India reported about 2.9 million new cases of TB, contributing to about 27% of all TB cases worldwide[33]. However, India started its TB control program early, in 1960, but failed to significantly reduce the incidence of new TB cases compared to other countries with similar epidemiological transitions[34,35]. Concerns have been raised about the spread of TB and NCDs, specifically, diabetes mellitus, which are associated with a more fulminant course of TB[36,37].

Besides TB, multiple endemic infections affect Indian cities and states, such as cutaneous anthrax, dengue fever, malaria, cholera and viral hepatitis (A and B)[38-43]. Some of these infections are substantially preventable by vaccines[44]. Unfortunately, India contributes to about 10% of 20 million unimmunized and partially immunized populations[45]. Additionally, India is considered to have one of the largest rates of endemic hepatitis B, with the second largest burden of chronic hepatitis B, with > 50 million cases[46]. Despite being integrated into the Indian National Immunization Program in 2011, about 23.2% of children aged 5–8 years were vaccinated against hepatitis B virus[47]. Different causes have been proposed behind the low vaccination coverage of hepatitis in India; for instance, major causes are related to the poor management of the available health resources such as poor record-keeping, improper management of vaccine stocks and lack of inventory control, lack of staff training, and use of multidose vials. Strikingly, healthcare workers have been reported to be reluctant to open a vial of the

vaccine when there are a few children to be vaccinated for fear of wastage[48]. It is well noted that even before the COVID-19 pandemic, India's healthcare system was strained between the pre-existing communicable disease challenges and the evolving NCD pattern created by the epidemiological transition. All of the above challenges are further aggravated by the limited Government funds allocated to developing the healthcare system (Figure 2).

DISCUSSION

COVID-19 situation in India

The number of people infected with COVID-19 has exceeded 9 million since the report of the first cases in the state of Kerala on January 30, 2020[1,6]. Following this, the country has witnessed a drastic increase in the total number of reported cases. The recovery rate across India was 80.83% as of September 22, 2020, with a case fatality rate of 2.82% as of June 1, 2020[49]. The development of the pandemic has primarily affected the rapidly developing Indian economy with shrinkage of the GDP by about 23.9% in April-June 2020[50]. Today, Indian citizens continue to be frightened into compliance and are afraid to restart their lives normally. Although many states of India have flattened their COVID-19 infection curve, authorities across the nation are now in fear from the onset of other subsequent waves of the COVID-19 pandemic secondary to a decreased commitment of health directives of taking precautionary measures, *i.e.*, social distancing and wearing face masks. Government authorities have advised citizens to take precautionary measures like social distancing and wearing masks during public gatherings. Furthermore, a few states, such as Maharashtra, Rajasthan and Gujarat, have introduced new restrictions such as travel restrictions and night curfew to battle the subsequent waves of the COVID-19 pandemic[50].

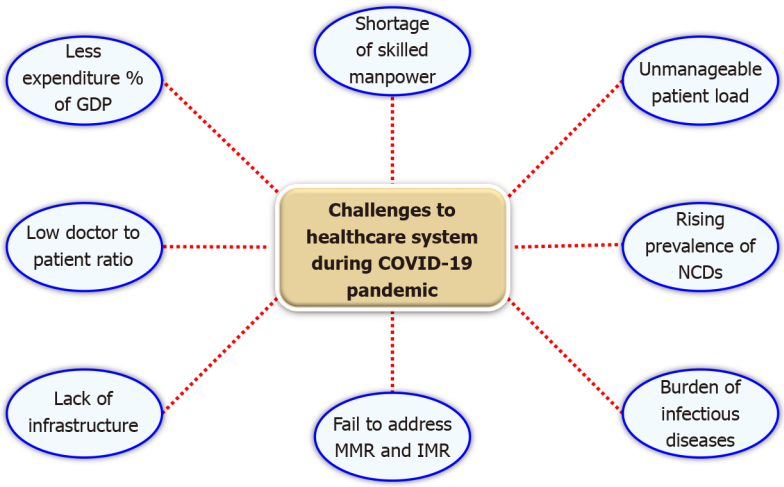
Lack of health resources to fight the COVID-19 pandemic

In India, besides the chronic shortage of healthcare workers, there were significant deficiencies in different domains of healthcare services and their logistic determinants[51]. For instance, healthcare facilities have severe deficiencies in infection control measures, *i.e.*, advance infection prevention and control facilities to contain infected patients and prevent the spread of COVID-19. In 2010, the Indian Government adopted national guidelines on airborne infection control in healthcare facilities with a special focus on preventing TB transmission[52]. Five years later, a baseline survey of healthcare facilities has demonstrated poor adherence to infection control measures aimed to control airborne infection[53]. Multiple studies have demonstrated several loopholes in the infection control policy, including insufficient training of staff, unavailability of protective masks, poor compliance to personal protective practices by health workers, *i.e.*, proper use and disposal of personal protective equipment (PPE) and other control measures, inadequate disinfection, and sterilization of equipment, lack of health workers surveillance, lack of counseling of cough etiquette and sputum disposal at registration of hospitals[54-56].

In 2020, Indian health authorities recently updated the comprehensive national guidelines for infection control[51]. However, infection control measures across different PHC centers in Indian districts were grossly deficient, especially related to airborne infection[15]. The shortage was limited to the infection control measures, but it further extended to the PPE intended to protect the workforce from infection during the COVID-19 pandemic. It is reported that there is a persistent dearth of PPE in two private hospitals in Mumbai[57]. Reports from different areas across India have reported that doctors treat patients suspected of severe acute respiratory syndrome coronavirus 2 infection without masks or with less-protective surgical masks instead of recommended NK95 masks for healthcare providers[58]. Unfortunately, the shortage of PPE and high demands have forced healthcare workers to reuse or extend the use of PPE, which increases their risk of COVID-19[59]. The above behavior, despite being expected, highlights a lack of proper knowledge and training regarding infection control measures, usage of PPE, and their proper disposal. In fact, it is one of the rights of healthcare workers to be adequately trained before exposure to COVID-19 patients[60]. The lack of essential training of healthcare workers has been reported in several South Asian countries, including India[61]. Multiple studies have highlighted suboptimal knowledge and practice regarding infection control measures across Indian health workers[62,63]. Raj *et al*[54] have reported that only less than half of the healthcare workers of Kerala, India, were trained on proper infection control practices.

COVID-19 pandemic and provision of childhood and maternal healthcare services

The growing distribution of the pandemic across different countries has delayed or even stopped the basic childhood vaccination programs as a response to the lockdown or the stretching of the healthcare resources as a response to the COVID-19 pandemic[64]. The World Health Organization (WHO) has reported that > 80 million children did not receive routine vaccination globally[65]. This may have serious long-term consequences even more than COVID-19 itself. For instance, the evolution of the Ebola outbreak in Africa resulted in halting multiple essential healthcare services, which increased mortality related to several other infections, including TB, human immunodeficiency virus, and measles



DOI: 10.5501/wjv.v11.i4.186

Figure 2 Challenges faced by healthcare system during coronavirus disease 2019 pandemic. COVID-19: Coronavirus disease 2019; GDP: Gross domestic product; NCDs: Non-communicable diseases; IMR: Infant mortality rate; MMR: Maternal mortality ratio.

which have exceeded the mortality rate from Ebola[66].

In India, the evolution of the pandemic has initially enforced complete stoppage of the whole childhood vaccination programs secondary to the major lockdown. It was estimated that about 27 million children missed diphtheria tetanus pertussis, resulting in a 40% increase in mortality in the next year. It has also been estimated that there is an expected 49000 child deaths and 2300 maternal deaths within a month if the PHC services continue to be disrupted[67,68]. As a response, the Indian Government has approved the continuation of the vaccination services and consider it an essential health service[69]. The resumption of the immunization activities was based on the WHO guidelines to minimize both morbidity and mortality from other diseases[70,71].

Maternal healthcare services have also been severely affected by the development of the pandemic. Globally, healthcare services have restricted pregnant women's access to healthcare facilities for fear of virus transmission and the unknown adverse effects on the newborn, considering the Zika virus in the background[72,73]. The Health and Family Welfare Ministry has declared pregnant women as high risk during the COVID-19 pandemic and provides guidelines to provide essential maternal healthcare services to pregnant women, including the suspected and confirmed cases of COVID-19[74]. Goyal *et al* [75] have demonstrated a 45.1% decline in deliveries during the pandemic at their center. They have also noticed a surge in the number of high-risk pregnancies to about 7.2%. Additionally, more than one-third of women had no or inadequate prenatal visits, with more than half of them mentioning the lockdown as a cause of inadequacy of antenatal care.

Effects of COVID-19 pandemic on management of patients with chronic diseases

Since reporting the first case of COVID-19, patients with chronic disease have had significant difficulties accessing their routine healthcare services worldwide[76]. The presence of chronic conditions like chronic kidney disease, cardiovascular disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and malignancy in a patient with COVID-19 has been tied to poorer outcome with about 10-fold higher risk than those without associated comorbidity[77,78]. WHO has reported that half of 163 countries have attempted partial or complete disruption of healthcare services for hypertension, diabetes mellitus, and related complications during the pandemic. Additionally, one-third of the countries have reported disruption of healthcare services designated for cardiovascular emergencies [79].

Low- and middle-income countries have sustained considerable difficulty in assuring access to healthcare services to patients with chronic conditions compared with western countries[80]. Pati *et al* [81] conducted a community-based study in Odisha, India, and found that 43% of the patients with comorbid conditions have reported difficulty in accessing healthcare services. They have also reported that the most challenging problem was the physician consultation, accounting for 43% of cases. Another telephone-based survey targeting more than 1000 chronic patients reported that > 80% of the participants found it challenging to access healthcare services, and 17% of the participants found it difficult to obtain their medications. The same study also reported that > 50% of the participants reported a loss of income, and 38% had completely lost their jobs[82]. These clear negative impacts have forced health authorities to search for more cost-effective approaches to continue healthcare services to those patients with chronic medical conditions.

Telemedicine is defined by the WHO as the delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for the diagnosis, treatment and prevention of disease and injuries, research, and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities[83]. Before the COVID-19 pandemic, India had a few worthy examples of telemedicine models, including mammography services at Sri Ganga Ram Hospital, Delhi, and oncology at Regional Cancer Center, Trivandrum[84,85]. During the COVID-19 pandemic, the contribution of telemedicine in healthcare management has been highlighted. Kumar *et al*[86] reported that 71.43% of the orthopedic patients were managed without needing any physical visits to the outpatient clinics. Additionally, they have reported that 92% of the patients were satisfied with the telemedicine intervention.

Health-centered solutions learned from the COVID-19 pandemic

The catastrophic health expenditure of < 2% of GDP in India must be increased at least to meet the expenditures of the surrounding developing Asian countries[87]. The COVID-19 pandemic has indicated that dependence on the private healthcare sector, assuming that an increase in the overall income of the individuals can cover their health expenditures, cannot be a good approach to healthcare management[88]. India also needs to establish a national stock level of PPE and other essential medical supplies like ventilators together with an efficient network to monitor and deliver upon need[89]. Learning from other Asian neighbors, both Taiwan and Singapore have established a similar network of PPE management which proved to be critical and efficient in the PPE management during the pandemic [90,91].

Establishing national manufacturing units is also essential to maintain an adequate supply to the Indian hospitals and other healthcare facilities even at times of global catastrophes. The enhancement of local manufacturing on a mass scale should be essentially accompanied by maintaining the ban of PPE exportation[89,92]. Together with providing adequate equipment to fight the pandemic, there is an impending need to enhance and maintain the training of healthcare workers regarding critical topics like infection control practices[93]. Diwan *et al*[94] have reported that attending training sessions have significantly impacted and improved hand hygiene among healthcare workers in rural India. In adjacent countries/territory like Singapore, Japan and Hong Kong, a high level of readiness of healthcare workers has played a critical role in early controlling the pandemic[95].

Besides empowering the healthcare system, it is also essential to engage the healthcare professionals in decision-making to avoid collateral, sometimes fatal, damage of halting essential services like vaccination and maternal healthcare services even for a short period. Establishing and empowering telemedicine is another crucial lesson that should be considered in the future. Integration of telemedicine even after the pandemic should be encouraged and continue as it has proved to be effective in the diagnosis, management of chronic disease, and guiding the treatment for different medical conditions in a cost-effective way[96,97].

RCA was used in this manuscript to improve the results and highlights[98].

CONCLUSION

During the COVID-19 pandemic, India's healthcare system is overstretched in terms of resources, with all essential healthcare services, including maternal and child healthcare services, jeopardized. India needs to increase the investment and proportion of GDP in developing and improving its universal healthcare system to accommodate future pandemics/disasters or outbreaks. Intersectorial coordination and partnership with private entities, at a fast pace, are needed to meet the demands of the healthcare delivery system and provide universal standard healthcare to every citizen of India.

ARTICLE HIGHLIGHTS

Research background

India was one of the countries worst hit by the devastating effects of the coronavirus disease 2019 (COVID-19) pandemic. The healthcare system was unable to manage the situation.

Research motivation

The underperformed healthcare system during the pandemic exposed the crisis.

Research objectives

To identify the challenges faced by the Indian healthcare system during the pandemic.

Research methods

The review was conducted using a literature search from the database of PubMed, Web of Science, EMBASE, Scopus, *etc*. The main focus was on the Indian healthcare system and the impact of a pandemic.

Research results

The Indian healthcare system was already under pressure before the pandemic. The overburden of patients and essential health services were not handled efficiently. Many healthcare facilities were lacking the basic standards of patient care. The vaccination and chronic disease services were hampered due to the shifting of focus to COVID-19.

Research conclusions

Universal Health Coverage should be provided to each person. Increase in percentage expenditure of gross domestic product for the health sector, escalate infrastructure development, and increment of skilled manpower required.

Research perspectives

To meet the incremental demand in health care services during and after the pandemic, India needs to invest more in this sector with a goal of Universal Health Coverage.

FOOTNOTES

Author contributions: Nimavat N, Hasan MM and Charmode S contributed to the study conception and design; Nimavat N, Hasan MM, Charmode S, Mandala G, Parmar GR and Bhangu R search the databases for literature and prepared the manuscript; Nimavat N, Khan I, Singh S, Agarwal A, Shah A and Sachdeva V prepared the final draft of the manuscript; all authors have read the final version of the manuscript and approved it.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: India

ORCID number: Nirav Nimavat 0000-0003-4654-0910; Mohammad Mehedi Hasan 0000-0002-3871-889X; Sundip Charmode 0000-0002-0881-352X; Gowthamm Mandala 0000-0002-3355-0872; Ghanshyam R Parmar 0000-0002-4614-9797; Ranvir Bhangu 0000-0001-6620-2869; Israr Khan 0000-0002-9448-1137; Shruti Singh 0000-0003-3072-4686; Amit Agrawal 0000-0001-6316-6700; Ashish Shah 0000-0003-0817-5940; Vishi Sachdeva 0000-0002-3193-424X.

S-Editor: Gao CC
L-Editor: Kerr C
P-Editor: Gao CC

REFERENCES

1 **Kumar SU**, Kumar DT, Christopher BP, Doss CGP. The Rise and Impact of COVID-19 in India. *Front Med (Lausanne)* 2020; **7**: 250 [PMID: 32574338 DOI: 10.3389/fmed.2020.00250]
2 **Barach P**, Fisher SD, Adams MJ, Burstein GR, Brophy PD, Kuo DZ, Lipshultz SE. Disruption of healthcare: Will the COVID pandemic worsen non-COVID outcomes and disease outbreaks? *Prog Pediatr Cardiol* 2020; **59**: 101254 [PMID: 32837144 DOI: 10.1016/j.ppedcard.2020.101254]
3 **Blanchet K**, Alwan A, Antoine C, Cros MJ, Feroz F, Amsalu Guracha T, Haaland O, Hailu A, Hangoma P, Jamison D, Memirie ST, Miljeteig I, Jan Naeem A, Nam SL, Norheim OF, Verguet S, Watkins D, Johansson KA. Protecting essential health services in low-income and middle-income countries and humanitarian settings while responding to the COVID-19 pandemic. *BMJ Glob Health* 2020; **5** [PMID: 33028701 DOI: 10.1136/bmjgh-2020-003675]
4 **Gilbert M**, Pullano G, Pinotti F, Valdano E, Poletto C, Boëlle PY, D'Ortenzio E, Yazdanpanah Y, Eholie SP, Altmann M, Gutierrez B, Kraemer MUG, Colizza V. Preparedness and vulnerability of African countries against importations of COVID-19: a modelling study. *Lancet* 2020; **395**: 871-877 [PMID: 32087820 DOI: 10.1016/S0140-6736(20)30411-6]

5 **Zodpey SP**, Negandhi HN. Training in clinical research in India: potential and challenges. *Indian J Community Med* 2009; **34**: 173-174 [PMID: 20049290 DOI: 10.4103/0970-0218.55267]

6 **World Health Organization**. WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard. [cited 17 Jan 2022]. In: World Health Organization [Internet]. Available from: https://covid19.who.int/

7 **Williams OD**. COVID-19 and Private Health: Market and Governance Failure. *Development (Rome)* 2020; **63**: 181-190 [PMID: 33223765 DOI: 10.1057/s41301-020-00273-x]

8 **Dikid T**, Jain SK, Sharma A, Kumar A, Narain JP. Emerging & re-emerging infections in India: an overview. *Indian J Med Res* 2013; **138**: 19-31 [PMID: 24056553]

9 **Narain JP**. Public Health Challenges in India: Seizing the Opportunities. *Indian J Community Med* 2016; **41**: 85-88 [PMID: 27051080 DOI: 10.4103/0970-0218.177507]

10 **Narain JP**, Kumar R. Textbook of chronic noncommunicable diseases: the health challenge of 21st century. [cited 17 Jan 2022]. In: Jaypee Digital [Internet]. Available from: https://www.jaypeedigital.com/book/9789352500437

11 **Basu S**. Non-communicable disease management in vulnerable patients during Covid-19. *Indian J Med Ethics* 2020; **V**: 103-105 [PMID: 32393447 DOI: 10.20529/IJME.2020.041]

12 **Raman R**, Rajalakshmi R, Surya J, Ramakrishnan R, Sivaprasad S, Conroy D, Thethi JP, Mohan V, Netuveli G. Impact on health and provision of healthcare services during the COVID-19 Lockdown in India: a multicentre cross-sectional study. *BMJ Open* 2021; **11**: e043590 [PMID: 33468529 DOI: 10.1136/bmjopen-2020-043590]

13 **Singh AK**, Jain PK, Singh NP, Kumar S, Bajpai PK, Singh S, Jha M. Impact of COVID-19 pandemic on maternal and child health services in Uttar Pradesh, India. *J Family Med Prim Care* 2021; **10**: 509-513 [PMID: 34017779 DOI: 10.4103/jfmpc.jfmpc_1550_20]

14 **World Health Organization**. World Health Statistics. [cited 14 Oct 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/data/gho/publications/world-health-statistics

15 **Garg S**, Basu S, Rustagi R, Borle A. Primary Health Care Facility Preparedness for Outpatient Service Provision During the COVID-19 Pandemic in India: Cross-Sectional Study. *JMIR Public Health Surveill* 2020; **6**: e19927 [PMID: 32452819 DOI: 10.2196/19927]

16 **Kotlar B**, Gerson E, Petrillo S, Langer A, Tiemeier H. The impact of the COVID-19 pandemic on maternal and perinatal health: a scoping review. *Reprod Health* 2021; **18**: 10 [PMID: 33461593 DOI: 10.1186/s12978-021-01070-6]

17 **Poojary SA**, Bagadia JD. Reviewing literature for research: Doing it the right way. *Indian J Sex Transm Dis AIDS* 2014; **35**: 85-91 [PMID: 26396439 DOI: 10.4103/0253-7184.142387]

18 **Moynihan R**, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, Jones M, Kitchener E, Fox M, Johansson M, Lang E, Duggan A, Scott I, Albarqouni L. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. *BMJ Open* 2021; **11**: e045343 [PMID: 33727273 DOI: 10.1136/bmjopen-2020-045343]

19 **Chokshi M**, Patil B, Khanna R, Neogi SB, Sharma J, Paul VK, Zodpey S. Health systems in India. *J Perinatol* 2016; **36**: S9-S12 [PMID: 27924110 DOI: 10.1038/jp.2016.184]

20 **Golechha M**. Healthcare agenda for the Indian government. *Indian J Med Res* 2015; **141**: 151-153 [PMID: 25900948 DOI: 10.4103/0971-5916.155541]

21 **Peters DH**, Rao KS, Fryatt R. Lumping and splitting: the health policy agenda in India. *Health Policy Plan* 2003; **18**: 249-260 [PMID: 12917266 DOI: 10.1093/heapol/czg031]

22 **Balarajan Y**, Selvaraj S, Subramanian SV. Health care and equity in India. *Lancet* 2011; **377**: 505-515 [PMID: 21227492 DOI: 10.1016/S0140-6736(10)61894-6]

23 **Sageena G**, Sharma M, Kapur A. Evolution of Smart Healthcare: Telemedicine During COVID-19 Pandemic. *J Inst Eng Ser B* 2021; **102**: 1319-1324 [DOI: 10.1007/s40031-021-00568-8]

24 **Nethan S**, Sinha D, Mehrotra R. Non Communicable Disease Risk Factors and their Trends in India. *Asian Pac J Cancer Prev* 2017; **18**: 2005-2010 [PMID: 28749643 DOI: 10.22034/APJCP.2017.18.7.2005]

25 **Chakma JK**, Gupta S. Lifestyle and Non-Communicable Diseases: A double edged sword for future India. *Ind J Comm Heal* 2014; **26**: 325-332 [DOI: 10.1201/9781315368511-8]

26 **Reddy MM**, Kar SS. Unconditional probability of dying and age-specific mortality rate because of major non-communicable diseases in India: Time trends from 2001 to 2013. *J Postgrad Med* 2019; **65**: 11-17 [PMID: 29943745 DOI: 10.4103/jpgm.JPGM_529_17]

27 **Yadav S**, Arokiasamy P. Understanding epidemiological transition in India. *Glob Health Action* 2014; **7**: 23248 [PMID: 24848651 DOI: 10.3402/gha.v7.23248]

28 **Omran AR**. The epidemiologic transition: a theory of the epidemiology of population change. 1971. *Milbank Q* 2005; **83**: 731-757 [PMID: 16279965 DOI: 10.1111/j.1468-0009.2005.00398.x]

29 **Omran AR**. The epidemiologic transition theory. A preliminary update. *J Trop Pediatr* 1983; **29**: 305-316 [PMID: 6672237 DOI: 10.1093/tropej/29.6.305]

30 **Banerjee K**, Dwivedi LK. The burden of infectious and cardiovascular diseases in India from 2004 to 2014. *Epidemiol Health* 2016; **38**: e2016057 [PMID: 28092932 DOI: 10.4178/epih.e2016057]

31 **Dyson T**. India's population - the future. In: Dyson T, Cassen R, Visaria L. Twenty-First Century India: Population, Economy, Human Development, and the Environment. RePEc, 2004: 74-107

32 **John TJ**, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. *Lancet* 2011; **377**: 252-269 [PMID: 21227500 DOI: 10.1016/S0140-6736(10)61265-2]

33 **Wares DF**. Report on the review of Programmatic management of drug-resistant tuberculosis (PMDT) component of the Revised. *Natl TB Control Program* 2017 [DOI: 10.1111/resp.13206_153]

34 **Mahadev B**, Kumar P. History of tuberculosis control in India. *J Indian Med Assoc* 2003; **101**: 142-143 [PMID: 14603956]

35 **Pai M**, Bhaumik S, Bhuyan SS. India's plan to eliminate tuberculosis by 2025: converting rhetoric into reality. *BMJ Glob Health* 2016; **2**: e000326 [PMID: 28589035 DOI: 10.1136/bmjgh-2017-000326]

36 **Restrepo BI**. Diabetes and Tuberculosis. *Microbiol Spectr* 2016; **4** [PMID: 28084206 DOI: 10.1128/microbiolspec.TNMI7-0023-2016]

37 **Martinez N**, Kornfeld H. Tuberculosis and diabetes: from bench to bedside and back. *Int J Tuberc Lung Dis* 2019; **23**: 669-677 [PMID: 31315698 DOI: 10.5588/ijtld.18.0805]

38 **Bhavsar A**, Tam CC, Garg S, Jammy GR, Taurel AF, Chong SN, Nealon J. Estimated dengue force of infection and burden of primary infections among Indian children. *BMC Public Health* 2019; **19**: 1116 [PMID: 31412836 DOI: 10.1186/s12889-019-7432-7]

39 Meeting of the Strategic Advisory Group of Experts on immunization, October 2009 - conclusions and recommendations. *Wkly Epidemiol Rec* 2009; **84**: 517-532 [PMID: 19999831]

40 **Nayak P**, Sodha SV, Laserson KF, Padhi AK, Swain BK, Hossain SS, Shrivastava A, Khasnobis P, Venkatesh SR, Patnaik B, Dash KC. A cutaneous Anthrax outbreak in Koraput District of Odisha-India 2015. *BMC Public Health* 2019; **19**: 470 [PMID: 32326927 DOI: 10.1186/s12889-019-6787-0]

41 **Sarkar S**, Singh P, Lingala MAL, Verma P, Dhiman RC. Malaria risk map for India based on climate, ecology and geographical modelling. *Geospat Health* 2019; **14** [PMID: 31724378 DOI: 10.4081/gh.2019.767]

42 **Agrawal A**, Singh S, Kolhapure S, Hoet B, Arankalle V, Mitra M. Increasing Burden of Hepatitis A in Adolescents and Adults and the Need for Long-Term Protection: A Review from the Indian Subcontinent. *Infect Dis Ther* 2019; **8**: 483-497 [PMID: 31679118 DOI: 10.1007/s40121-019-00270-9]

43 **Mourya DT**, Yadav PD, Ullas PT, Bhardwaj SD, Sahay RR, Chadha MS, Shete AM, Jadhav S, Gupta N, Gangakhedkar RR, Khasnobis P, Singh SK. Emerging/re-emerging viral diseases & new viruses on the Indian horizon. *Indian J Med Res* 2019; **149**: 447-467 [PMID: 31411169 DOI: 10.4103/ijmr.IJMR_1239_18]

44 **Orenstein WA**, Ahmed R. Simply put: Vaccination saves lives. *Proc Natl Acad Sci U S A* 2017; **114**: 4031-4033 [PMID: 28396427 DOI: 10.1073/pnas.1704507114]

45 **World Health Organization**. Progress and Challenges with Achieving Universal Immunization Coverage. [cited 14 Oct 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/m/item/progress-and-challenges-with-achievinguniversal-immunization-coverage

46 **Komatsu H**. Hepatitis B virus: where do we stand and what is the next step for eradication? *World J Gastroenterol* 2014; **20**: 8998-9016 [PMID: 25083074]

47 **Murhekar MV**, Santhosh Kumar M, Kamaraj P, Khan SA, Allam RR, Barde P, Dwibedi B, Kanungo S, Mohan U, Mohanty SS, Roy S, Sagar V, Savargaonkar D, Tandale BV, Topno RK, Girish Kumar CP, Sabarinathan R, Bitragunta S, Grover GS, Lakshmi PVM, Mishra CM, Sadhukhan P, Sahoo PK, Singh SK, Yadav CP, Kumar R, Dutta S, Toteja GS, Gupta N, Mehendale SM; ICMR – Serosurvey group. Hepatitis-B virus infection in India: Findings from a nationally representative serosurvey, 2017-18. *Int J Infect Dis* 2020; **100**: 455-460 [PMID: 32896662 DOI: 10.1016/j.ijid.2020.08.084]

48 **Lahariya C**, Subramanya BP, Sosler S. An assessment of hepatitis B vaccine introduction in India: Lessons for roll out and scale up of new vaccines in immunization programs. *Indian J Public Health* 2013; **57**: 8-14 [PMID: 23649136 DOI: 10.4103/0019-557X.111357]

49 **Z Ansari AA**, Desai HD, Sharma K, Jadeja DM, Patel R, Patel Y, Desai HM. Prevalence and cross states comparison of case fatality rate and recovery rate of COVID 19/SARS-COV-2 in India. *J Family Med Prim Care* 2021; **10**: 475-480 [PMID: 34017773 DOI: 10.4103/jfmpc.jfmpc_1088_20]

50 **Jabaris S SL**, V A. The current situation of COVID-19 in India. *Brain Behav Immun Health* 2021; **11**: 100200 [PMID: 33521689 DOI: 10.1016/j.bbih.2021.100200]

51 **Behera D**, Praveen D, Behera MR. Protecting Indian health workforce during the COVID-19 pandemic. *J Family Med Prim Care* 2020; **9**: 4541-4546 [PMID: 33209760 DOI: 10.4103/jfmpc.jfmpc_925_20]

52 **Central TB Division**. Guidelines_on_Airborne_Infection_Control: Ministry of Health and Family Welfare. [cited 14 Oct 2021]. In: Central TB Division [Internet]. Available from: https://tbcindia.gov.in/showfile.php?lid=2858

53 **Parmar MM**, Sachdeva KS, Rade K, Ghedia M, Bansal A, Nagaraja SB, Willis MD, Misquitta DP, Nair SA, Moonan PK, Dewan PK. Airborne infection control in India: Baseline assessment of health facilities. *Indian J Tuberc* 2015; **62**: 211-217 [PMID: 26970461 DOI: 10.1016/j.ijtb.2015.11.006]

54 **Raj A**, Ramakrishnan D, Thomas CRMT, Mavila AD, Rajiv M, Suseela RPB. Assessment of Health Facilities for Airborne Infection Control Practices and Adherence to National Airborne Infection Control Guidelines: A Study from Kerala, Southern India. *Indian J Community Med* 2019; **44**: S23-S26 [PMID: 31728084 DOI: 10.4103/ijcm.IJCM_25_19]

55 **Sachdeva KS**, Deshmukh RD, Seguy NS, Nair SA, Rewari BB, Ramchandran R, Parmar M, Vohra V, Singh S, Ghedia M, Agarwal R, Shah AN, Balasubramanian D, Bamrotiya M, Sikhamani R, Gupta RS, Khaparde SD. Tuberculosis infection control measures at health care facilities offering HIV and tuberculosis services in India: A baseline assessment. *Indian J Tuberc* 2018; **65**: 280-284 [PMID: 30522613 DOI: 10.1016/j.ijtb.2018.04.004]

56 **Akshaya KM**, Shewade HD, Aslesh OP, Nagaraja SB, Nirgude AS, Singarajipura A, Jacob AG. *"Who has to do it at the end of the day?"* Airborne infection control at drug resistant tuberculosis (DR-TB) centres of Karnataka, India: a mixed-methods study. *Antimicrob Resist Infect Control* 2017; **6**: 111 [PMID: 29142744 DOI: 10.1186/s13756-017-0270-4]

57 **Rada AG**. Covid-19: Almost 100 ICU staff from Malaga hospital test positive after Christmas lunch. *BMJ* 2021; **375**: n3085 [PMID: 34907009 DOI: 10.1136/bmj.n3085]

58 **Bhanot D**, Singh T, Verma SK, Sharad S. Stigma and Discrimination During COVID-19 Pandemic. *Front Public Health* 2020; **8**: 577018 [PMID: 33585379 DOI: 10.3389/fpubh.2020.577018]

59 **Chughtai AA**, Seale H, Islam MS, Owais M, Macintyre CR. Policies on the use of respiratory protection for hospital health workers to protect from coronavirus disease (COVID-19). *Int J Nurs Stud* 2020; **105**: 103567 [PMID: 32203757 DOI: 10.1016/j.ijnurstu.2020.103567]

60 **International Council of Nurses**. More than 600 nurses die from COVID-19 worldwide | ICN - International Council of Nurses. [cited 14 Oct 2021]. In: International Council of Nurses [Internet]. Available from: https://www.icn.ch/news/more-600-nurses-die-covid-19-worldwide

61 **Gupta SK**, Siddharth V, Belagere MR, Stewardson AJ, Kant S, Singh S, Singh N. National survey of infection control programmes in South Asian association for Regional Cooperation countries in the era of patient safety. *Indian J Med Microbiol* 2018; **36**: 577-581 [PMID: 30880710 DOI: 10.4103/ijmm.IJMM_18_82]

62 **Lobo D**, Sams L, Fernandez S. Correlation between health professionals knowledge, attitude and practice about infection control measures. *J Med Allied Sci* 2019; **9**: 26 [DOI: 10.5455/jmas.17740]

63 **Vinodhini K**, Bhoomadevi A. Study On Infection Control Practices Among Healthcare Workers In A Speciality Hospital, Chennai. *Pollut Res* 2016; **35**: 549-555

64 **McNally VV**, Bernstein HH. The Effect of the COVID-19 Pandemic on Childhood Immunizations: Ways to Strengthen Routine Vaccination. *Pediatr Ann* 2020; **49**: e516-e522 [PMID: 33290569 DOI: 10.3928/19382359-20201115-01]

65 **The United Nations Children's Fund**. At least 80 million children under one at risk of diseases such as diphtheria, measles and polio as COVID-19 disrupts routine vaccination efforts, warn Gavi, WHO and UNICEF. [cited 14 Oct 2021]. In: The United Nations Children's Fund [Internet]. Available from: https://www.unicef.org/press-releases/least-80-million-children-under-one-risk-diseases-such-diphtheria-measles-and-polio

66 **Takahashi S**, Metcalf CJ, Ferrari MJ, Moss WJ, Truelove SA, Tatem AJ, Grenfell BT, Lessler J. Reduced vaccination and the risk of measles and other childhood infections post-Ebola. *Science* 2015; **347**: 1240-1242 [PMID: 25766232 DOI: 10.1126/science.aaa3438]

67 **Shet A**, Dhaliwal B, Banerjee P, DeLuca A, Carr K, Britto C, Seth R, Parekh B, Basavaraj GV, Shastri D, Gupta P. Childhood immunisations in India during the COVID-19 pandemic. *BMJ Paediatr Open* 2021; **5**: e001061 [PMID: 33928197 DOI: 10.1136/bmjpo-2021-001061]

68 **Roberton T**, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, Sawadogo-Lewis T, Walker N. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. *Lancet Glob Health* 2020; **8**: e901-e908 [PMID: 32405459 DOI: 10.1016/S2214-109X(20)30229-1]

69 **Indira Gandhi Government General Hospital And Post Graduation Institute**. Immunization Services during and post COVID-19 Outbreak. [cited 14 Oct 2021]. In: Indira Gandhi Government General Hospital And Post Graduation Institute [Internet]. Available from: https://ghp.py.gov.in/immunization-services-during-and-post-covid-19-outbreak

70 **World Health Organization**. Maintaining essential health services: operational guidance for the COVID-19 context, interim guidance, 1 June 2020. [cited 14 Oct 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-essential_health_services-2020.2

71 **Bharadwaj J**, Sharma SK, Darbari A, Patil P. Immunization and vaccination of children during current COVID-19 pandemic: Impact and recommendation guidelines for India. *J Family Med Prim Care* 2020; **9**: 5411-5412 [PMID: 33409236 DOI: 10.4103/jfmpc.jfmpc_1508_20]

72 **Montagnoli C**, Zanconato G, Ruggeri S, Cinelli G, Tozzi AE. Restructuring maternal services during the covid-19 pandemic: Early results of a scoping review for non-infected women. *Midwifery* 2021; **94**: 102916 [PMID: 33412360 DOI: 10.1016/j.midw.2020.102916]

73 **Reale SC**, Fields KG, Lumbreras-Marquez MI, King CH, Burns SL, Huybrechts KF, Bateman BT. Association Between Number of In-Person Health Care Visits and SARS-CoV-2 Infection in Obstetrical Patients. *JAMA* 2020; **324**: 1210-1212 [PMID: 32797148 DOI: 10.1001/jama.2020.15242]

74 **Chawla D**, Chirla D, Dalwai S, Deorari AK, Ganatra A, Gandhi A, Kabra NS, Kumar P, Mittal P, Parekh BJ, Sankar MJ, Singhal T, Sivanandan S, Tank P; Federation of Obstetric and Gynaecological Societies of India (FOGSI), National Neonatology Forum of India (NNF) and Indian Academy of Pediatrics (IAP). Perinatal-Neonatal Management of COVID-19 Infection - Guidelines of the Federation of Obstetric and Gynaecological Societies of India (FOGSI), National Neonatology Forum of India (NNF), and Indian Academy of Pediatrics (IAP). *Indian Pediatr* 2020; **57**: 536-548 [PMID: 32238615 DOI: 10.1007/s13312-020-1852-4]

75 **Goyal M**, Singh P, Singh K, Shekhar S, Agrawal N, Misra S. The effect of the COVID-19 pandemic on maternal health due to delay in seeking health care: Experience from a tertiary center. *Int J Gynaecol Obstet* 2021; **152**: 231-235 [PMID: 33128794 DOI: 10.1002/ijgo.13457]

76 **Kendzerska T**, Zhu DT, Gershon AS, Edwards JD, Peixoto C, Robillard R, Kendall CE. The Effects of the Health System Response to the COVID-19 Pandemic on Chronic Disease Management: A Narrative Review. *Risk Manag Healthc Policy* 2021; **14**: 575-584 [PMID: 33623448 DOI: 10.2147/RMHP.S293471]

77 **Sinclair AJ**, Abdelhafiz AH. Age, frailty and diabetes - triple jeopardy for vulnerability to COVID-19 infection. *EClinicalMedicine* 2020; **22**: 100343 [PMID: 32328575 DOI: 10.1016/j.eclinm.2020.100343]

78 **Emami A**, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med* 2020; **8**: e35 [PMID: 32232218]

79 **World Health Organization**. The impact of the COVID-19 pandemic on noncommunicable disease resources and services: results of a rapid assessment. [cited 14 Oct 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/i/item/9789240010291

80 **Chudasama YV**, Gillies CL, Zaccardi F, Coles B, Davies MJ, Seidu S, Khunti K. Impact of COVID-19 on routine care for chronic diseases: A global survey of views from healthcare professionals. *Diabetes Metab Syndr* 2020; **14**: 965-967 [PMID: 32604016 DOI: 10.1016/j.dsx.2020.06.042]

81 **Pati S**, Mahapatra P, Kanungo S, Uddin A, Sahoo KC. Managing Multimorbidity (Multiple Chronic Diseases) Amid COVID-19 Pandemic: A Community Based Study From Odisha, India. *Front Public Health* 2020; **8**: 584408 [PMID: 33598442 DOI: 10.3389/fpubh.2020.584408]

82 **Singh K**, Kondal D, Mohan S, Jaganathan S, Deepa M, Venkateshmurthy NS, Jarhyan P, Anjana RM, Narayan KMV, Mohan V, Tandon N, Ali MK, Prabhakaran D, Eggleston K. Health, psychosocial, and economic impacts of the COVID-19 pandemic on people with chronic conditions in India: a mixed methods study. *BMC Public Health* 2021; **21**: 685 [PMID: 33832478 DOI: 10.1186/s12889-021-10708-w]

83 **World Health Organization**. Opportunities and developments Report on the second global survey on eHealth Global Observatory for eHealth series-Volume 2 Telemedicine in Member States. 2010. [cited 14 Oct 2021]. In: World Health Organization [Internet]. Available from: https://apps.who.int/iris/handle/10665/44497

84 **Sudhamony S**, Nandakumar K, Binu PJ, Issac Niwas S. Telemedicine and tele-health services for cancer-care delivery in India. *IET Commun* 2008; **2**: 231 [DOI: 10.1049/iet-com:20060701]

85 **Agarwal N**, Jain P, Pathak R, Gupta R. Telemedicine in India: A tool for transforming health care in the era of COVID-19 pandemic. *J Educ Health Promot* 2020; **9**: 190 [PMID: 32953916 DOI: 10.4103/jehp.jehp_472_20]

86 **Kumar S**, Kumar A, Kumar M, Arora R, Sehrawat R. Feasibility of telemedicine in maintaining follow-up of orthopaedic patients and their satisfaction: A preliminary study. *J Clin Orthop Trauma* 2020; **11**: S704-S710 [PMID: 32837105 DOI: 10.1016/j.jcot.2020.07.026]

87 **Swetha NB**, Shobha S, Sriram S. Prevalence of catastrophic health expenditure and its associated factors, due to out-of-pocket health care expenses among households with and without chronic illness in Bangalore, India: a longitudinal study. *J Prev Med Hyg* 2020; **61**: E92-E97 [PMID: 32490274 DOI: 10.15167/2421-4248/jpmh2020.61.1.1191]

88 **Bhaduri SD**. Post-COVID healthcare reform in India: What to expect? *J Family Med Prim Care* 2020; **9**: 5427-5431 [PMID: 33532372 DOI: 10.4103/jfmpc.jfmpc_1548_20]

89 **Hindustan Time**. India must act now to protect its health workers | Opinion - Hindustan Times. [cited 14 Nov 2021]. In: Hindustan Time [Internet]. Available from: https://www.hindustantimes.com/analysis/india-must-act-now-to-protect-its-health-workers/story-idWQ1uyMrnARHc3PH7W86J.html

90 **Gan WH**, Lim JW, Koh D. Preventing Intra-hospital Infection and Transmission of Coronavirus Disease 2019 in Health-care Workers. *Saf Health Work* 2020; **11**: 241-243 [PMID: 32292622 DOI: 10.1016/j.shaw.2020.03.001]

91 **Feng S**, Shen C, Xia N, Song W, Fan M, Cowling BJ. Rational use of face masks in the COVID-19 pandemic. *Lancet Respir Med* 2020; **8**: 434-436 [PMID: 32203710 DOI: 10.1016/S2213-2600(20)30134-X]

92 **Zhou P**, Huang Z, Xiao Y, Huang X, Fan XG. Protecting Chinese healthcare workers while combating the 2019 novel coronavirus. *Infect Control Hosp Epidemiol* 2020; **41**: 745-746 [PMID: 32131906 DOI: 10.1017/ice.2020.60]

93 **Sodhi K**, Shrivastava A, Arya M, Kumar M. Knowledge of infection control practices among intensive care nurses in a tertiary care hospital. *J Infect Public Health* 2013; **6**: 269-275 [PMID: 23806701 DOI: 10.1016/j.jiph.2013.02.004]

94 **Diwan V**, Gustafsson C, Rosales Klintz S, Joshi SC, Joshi R, Sharma M, Shah H, Pathak A, Tamhankar AJ, Stålsby Lundborg C. Understanding Healthcare Workers Self-Reported Practices, Knowledge and Attitude about Hand Hygiene in a Medical Setting in Rural India. *PLoS One* 2016; **11**: e0163347 [PMID: 27711173 DOI: 10.1371/journal.pone.0163347]

95 **Legido-Quigley H**, Asgari N, Teo YY, Leung GM, Oshitani H, Fukuda K, Cook AR, Hsu LY, Shibuya K, Heymann D. Are high-performing health systems resilient against the COVID-19 epidemic? *Lancet* 2020; **395**: 848-850 [PMID: 32151326 DOI: 10.1016/S0140-6736(20)30551-1]

96 **Buvik A**, Bergmo TS, Bugge E, Smaabrekke A, Wilsgaard T, Olsen JA. Cost-Effectiveness of Telemedicine in Remote Orthopedic Consultations: Randomized Controlled Trial. *J Med Internet Res* 2019; **21**: e11330 [PMID: 30777845 DOI: 10.2196/11330]

97 **Snoswell CL**, Taylor ML, Comans TA, Smith AC, Gray LC, Caffery LJ. Determining if Telehealth Can Reduce Health System Costs: Scoping Review. *J Med Internet Res* 2020; **22**: e17298 [PMID: 33074157 DOI: 10.2196/17298]

98 **Baishideng Publishing Group**. Reference Citation Analysis. [cited 24 May 2022]. In: Baishideng Publishing Group [Internet]. Available from: https://www.referencecitationanalysis.com/

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 198-203

DOI: 10.5501/wjv.v11.i4.198

ISSN 2220-3249 (online)

CASE REPORT

COVID-19 presenting with persistent hiccup and myocardial infarction in a peritoneal dialysis patient: A case report

Dimitra Bacharaki, Panagiotis Giannakopoulos, Konstantinos Markakis, Christos Papas, Aikaterini Theodorou, Vasiliki Zoi, Georgios Tsivgoulis, Sophia Lionaki

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chen GX, United States; Rajcani J, Slovakia

Received: December 24, 2021
Peer-review started: December 24, 2021
First decision: March 16, 2022
Revised: May 1, 2022
Accepted: June 21, 2022
Article in press: June 21, 2022
Published online: July 25, 2022

Dimitra Bacharaki, Panagiotis Giannakopoulos, Vasiliki Zoi, Sophia Lionaki, Department of Nephrology, Attikon University Hospital, Chaidari 12462, Greece

Konstantinos Markakis, Department of Internal Medicine, Attikon University Hospital, Chaidari 12462, Greece

Christos Papas, Department of Cardiology, Attikon University Hospital, Chaidari 12462, Greece

Aikaterini Theodorou, Georgios Tsivgoulis, Second Department of Neurology, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece

Corresponding author: Dimitra Bacharaki, MD, PhD, Consultant Physician-Scientist, Department of Nephrology, Attikon University Hospital, Rimini 1, Chaidari 12462, Greece. bacharaki@gmail.com

Abstract

BACKGROUND

Persistent hiccups, lasting more than 48 h, have been described as an atypical presentation of coronavirus disease 19 (COVID-19) in the general population. To the best of our knowledge, this is the first report of persistent hiccups and non-ST elevation myocardial injury (NSTEMI) as an atypical presentation of COVID-19 in a peritoneal dialysis (PD) patient.

CASE SUMMARY

A 70-year old man, who had been on PD for 3 years with a history of ischemic heart failure and reduced ejection fraction, presented for a scheduled radionuclide myocardial scan. Upon arrival, he complained of anorexia, nausea for 5 d, and unremitting hiccups for the previous 48 h. Clinical and laboratory examinations revealed an NSTEMI plus a positive nasopharyngeal reverse transcriptase polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2. COVID-19 lung involvement was mild and was resolved without specific treatment. Myocardial injury was managed by coronary catheterization and stenting, while hiccups responded only to baclofen *per os*.

CONCLUSION

Persistent hiccups and NSTEMI can be atypical presentations of COVID-19 in peritoneal dialysis patients, which may be due to involvement of the central

nervous system and myocardial injuries.

Key Words: COVID-19; Peritoneal dialysis; Atypical presentation; Hiccup; Myocardial infarction; Baclofen; Case report

Core Tip: A 70-year old man with end-stage kidney disease on peritoneal dialysis, presented for a scheduled myocardial scan due to ischemic heart failure. Upon arrival, he complained of persistent hiccups during the last 2 d along with anorexia and vomiting for the last 5 d. He was diagnosed with coronavirus disease 2019 (COVID-19) and non-ST elevation myocardial infarction (NSTEMI). Hiccups and NSTEMI are postulated to represent atypical COVID-19 manifestations involving the nervous system and the heart.

Citation: Bacharaki D, Giannakopoulos P, Markakis K, Papas C, Theodorou A, Zoi V, Tsivgoulis G, Lionaki S. COVID-19 presenting with persistent hiccup and myocardial infarction in a peritoneal dialysis patient: A case report. *World J Virol* 2022; 11(4): 198-203
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/198.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.198

INTRODUCTION

The usual presentation of coronavirus disease 19 (COVID-19) includes fever and cough in the general population and in dialysis patients[1]. Gastrointestinal symptoms including anorexia, nausea, and vomit have also been described, although more rarely than in chronic renal patients[2]. Persistent hiccups, *i.e.*, lasting more than 48 h, have been infrequently described in the general population with COVID-19[3,4]. To the best of our knowledge, this is the first case of COVID-19 presenting with persistent hiccups and non-ST elevation myocardial injury (NSTEMI) in a peritoneal dialysis (PD) patient.

CASE PRESENTATION

Chief complaints

A 70-year-old man with end-stage kidney disease (ESKD) maintained on PD, presented in April 2021 for a scheduled myocardial scan, having ischemic heart failure with reduced ejection fraction (35%). Upon arrival, he complained for anorexia, nausea, and vomit tendency and unremitting hiccups.

History of present illness

Gastrointestinal (GI) symptoms started 5 d ago and persistent hiccups 2 d ago, preventing him from eating and considerable sleeping. He denied any abdominal pain, stool change, cloudy PD fluids, fever, chest discomfort, symptoms suggestive of gastroesophageal reflux, or change of his custom PD regimen. His medications included metoprolol, monosorbide, ramipril, simvastatin/ezetimibe, furosemide, acetylsalicylic acid, pantoprazole, folic acid, and darbepoetin injections. He denied any new drug initiation or new dietary habits.

History of past illness

The patient's past medical history was significant for cardiorenal syndrome following myocardial infarction in 2000, with coronary angioplasty and stent insertion, arterial hypertension, dyslipidemia, and a recent diagnosis (one month) of seronegative rheumatoid arthritis. Notably, 15 d prior to presentation, he had been admitted due to anemia (hemoglobin fall to 7.7 g/dL), nausea, and appetite loss, all attributed to recent initiation of leflunomide 10 mg daily for rheumatoid arthritis. At that time, C reactive protein was 141mg/L (reference < 6 mg/L), white blood cell count 6280/μL, serum urea 89 mg/dL, creatinine 6.5 mg/dL, and ferritin 642 ng/mL.

He was managed with red blood cells infusions and discontinuation of leflunomide. He was discharged in 2 d with Hb 9.4 g/dL, stable high sensitive troponin 209 pg/mL (reference < 14 pg/mL, while the patient's high sensitive troponin routine assessment values were between 255-430 pg/mL), free of gastrointestinal symptoms, with good appetite and negative nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Personal and family history

ESKD due to cardiorenal syndrome; PD initiated 3 years ago; carpal tunnel syndrome diagnosed 1 year ago; former truck driver; and no special family history.

Physical examination

Physical examination revealed a weight loss of nearly 2 kg (74 kg), temperature of 36.5 °C, oxygen saturation 98% on room air, and low blood pressure (117/73 mmHg, heart rate 90 beats per minute in sitting position). No signs of peripheral edema nor pulmonary congestion were noted. Abdominal examination was negative, as was heart and lung auscultation. The patient appeared ill with persistent hiccups, weakness, anorexia, and vomit tendency, in contrast with his relatively good clinical condition on discharge 13 d ago.

Laboratory examinations

Peritoneal dialysis fluid analysis revealed a normal cytology and biochemistry and negative Gram staining. Serum laboratory examination revealed C reactive protein of 36.8 mg/L, hemoglobulin of 9.8 g/dL, white blood cell count 4530/μL (neutrophils 58%, lymphocytes 28%), stable serum urea and creatinine, ferritin 855 ng/L, but troponin elevation to 1650 pg/mL.

Electrocardiography showed a sinus rhythm with left bundle branch block, not different compared to previous tracings while echocardiography revealed worsening of ejection fraction to 25%. Routine nasopharyngeal RT-PCR arranged upon admission revealed a positive result and he was transferred to the COVID clinic.

Imaging examinations

Due to severe co-morbidities and a positive RT-PCR test for SARS-CoV-2, chest computed tomography was performed, showing signs of mild COVID-19 pneumonia, *i.e.*, less than 10% degree of lung infiltration in the right upper lobe, as small areas of ground glass opacities and small areas of atelectasis (Figure 1).

FINAL DIAGNOSIS

Mild COVID-19 pneumonia; NSTEMI; and persistent hiccups due to SARS-CoV-2 nervous system involvement.

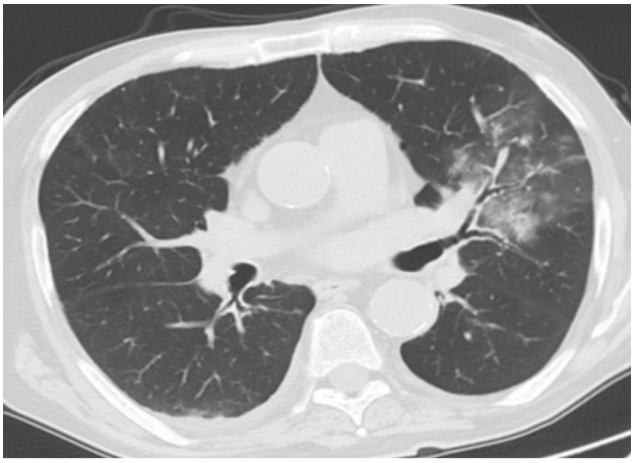
TREATMENT

Due to mild pneumonia, the patient did not receive any specific treatment for COVID-19. Regarding NSTEMI, he received dual antiplatelet therapy and Enoxaparin subcutaneously on a daily basis. He continued his usual ambulatory PD regimen of four daily glucose-based PD exchanges, 2000 mL each (glucose 1.5% and 2.25% alternating) with a daily ultrafiltration of 1000-1200 mL. Due to persistent hiccups and anorexia that prevented him from eating and drinking, he received intravenously one liter of semi-isotonic glucose solution daily with potassium supplementation. Metoclopramide injections three times per day were prescribed for hiccups and then replaced by Chlorpropamide 25 mg three times per day after 2 d of intractable hiccups. On the 7th day, Baclofen tablets was given orally, at a dose of 10 mg *per os* daily for 5 d.

OUTCOME AND FOLLOW-UP

Upon initiation of baclofen tablets, the patient's hiccups improved significantly and they ceased completely within 48 h. As a result, the patient was able to eat and sleep, claiming to be in good condition despite NSTEMI and COVID-19. He remained euvolemic with stable arterial pressure records (around 110/70 mmHg, 70 pulses/min). He did not experience any chest discomfort and his troponin values gradually fell to previous baseline levels. Maximum temperature was 37.3 °C but oxygen saturation remained stable at 98% on room air.

A coronary angiogram was performed on the 12th day of hospitalization (on negative COVID-19 PCR), which revealed a significant stenosis at the proximal segment of the first obtuse marginal branch, while the previous stent was intact. A coronary angioplasty was performed 1 mo later with stent implantation and recovering of ejection fraction to 35%.



DOI: 10.5501/wjv.v11.i4.198

Figure 1 Chest computed tomography at admission.

DISCUSSION

This patient presented for as scheduled appointment, complaining of nausea, anorexia, and unremitting hiccups. He had not changed his PD regimen, nor his dietary habits or medical prescription. Clinical assessment revealed NSTEMI and mild COVID-19 pneumonia of the upper right lobe. Unremitting hiccups remained his main problem while hospitalized.

Hiccup is caused by diaphragmatic muscle contractions with early glottis closure terminating inspiration. Its pathogenesis is still obscure but lately is considered a deranged neural loop connecting the brain stem and diaphragm[5]. Persistent hiccups, lasting more than 48 h, have been associated with central nervous system, cardiovascular, thoracic, metabolic, and gastrointestinal disorders[5].

Uremia as a potential cause of gastrointestinal symptoms and/or hiccups was excluded, due to stable biochemical parameters and unchanged urinary output or PD regimen. Electrolyte and acid base disturbances were absent. Another potential cause of persistent hiccups could be gastro-esophageal reflux[6], which is a common complication of PD[7], but the symptoms were missing. Pneumonia caused by common pathogens[8] as well as by SARS-CoV-2[3,4] has been reported as a cause of persistent hiccups. Interestingly, apart from cases of lower lobe pneumonia, which would suggest direct irritation of the diaphragm as a potential mechanism resulting in hiccups[8], the association of persistent hiccups with COVID-19 has increasing publications with other sites of lung involvement[9]. Noteworthily, our patient had only minor infiltration in the upper lobe on chest computed tomography (Figure 1). Persistent hiccups have also been reported as an associated symptom in cases of myocardial infarction, primarily in the inferior myocardial wall, thus in proximity with the diaphragm, suggesting that hiccups could be triggered by irrigation of the phrenic nerves or alternatively by the vagus nerve supplying the pericardium, but rarely as the only presenting symptom[10]. There is a case report of persistent hiccups as an atypical presentation of non-ST elevation myocardial injury[11]. In our case, there was a gradual fall of cardiac troponin levels while the hiccup was still persisting, responding eventually only to baclofen. The stenosed vessel, as revealed by angiography (the proximal segment of the first obtuse marginal branch), perfuses the infero-lateral myocardial wall.

Furthermore, nausea and vomiting can be associated symptoms of myocardial infarction[12] and more rarely the presenting symptom in atypical cases[13].

On the other hand, there are numerous reports associating myocardial injuries and infarctions with COVID-19, with potential causes being direct myocyte injury and prothrombotic effect of SARS-CoV-2 infection[12]. Nevertheless, it is still difficult to differentiate between non-COVID acute coronary syndrome and COVID-19 induced acute myocardial injury[14]. Noteworthy, gastrointestinal symptoms, such as diarrhea (more often) nausea and vomiting, often accompany COVID-19, either by direct infection of GI cells or indirectly[15], although diarrhea was absent in our patient. Since the underlying mechanisms of persistent hiccups are various disorders (structural, infectious, and inflammatory) that impact either the central nervous system or the phrenic nerves or their branches[16], one could speculate that COVID-19 could be linked causally with hiccups by nervous system involvement[17].

Baclofen is a gamma-aminobutyric acid B receptor agonist approved as a medication to control spasticity[18]. It has been used successfully for persistent hiccups of different etiologies with an action attributed to either reduction of dopamine release in the central nervous system, which could interrupt hiccup's reflex arc or induction of transient lower esophageal sphincter relaxations, by stimulating gamma-aminobutyric acid B receptors in the motor nucleus of the vagal nerve and nucleus tract solitarious[18]. Hiccups attributed to COVID-19 have been managed with hydroxychloroquine, metoclopramide, and chlorpropamide, as well as a combination scheme with baclofen included[3,4,9]. In this

case, hiccups did not respond to metoclopropamide nor chlorpropamide, but on the contrary had an immediate and complete response to baclofen.

Based on the above, COVID-19 may be the unifying cause of all. Anorexia, vomit tendency, and hiccup could be manifestations of SARS-CoV-2 gastrointestinal[15] and/or nervous system involvement [16,17,18,19]. Non-ST myocardial infraction could also be a manifestation of COVID-19[11]. COVID-19 induced endotheliitis could be the underlying pathophysiology of nervous system and heart involvement[18,20].

CONCLUSION

A case of atypical presentation of COVID-19 in a PD patient with persistent hiccups and NSTEMI is described here. We may speculate that they could be the result of SARS-CoV-2 involvement of the nervous system and heart, respectively. Baclofen seems to be the drug of choice for persistent hiccups even in patients with ESKD.

ACKNOWLEDGEMENTS

We acknowledge the support and contribution in the management of the COVID-19 patient of the nurses of Hemodialysis and Peritoneal Dialysis Unit: Irene Zorba, Dimitra Siopi, Athina Maniati, Zoi Polymerou, and Lambrini Xoxakou.

FOOTNOTES

Author contributions: Bacharaki D was the attending consultant nephrologist and wrote the article; Giannakopoulos P was the resident nephrologist; Markakis K was the attending physician of the Infectious Department; Papas C was the attending cardiologist; Theodorou A as Resident of Neurology and Tsivgoulis G as Professor of Neurology were the neurologists consulted for hiccup; Zoi V was the peritoneal dialysis nurse; Lionaki S supervised the manuscript and was responsible for the language editing; all authors have read and approved the final manuscript.

Informed consent statement: The study participant provided informed written consent for the case report.

Conflict-of-interest statement: The authors have nothing to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Greece

ORCID number: Dimitra Bacharaki 0000-0002-1722-2131; Panagiotis Giannakopoulos 0000-0001-8204-0820; Konstantinos Markakis 0000-0002-4774-9049; Christos Papas 0000-0003-2939-531X; Aikaterini Theodorou 0000-0001-7229-2610; Vasiliki Zoi 0000-0001-8162-0225; Georgios Tsivgoulis 0000-0002-0640-3797; Sophia Lionaki 0000-0003-1643-8923.

S-Editor: Yan JP
L-Editor: Wang TQ
P-Editor: Yan JP

REFERENCES

1 **Valeri AM**, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhakrishnan J, Gharavi AG, Mohan S, Husain SA. Presentation and Outcomes of Patients with ESKD and COVID-19. *J Am Soc Nephrol* 2020; **31**: 1409-1415 [PMID: 32467113 DOI: 10.1681/ASN.2020040470]

2 **Cao C**, Chen M, He L, Xie J, Chen X. Clinical features and outcomes of COVID-19 patients with gastrointestinal symptoms. *Crit Care* 2020; **24**: 340 [PMID: 32539863 DOI: 10.1186/s13054-020-03034-x]

3 **Prince G**, Sergel M. Persistent hiccups as an atypical presenting complaint of COVID-19. *Am J Emerg Med* 2020; **38**: 1546.e5-1546.e6 [PMID: 32345563 DOI: 10.1016/j.ajem.2020.04.045]

4 **Ali SK**, Muturi D, Sharma K. Be Wary of Hiccups: An Unusual Case of COVID-19. *Cureus* 2021; **13**: e12974 [PMID: 33654635 DOI: 10.7759/cureus.12974]

5 **Brañuelas Quiroga J**, Urbano García J, Bolaños Guedes J. Hiccups: a common problem with some unusual causes and cures. *Br J Gen Pract* 2016; **66**: 584-586 [PMID: 27789508 DOI: 10.3399/bjgp16X687913]

6 **Fisher MJ**, Mittal RK. Hiccups and gastroesophageal reflux: cause and effect? *Dig Dis Sci* 1989; **34**: 1277-1280 [PMID: 2752874 DOI: 10.1007/BF01537278]

7 **Song HJ**, Kim SM, Lee YM, Hwang JA, Moon KM, Moon CG, Koo HS, Song KH, Kim YS, Lee TH, Huh KC, Choi YW, Kang YW, Hwang WM, Yun SR. Is there a difference in the prevalence of gastroesophageal reflux disease between peritoneal dialysis and hemodialysis patients? *Korean J Gastroenterol* 2013; **62**: 206-212 [PMID: 24162707 DOI: 10.4166/kjg.2013.62.4.206]

8 **Karakonstantis S**, Pitsigavdaki S, Korela D, Galani D. Lower lobe pneumonia presenting as singultus (hiccups). *Caspian J Intern Med* 2018; **9**: 403-405 [PMID: 30510657 DOI: 10.22088/cjim.9.4.403]

9 **Sene DR**, Watashi DM, Bilitardo IO, Moreno CEC, Moreno MFF. COVID-19 presenting as persistent hiccups: a case report. *Rev Inst Med Trop Sao Paulo* 2021; **63**: e62 [PMID: 34378765 DOI: 10.1590/S1678-9946202163062]

10 **Shaikh N**, Raj R, Movva S, Mattina C. Persistent Hiccups as the Only Presenting Symptom of ST Elevation Myocardial Infarction. *Case Rep Cardiol* 2018; **2018**: 7237454 [PMID: 29713552 DOI: 10.1155/2018/7237454]

11 **Davenport J**, Duong M, Lanoix R. Hiccups as the only symptom of non-ST-segment elevation myocardial infarction. *Am J Emerg Med* 2012; **30**: 266.e1-266.e2 [PMID: 21277137 DOI: 10.1016/j.ajem.2010.12.004]

12 **Herlihy T**, McIvor ME, Cummings CC, Siu CO, Alikahn M. Nausea and vomiting during acute myocardial infarction and its relation to infarct size and location. *Am J Cardiol* 1987; **60**: 20-22 [PMID: 3604939 DOI: 10.1016/0002-9149(87)90976-3]

13 **Brieger D**, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G; GRACE Investigators. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004; **126**: 461-469 [PMID: 15302732 DOI: 10.1378/chest.126.2.461]

14 **Bae JY**, Hussein KI, Howes CJ, Setaro JF. The Challenges of ST-Elevation Myocardial Infarction in COVID-19 Patients. *Case Rep Cardiol* 2021; **2021**: 9915650 [PMID: 34426772 DOI: 10.1155/2021/9915650]

15 **Cameli M**, Pastore MC, Mandoli GE, D'Ascenzi F, Focardi M, Biagioni G, Cameli P, Patti G, Franchi F, Mondillo S, Valente S. COVID-19 and Acute Coronary Syndromes: Current Data and Future Implications. *Front Cardiovasc Med* 2020; **7**: 593496 [PMID: 33585577 DOI: 10.3389/fcvm.2020.593496]

16 **Jin B**, Singh R, Ha SE, Zogg H, Park PJ, Ro S. Pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19. *World J Gastroenterol* 2021; **27**: 2341-2352 [PMID: 34040326 DOI: 10.3748/wjg.v27.i19.2341]

17 **Alvarez-Cisneros T**, Lara-Reyes A, Sansón-Tinoco S. Hiccups and psychosis: two atypical presentations of COVID-19. *Int J Emerg Med* 2021; **14**: 8 [PMID: 33472577 DOI: 10.1186/s12245-021-00333-0]

18 **Norouzi M**, Miar P, Norouzi S, Nikpour P. Nervous System Involvement in COVID-19: a Review of the Current Knowledge. *Mol Neurobiol* 2021; **58**: 3561-3574 [PMID: 33765290 DOI: 10.1007/s12035-021-02347-4]

19 **Mirijello A**, Addolorato G, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, Leggio L, Landolfi R. Baclofen in the treatment of persistent hiccup: a case series. *Int J Clin Pract* 2013; **67**: 918-921 [PMID: 23834241 DOI: 10.1111/ijcp.12184]

20 **Calabretta E**, Moraleda JM, Iacobelli M, Jara R, Vlodavsky I, O'Gorman P, Pagliuca A, Mo C, Baron RM, Aghemo A, Soiffer R, Fareed J, Carlo-Stella C, Richardson P. COVID-19-induced endotheliitis: emerging evidence and possible therapeutic strategies. *Br J Haematol* 2021; **193**: 43-51 [PMID: 33538335 DOI: 10.1111/bjh.17240]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 204-207

DOI: 10.5501/wjv.v11.i4.204

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Management of SARS-CoV-2 infection is a major challenge in patients with lymphoid malignancies: Warrants a clear therapeutic strategy

Tarun Sahu, Henu Kumar Verma, Bhaskar Lvks

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Riches JC, United Kingdom; Sageena G, India; Sivanand N, India

A-Editor: Ma L, United States

Received: June 5, 2021
Peer-review started: June 5, 2021
First decision: July 27, 2021
Revised: July 28, 2021
Accepted: May 27, 2022
Article in press: May 27, 2022
Published online: July 25, 2022

Tarun Sahu, Physiology, All India Institute of Medical Science, Raipur 492001, Chhattisgarh, India

Henu Kumar Verma, Department of Immunopathology, Institute of Lung Health and Immunity, Comprehensive Pneumology Center, Helmholtz Zentrum, Munich 80331, Bayren, Germany

Bhaskar Lvks, Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur 495001, Chhattisgarh, India

Corresponding author: Henu Kumar Verma, PhD, Research Scientist, Department of Immunopathology, Institute of Lung Health and Immunity, Comprehensive Pneumology Center, Helmholtz Zentrum, Ingolstädter Landstrasse 1, Munich 80331, Bayren, Germany, henu.verma@yahoo.com

Abstract

Patients with lymphoid malignancies are at a higher risk of coronavirus disease 2019 (COVID-19) infection due to their immunocompromised state and results in higher mortality rates in these patients. Anti-CD 20 therapy is one of the leading causes of immunosuppression that worsens in COVID-19 cases. COVID-19 vaccines, on the other hand, appear to be less beneficial to these patients. Appropriate treatment and recommendations are required for these COVID-19 patients with lymphoid malignancies.

Key Words: COVID-19; Lymphoid malignancy; Lymphoma; Vaccination; Immunosuppression

Core Tip: Patients with hematologic conditions are two times more likely than others to be admitted to the hospital. They are being treated with anti-cancer drugs, which weakens their immune system. As a result, these patients are always at risk of coronavirus disease 2019 (COVID-19). As we know, the COVID-19 is very lethal, and hematological malignancies are likely to increase the risk of negative outcomes from this viral infection. Currently, there are no guidelines for treating COVID-19 infected patients with hematological malignancies.

Citation: Sahu T, Verma HK, Lvks B. Management of SARS-CoV-2 infection is a major challenge in patients with lymphoid malignancies: Warrants a clear therapeutic strategy. *World J Virol* 2022; 11(4): 204-207
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/204.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.204

TO THE EDITOR

In March 2019, the World Health Organization declared the novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2, as a pandemic. Nearly one-third of patients with lymphoid malignancies experienced severe complications of COVID-19 and required hospitalization[1,2]. According to the 2017 World Health Organization classification, there are more than 80 different types of mature lymphoma, which are divided into three major categories: B-cell neoplasms, T-cell and natural killer cell neoplasms, and Hodgkin lymphomas[3]. We recently read the paper from Riches[4] entitled "Impact of COVID-19 in patients with lymphoid malignancies" in your prestigious journal "World Journal of Virology". I sincerely thank the author for providing vital information about the effect of COVID-19 in patients with lymphoid malignancies.

Patients with lymphoid malignancies are highly susceptible to COVID-19 infection because they are already immunocompromised due to active cancer treatments. In this review article, the author mainly focused on the impact of COVID-19 on chronic lymphocytic leukemia, which is the most common form of leukemia in western countries[5]. In the present article the author included case studies, cohort studies, systematic reviews, and meta-analyses. Several lines of evidence suggested that the type of hematological malignancy and target antineoplastic therapy, older age, and various preexisting conditions such as hypertension and diabetes are all linked to mortality in lymphoma patients[6-8]. A retrospective study of 343 patients with hematologic malignancies and hematopoietic stem cell transplantation found that severe acute respiratory syndrome coronavirus 2 infection progressed to pneumonia in 119 patients (35%), including those with leukemia, those over the age of 65 years, and those with severe neutropenia or lymphopenia. It also found that more than 85% of patients with lymphoid malignancies required hospital admission, with 9% admitted to the intensive care unit and an overall mortality rate of 34.5%[9].

The information available on the effects of COVID-19 in patients with various hematologic diseases is limited. A series of case reports of COVID-19 patients with various hematological malignancies increases the risk of adverse complications due to immunosuppression caused by the underlying cancer and treatment effects[10-13].

The author does not have much data to show the impact of lymphoma on COVID-19 vaccination at the time of writing his paper. In this context, we would like to mention two recent studies that analyzed the efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia and multiple myeloma. According to these studies, BNT162b2 mRNA COVID-19 vaccine negatively affects the production of neutralizing antibodies in patients treated with anti-chronic lymphocytic leukemia and anti-myeloma therapies[14-16]. As hematologic malignancies are life-threatening conditions and the majority of the medications are immunosuppressive agents that progress to the severe/critical stage and collapse of patients, data for medications in these conditions with COVID-19 are limited[17,18]. To avoid severe conditions and death, researchers/clinicians must develop an appropriate medication guideline for lymphoma patients infected with COVID-19. Percival *et al*[19] compiled a list of treatment recommendations for patients with hematologic malignancies during the COVID-19 pandemic. Further, more trials on COVID-19 vaccines on these patients should be done along with current therapies of hematologic disease to reveal the appropriate therapies in which these vaccines are effective.

FOOTNOTES

Author contributions: Sahu T, Verma HK, Lvks B wrote and revised the letter.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Germany

ORCID number: Tarun Sahu 0000-0002-2721-7432; Henu Kumar Verma 0000-0003-1130-8783; Bhaskar Lvks 0000-0003-2977-6454.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ

REFERENCES

1 **Passamonti F**, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, Angelucci E, Krampera M, Cairoli R, Della Porta MG, Fracchiolla N, Ladetto M, Gambacorti Passerini C, Salvini M, Marchetti M, Lemoli R, Molteni A, Busca A, Cuneo A, Romano A, Giuliani N, Galimberti S, Corso A, Morotti A, Falini B, Billio A, Gherlinzoni F, Visani G, Tisi MC, Tafuri A, Tosi P, Lanza F, Massaia M, Turrini M, Ferrara F, Gurrieri C, Vallisa D, Martelli M, Derenzini E, Guarini A, Conconi A, Cuccaro A, Cudillo L, Russo D, Ciambelli F, Scattolin AM, Luppi M, Selleri C, Ortu La Barbera E, Ferrandina C, Di Renzo N, Olivieri A, Bocchia M, Gentile M, Marchesi F, Musto P, Federici AB, Candoni A, Venditti A, Fava C, Pinto A, Galieni P, Rigacci L, Armiento D, Pane F, Oberti M, Zappasodi P, Visco C, Franchi M, Grossi PA, Bertù L, Corrao G, Pagano L, Corradini P; ITA-HEMA-COV Investigators. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol* 2020; **7**: e737-e745 [PMID: 32798473 DOI: 10.1016/S2352-3026(20)30251-9]

2 **Sahu T**, Mehta A, Ratre YK, Jaiswal A, Vishvakarma NK, Bhaskar LVKS, Verma HK. Current understanding of the impact of COVID-19 on gastrointestinal disease: Challenges and openings. *World J Gastroenterol* 2021; **27**: 449-469 [PMID: 33642821 DOI: 10.3748/wjg.v27.i6.449]

3 **de Leval L**, Jaffe ES. Lymphoma Classification. *Cancer J* 2020; **26**: 176-185 [PMID: 32496451 DOI: 10.1097/PPO.0000000000000451]

4 **Riches JC**. Impact of COVID-19 in patients with lymphoid malignancies. *World J Virol* 2021; **10**: 97-110 [PMID: 34079692 DOI: 10.5501/wjv.v10.i3.97]

5 **Hallek M**. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. *Am J Hematol* 2017; **92**: 946-965 [PMID: 28782884 DOI: 10.1002/ajh.24826]

6 **Lee LY**, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, Chackathayil J, Cheng VW, Curley HM, Fittall MW, Freeman-Mills L, Gennatas S, Goel A, Hartley S, Hughes DJ, Kerr D, Lee AJ, Lee RJ, McGrath SE, Middleton CP, Murugaesu N, Newsom-Davis T, Okines AF, Olsson-Brown AC, Palles C, Pan Y, Pettengell R, Powles T, Protheroe EA, Purshouse K, Sharma-Oates A, Sivakumar S, Smith AJ, Starkey T, Turnbull CD, Várnai C, Yousaf N; UK Coronavirus Monitoring Project Team, Kerr R, Middleton G. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet* 2020; **395**: 1919-1926 [PMID: 32473682 DOI: 10.1016/S0140-6736(20)31173-9]

7 **Shah V**, Ko Ko T, Zuckerman M, Vidler J, Sharif S, Mehra V, Gandhi S, Kuhnl A, Yallop D, Avenoso D, Rice C, Sanderson R, Sarma A, Marsh J, de Lavallade H, Krishnamurthy P, Patten P, Benjamin R, Potter V, Ceesay MM, Mufti GJ, Norton S, Pagliuca A, Galloway J, Kulasekararaj AG. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. *Br J Haematol* 2020; **190**: e279-e282 [PMID: 32526039 DOI: 10.1111/bjh.16935]

8 **Vijenthira A**, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, Martín-Moro F, Razanamahery J, Riches JC, Zwicker J, Patell R, Vekemans MC, Scarfò L, Chatzikonstantinou T, Yildiz H, Lattenist R, Mantzaris I, Wood WA, Hicks LK. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 2020; **136**: 2881-2892 [PMID: 33113551 DOI: 10.1182/blood.2020008824]

9 **Regalado-Artamendi I**, Jiménez-Ubieto A, Hernández-Rivas JÁ, Navarro B, Núñez L, Alaez C, Córdoba R, Peñalver FJ, Cannata J, Estival P, Quiroz-Cervantes K, Riaza Grau R, Velasco A, Martos R, Domingo-González A, Benito-Parra L, Gómez-Sanz E, López-Jiménez J, Matilla A, Herraez MR, Penalva MJ, García-Suárez J, Díez-Martín JL, Bastos-Oreiro M. Risk Factors and Mortality of COVID-19 in Patients With Lymphoma: A Multicenter Study. *Hemasphere* 2021; **5**: e538 [PMID: 33604516 DOI: 10.1097/HS9.0000000000000538]

10 **Hoffmann MS**, Ganguly S. Delayed COVID-19 Respiratory Failure in Patients with Lymphoma on Rituximab-based Chemoimmunotherapy. *Clin Lymphoma Myeloma Leuk* 2021; **21**: e548-e550 [PMID: 33712408 DOI: 10.1016/j.clml.2021.02.009]

11 **Yonal-Hindilerden I**, Hindilerden F, Mastanzade M, Tiryaki TO, Tasan-Yenigun S, Bilen Y, Aksoz S, Cagatay AA, Nalcaci M. Case Report: Severe COVID-19 Pneumonia in a Patient With Relapsed/Refractory Hodgkin's Lymphoma. *Front Oncol* 2021; **11**: 601709 [PMID: 33816231 DOI: 10.3389/fonc.2021.601709]

12 **Jin XH**, Zheng KI, Pan KH, Xie YP, Zheng MH. COVID-19 in a patient with chronic lymphocytic leukaemia. *Lancet Haematol* 2020; **7**: e351-e352 [PMID: 32220344 DOI: 10.1016/S2352-3026(20)30074-0]

13 **Zhang X**, Song K, Tong F, Fei M, Guo H, Lu Z, Wang J, Zheng C. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* 2020; **4**: 1307-1310 [PMID: 32243501 DOI: 10.1182/bloodadvances.2020001907]

14 **Herishanu Y**, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, Morales M, Ziv T, Shorer Arbel Y, Scarfò L, Joffe E, Perry C, Ghia P. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood* 2021; **137**: 3165-3173 [PMID: 33861303 DOI: 10.1182/blood.2021011568]

15 **Terpos E**, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, Papanagnou ED, Fotiou D, Kastritis E, Dimopoulos MA. Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. *Blood* 2021; **137**: 3674-3676 [PMID: 33861315 DOI: 10.1182/blood.2021011904]

16 **Gavriatopoulou M**, Ntanasis-Stathopoulos I, Korompoki E, Terpos E, Dimopoulos MA. SARS-CoV-2 Vaccines in Patients With Multiple Myeloma. *Hemasphere* 2021; **5**: e547 [PMID: 33623886 DOI: 10.1097/HS9.0000000000000547]

17 **Li W**, Wang D, Guo J, Yuan G, Yang Z, Gale RP, You Y, Chen Z, Chen S, Wan C, Zhu X, Chang W, Sheng L, Cheng H, Zhang Y, Li Q, Qin J; Hubei Anti-Cancer Association, Meng L, Jiang Q. COVID-19 in persons with chronic myeloid leukaemia. *Leukemia* 2020; **34**: 1799-1804 [PMID: 32424293 DOI: 10.1038/s41375-020-0853-6]

18 **García-Suárez J**, de la Cruz J, Cedillo Á, Llamas P, Duarte R, Jiménez-Yuste V, Hernández-Rivas JÁ, Gil-Manso R, Kwon M, Sánchez-Godoy P, Martínez-Barranco P, Colás-Lahuerta B, Herrera P, Benito-Parra L, Alegre A, Velasco A, Matilla A, Aláez-Usón MC, Martos-Martínez R, Martínez-Chamorro C, Susana-Quiroz K, Del Campo JF, de la Fuente A, Herráez R, Pascual A, Gómez E, Pérez-Oteyza J, Ruiz E, Alonso A, González-Medina J, Martín-Buitrago LN, Canales M, González-Gascón I, Vicente-Ayuso MC, Valenciano S, Roa MG, Monteliu PE, López-Jiménez J, Escobar CE, Ortiz-Martín J, Diez-Martin JL, Martinez-Lopez J; Asociación Madrileña de Hematología y Hemoterapia (AMHH). Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. *J Hematol Oncol* 2020; **13**: 133 [PMID: 33032660 DOI: 10.1186/s13045-020-00970-7]

19 **Percival MM**, Lynch RC, Halpern AB, Shadman M, Cassaday RD, Ujjani C, Shustov A, Tseng YD, Liu C, Pergam S, Libby EN, Scott BL, Smith SD, Green DJ, Gopal AK, Cowan AJ. Considerations for Managing Patients With Hematologic Malignancy During the COVID-19 Pandemic: The Seattle Strategy. *JCO Oncol Pract* 2020; **16**: 571-578 [PMID: 32369409 DOI: 10.1200/OP.20.00241]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 208-211

DOI: 10.5501/wjv.v11.i4.208

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Chemsex and its risk factors associated with human immunodeficiency virus among men who have sex with men in Hong Kong

Alex Siu Wing Chan, Patrick Ming Kuen Tang, Elsie Yan

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Goh KK, Taiwan; He ST, United States

Received: January 26, 2022
Peer-review started: January 26, 2022
First decision: May 30, 2022
Revised: June 8, 2022
Accepted: June 23, 2022
Article in press: June 23, 2022
Published online: July 25, 2022

Alex Siu Wing Chan, Elsie Yan, Department of Applied Social Sciences, The Hong Kong Polytechnic University, Hong Kong 999077, China

Patrick Ming Kuen Tang, Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong 999077, China

Corresponding author: Elsie Yan, PhD, Professor, Department of Applied Social Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong 999077, China.
elsie.yan@polyu.edu.hk

Abstract

We were intrigued by Hanum *et al*, who published a study on the prevalence of human immunodeficiency virus (HIV) in homosexual, bisexual, and other men who have sex with men at sexual health clinics in England and the relationship between baseline variables and future HIV occurrence. Chemically-enhanced sexual experience (chemsex) is becoming a global phenomenon. There are increasing medical and academic concerns about chemsex, where substances are used to boost sexual satisfaction, which is prevalent in groups, especially among homosexuals. Lesbians, gays, bisexuals, transgenders, and queers have become increasingly visible, valued, and committed community. However, chemsex requires urgent attention.

Key Words: Men who have sex with men; Methamphetamine; Application of novel psychoactive substances; Drug abuse; Lesbians, gays, bisexuals, transgenders; Chemsex

Core Tip: The human immunodeficiency virus/acquired immunodeficiency syndrome epidemic and substance abuse have become global concerns in Hong Kong and everywhere else. It is our opinion that chem-sex exposes the risk factor and affects the men who have sex with men (MSM) subset of homosexual men and other MSM.

Citation: Chan ASW, Tang PMK, Yan E. Chemsex and its risk factors associated with human immunodeficiency virus among men who have sex with men in Hong Kong. *World J Virol* 2022; 11(4): 208-211
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/208.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.208

TO THE EDITOR

In Hong Kong, men who have sex with men (MSM) have coined the phrase "chemfun" to describe having sex while high on drugs such as methamphetamine and γ-hydroxybutyric acid (GHB). It is also called chemsex or sexualized drug usage elsewhere[1]. Since time immemorial, MSM have used drugs to enhance the experience of sex, regardless of sexual orientation. Public concern has only recently surfaced, however, as we have seen some of the serious ramifications of this habit. Resurging sexually transmitted infections, including human immunodeficiency virus (HIV) and hepatitis C, addiction-related social and mental health issues, and overdose fatalities, are all part of the problem[2].

Chemsex involves various complicated relationships between sexual and drug-use behaviors[1,3]. It may include two or more people and may take place at sex-on-premises establishments such as saunas or clubs. However, it is most often seen in private settings such as houses or leased rooms. Because methamphetamine has a longer half-life than other stimulants such as cocaine, chemsex sometimes lasts for a lengthy period of time, such as 10-12 h or even several days. Individuals exhibit various chemsex patterns and frequencies. They may opt to discontinue after their first experience of usage, prolong, or increase the intensity or frequency of their usage at various stages in their life. In the United Kingdom, approximately 20% of HIV-negative MSM surveyed in sexual health clinics and 30% of sexually active HIV-positive men recently had chemsex[4].

According to the recommended HIV/acquired immunodeficiency syndrome (AIDS) Strategies for Hong Kong by the Hong Kong Advisory Council on AIDS (2022), chemsex is now a slang term used by homosexual men and other MSMs to describe sex involving psychotropic substances, typically methamphetamine and GHB, to improve sex lives. In the HIV and AIDS Response indicator Survey (HARiS) 2020, 8.6% of MSM participants admitted engaging in chemsex over the last half year, a small increase from 7.3% in HARiS 2018[5]. According to this report, poppers, ice, and GHB were the most popular drugs. Usually, chemsex users have a better understanding of health issues than those who do not. This may be due to the greater perceived danger of contracting HIV among MSM. Specifically, chemsex participants revealed higher levels of HIV testing and pre-exposure prophylaxis (PrEP) use than non-chemsex participants.

There is a risk of developing addiction to psychotropic chemicals used in chemsex. This includes symptoms such as high cravings, psychological problems such as impatience, and trouble managing the dosage. A person's genetic or biological susceptibility, the type of drugs taken, and the frequency, duration, and method of administration all play a role in the likelihood of acquiring this problem. Epidemiological research shows that those with a history of drug use disorders have a 2-5 times greater chance of having psychiatric problems, including depression. It is possible that both mental health issues and drug use come from shared risk factors including a history of trauma and underprivileged upbringing.

Depending on the chemsex behavior, protective or behavioral risk factors may be identified. This study examined the prevalence of condom usage among important demographics in Hong Kong. Among MSM, condom use for sexual activity with ordinary partners was relatively low. The prevalence of persistent condom usage among MSM is inadequate and far below the objective. MSM may use condoms arbitrarily based on the sex partner/activity[1,6]. Recently, the use of PrEP has increased, which may be partially responsible for the decline in condom usage[7]. In 2019, there was a near-successful effort to reduce sharing of needles with other individuals among persons who inject drugs (PWID); however, there was a resurgence of this trend in 2020. The frontline non-government organization in Hong Kong stated that the coronavirus disease 2019 pandemic had caused the majority of PWID to remain at home, and pharmacies to shut down due to insufficient needle supplies[8].

Majority of the data regarding the mental health repercussions of chemsex come from studies of drug use among homosexual males, regardless of the context of usage. Being part of a sexual minority group increases the risk of developing a mental illness by around 2-3 times than that of heterosexual colleagues. The total prevalence of mental illnesses among sexual minority groups associated with drug use disorders was significantly greater. A recent Australian study discovered that 20%-30% of an online sample of homosexual males tested positive for mild anxiety or depression. A greater prevalence of mental disorders was associated with earlier cannabis and methamphetamine use. Moreover, almost half of these males (46%) had signs of depression. Depression is often characterized by persistent poor mood, loss of interest in formerly enjoyable activities, changes in sleeping habits and food, and, in extreme cases, a sense of regret, despair, and suicidal ideation[9,10]. Methamphetamine can cause psychosis with characteristics comparable to those of schizophrenia[1]. According to a previous study, up to 15% of chronic methamphetamine users developed psychosis. This danger is greater for

individuals who use marijuana on a regular, chronic, or injectable basis. They are often characterized by auditory hallucinations and inability to suspend one's views in the absence of adequate proof (delusions), which are frequently persecutory in nature, as though one is being observed or plotted against. Consequently, disordered, aggressive, or self-harming behaviors may develop[6]

Over 50% of the research participants recently engaged in condomless anal intercourse, including 26 who ultimately tested positive [hazard risk (HR): 3.75, 95%CI: 1.31–10.74]. The number of sexual partners and the chances of contracting HIV have increased progressively. For instance, five of 60 males who had five to ten condom-free relationships in the preceding three months tested positive (HR: 9.60, 95%CI: 2.58–35.76)[9].

HIV infection is not linked to age, housing status, economic standing, family situation, previous HIV screening, fisting, sex toys, PrEP, tobacco use, drinking, or depressive or anxiety disorders. In an era of expanding access to rapid HIV therapy and PrEP, the findings underscore dangerous situations and behaviors[7]. The increased risk associated with drug use may reflect subsequent sexual behavior; however, transmission *via* shared needles is also a factor.

ACKNOWLEDGEMENTS

The preparation of this manuscript was partially supported by funding's from the Department of Applied Social Sciences, The Hong Kong Polytechnic University.

FOOTNOTES

Author contributions: Chan ASW and Yan E carried out the outline of this manuscript; Chan ASW wrote the manuscript with support from Yan E and Tang PMK; Yan E and Tang PMK gave valuable comments and suggestion; Yan E helped to supervise the whole manuscript; All authors contributed to the article and approved the submitted version.

Conflict-of-interest statement: No potential conflict of interest was reported by the authors.

Country/Territory of origin: China

ORCID number: Alex Siu Wing Chan 0000-0003-4420-8789; Patrick Ming Kuen Tang 0000-0002-3194-3736; Elsie Yan 0000-0002-0604-6259.

S-Editor: Zhang H
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Chan ASW**, Tang PMK. Application of Novel Psychoactive Substances: Chemsex and HIV/AIDS Policies Among Men Who Have Sex With Men in Hong Kong. *Front Psychiatry* 2021; **12**: 680252 [PMID: 34335329 DOI: 10.3389/fpsyt.2021.680252]
2 **Smiles C**, O'Donnell A, Jackson K. Needle exchange practitioners accounts of delivering harm reduction advice for chemsex: implications for policy and practice. *Drugs: Educ, Prev Policy* 2022; 1-9 [DOI: 10.1080/09687637.2022.2027345]
3 **Nimbi FM**, Rosati F, Esposito RM, Stuart D, Simonelli C, Tambelli R. Chemsex in Italy: Experiences of Men Who Have Sex With Men Consuming Illicit Drugs to Enhance and Prolong Their Sexual Activity. *J Sex Med* 2020; **17**: 1875-1884 [PMID: 32727698 DOI: 10.1016/j.jsxm.2020.07.001]
4 **Yan H**, Peters H, Thorne C. Neonatal deaths among infants born to women living with HIV in the UK and Ireland. *AIDS* 2022; **36**: 287-296 [PMID: 34628441 DOI: 10.1097/QAD.0000000000003095]
5 **Tam G**, Lee SS. Acceptance of opt-out HIV testing in out-patient clinics in Hong Kong. *Hong Kong Med J* 2022; **28**: 86-87 [PMID: 35260500 DOI: 10.12809/hkmj209222]
6 **Songtachalert T**, Roomruangwong C, Carvalho AF, Bourin M, Maes M. Anxiety Disorders: Sex Differences in Serotonin and Tryptophan Metabolism. *Curr Top Med Chem* 2018; **18**: 1704-1715 [PMID: 30430940 DOI: 10.2174/1568026618666181115093136]
7 **Flores Anato JL**, Panagiotoglou D, Greenwald ZR, Blanchette M, Trottier C, Vaziri M, Charest L, Szabo J, Thomas R,

Maheu-Giroux M. Chemsex and incidence of sexually transmitted infections among Canadian pre-exposure prophylaxis (PrEP) users in the l'Actuel PrEP Cohort (2013-2020). *Sex Transm Infect* 2022 [PMID: 35039437 DOI: 10.1136/sextrans-2021-055215]

8 **Suen YT**, Chidgey A. Disruption of HIV Service Provision and Response in Hong Kong During COVID-19: Issues of Privacy and Space. *J Int Assoc Provid AIDS Care* 2021; **20**: 23259582211059588 [PMID: 34841949 DOI: 10.1177/23259582211059588]

9 **Hanum N**, Cambiano V, Sewell J, Rodger AJ, Nwokolo N, Asboe D, Gilson R, Clarke A, Miltz AR, Collins S, Delpech V, Croxford S, Phillips AN, Lampe FC; AURAH2 Study Group. Trends in HIV incidence between 2013-2019 and association of baseline factors with subsequent incident HIV among gay, bisexual, and other men who have sex with men attending sexual health clinics in England: A prospective cohort study. *PLoS Med* 2021; **18**: e1003677 [PMID: 34143781 DOI: 10.1371/journal.pmed.1003677]

10 **Schmidt AJ**, Bourne A, Weatherburn P, Reid D, Marcus U, Hickson F; EMIS Network. Illicit drug use among gay and bisexual men in 44 cities: Findings from the European MSM Internet Survey (EMIS). *Int J Drug Policy* 2016; **38**: 4-12 [PMID: 27788450 DOI: 10.1016/j.drugpo.2016.09.007]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 212-215

DOI: 10.5501/wjv.v11.i4.212

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Cautious optimism in anticipation of hepatitis B curative therapies

Alla Turshudzhyan, Micheal Tadros

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chi G, China; Gao P, China; Morozov S, Russia; Sira AM, Egypt

Received: February 19, 2022
Peer-review started: February 19, 2022
First decision: May 12, 2022
Revised: May 15, 2022
Accepted: July 16, 2022
Article in press: July 16, 2022
Published online: July 25, 2022

Alla Turshudzhyan, Department of Medicine, University of Connecticut, Farmington, CT 06030-1235, United States

Micheal Tadros, Department of Gastroenterology and Hepatology, Albany Medical College, Albany, NY 12208, United States

Corresponding author: Alla Turshudzhyan, DO, Department of Medicine, University of Connecticut, 263 Farmington Avenue, Farmington, CT 06030-1235, United States.
turshudzhyan@uchc.edu

Abstract

Despite relative effectiveness of current hepatitis B therapies, there is still no curative agents available. The new emerging approaches hold promise to achieve cure and loss of hepatitis B surface antigen. Studies or clinical trials investigating new therapies remain small and either focus on patients with low viral load and without hepatotoxic injury or patients with hepatitis D co-infection, which makes it challenging to assess their effectiveness and side effect profile in hepatitis B population.

Key Words: Hepatitis B; Hepatitis B virus; Hepatitis B virus entry inhibitor; Bulevirtide; Transcription activator-like effector nucleases; Zinc-finger nucleases; Clustered regularly interspaced short palindromic repeats-associated 9; Nucleocapsid assembly modulators; Hepatitis B virus transcription inhibitors; Hepatitis B surface antigen release inhibitors

Core Tip: Hepatitis B could become a curable disease in the near future. As our understanding of pathophysiology of hepatitis B infection advances, more therapeutic targets are becoming available. Many new therapies have only been investigated in small groups of patients with low viral load and without hepatotoxic injury or in patients with hepatitis D co-infection, which makes it difficult to predict efficacy and side effect profile when applied to the population of interest. Larger clinical trials in hepatitis B patients are needed to further investigate the emerging new therapies, so that more patients can safely benefit from them.

Citation: Turshudzhyan A, Tadros M. Cautious optimism in anticipation of hepatitis B curative therapies. *World J Virol* 2022; 11(4): 212-215
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/212.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.212

TO THE EDITOR

We read with great pleasure the article by Leowattana *et al*[1] about new emerging therapies in treatment of chronic hepatitis B. They presented a comprehensive review of currently available therapies, pathophysiology of the hepatitis B infection, and developing new therapies. While current therapies, such as nucleosides, are effective in suppressing viral replication and preventing progression of chronic hepatitis to cirrhosis or hepatocellular carcinoma, they are unable to achieve cure from hepatitis B infection. As a result, new therapies are now being investigated that are aimed at a complete cure and loss of hepatitis B surface antigen (HBsAg). Leowattana *et al*[1] presented a comprehensive discussion of developing new therapies, which include agents that inhibit entry of hepatitis B virus (HBV) into hepatocytes, interfere with cccDNA or HBV transcription, alternate nucleocapsid assembly, and prevent HBsAg release from the hepatocytes. The authors are hopeful that given currently available evidence on these emerging therapies, chronic hepatitis B could become a curable disease in the near future. While we share their sentiment and are hopeful for these therapies to be successful in curing hepatitis B infection, we would like to recommend cautious optimism when assessing these new therapeutic agents.

HBV entry inhibitor, bulevirtide, was originally intended to be used for hepatitis D treatment. Wedemeyer *et al*[2] presented results of a phase 2b trial in 2019 which included 60 patients with chronic HBV/ hepatitis D virus (HDV) co-infection. While their results were encouraging, the population under investigation was small and all of the patients had both viruses present, which makes it more difficult to apply these results to patients with HBV infection alone. Wedemeyer *et al*[2] documented increased bile acid concentration in patients on bulevirtide and rebound in viral load after therapy discontinuation, which may cause more liver damage. The increase in bile acid concentration while on bulevirtide was also investigated by the Blank *et al*[3] They confirmed increased bile acid concentration associated with bulevirtide without cholestasis, however, their study was limited to 12 healthy volunteers and did not include patients with pre-existing chronic liver disease or with hepatitis B infection, which makes it less applicable to the population of interest. While there are no ongoing clinical trials with hepaitits B patients on bulevirtire, there is phase 3 trial on bulevirtide use in HDV infection which includes 150 adults with HDV infection[4]. It will help reveal long term effects of therapy and help us better understand the adverse events associated with it. The downside of this phase 3 trial is that it is limited to HDV patients. There is still no long-term data on side effect profile of bulevirtide in HBV patients exclusively. We hope there will be new trials to investigate its application in HBV patients.

Gene editing tools such as the transcription activator-like effector nucleases, zinc-finger nucleases, and clustered regularly interspaced short palindromic repeats-associated 9 could be a new exciting therapy option in curing chronic hepatitis B. The authors did a comprehensive review of the available options for gene editing. It is important to note, however, that like with any genetic intervention there is a risk of off-target cleavage[5], so more studies and large clinical trials are needed to investigate this therapeutic option.

Nucleocapsid assembly modulators are another exciting modality reported by Leowattana *et al*[1] but it is another therapy that should be treated with caution until more data from larger clinical trials is available. Zhang *et al*[6] reported that 75% of patients in their study evaluating nucleocapsid assembly modulators experienced elevations in aminotransferases with 4 out of 24 patients requiring to stop therapy and receive glutathione.

HBV transcription inhibitors are another emerging therapy that is currently being investigated. There were two clinical trials evaluating HBV transcription inhibitors in phase II[7,8] and one clinical trial in phase I[9] that were discontinued because of the observed lethal toxicity of the EX1 delivery formulation. More studies are needed to investigate the safety profile of this therapy before it can be considered for clinical application. Another practical consideration with any emerging therapy that requires a viral vector to be delivered into the cells is the risk of pre-existing immunity to vectors or development of host immunity to vectors during treatment, which will ultimately render therapy ineffective[10].

Lastly, HBsAg release inhibitors have been under investigation in various clinical trials. Alanine aminotransferase flares were observed in 90% of patients treated with HBsAg release inhibitors[11,12]. Additionally, because most of the data came from patients with low viral load, safety and efficacy in patients with high viral load is still to be determined. Similar to bulivertide, there were reports that discontinuation of HBsAg release inhibitors caused viral rebound precipitating liver decompensation in patient with significant chronic liver disease[13].

We commend Leowattana *et al*[1] for their comprehensive review of the emerging new therapies that have the potential to cure chronic hepatitis B. Our goal was to merely add caution to the optimism and hopefully prompt larger clinical trial specific to hepatitis B population, so that more patients can safely benefit from the new therapies in the near future.

FOOTNOTES

Author contributions: Turshudzhyan A wrote the letter; and Tadros M revised the letter.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

Country/Territory of origin: United States

ORCID number: Alla Turshudzhyan 0000-0001-6867-7569; Micheal Tadros 0000-0003-3118-3893.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Leowattana W**, Leowattana T. Chronic hepatitis B: New potential therapeutic drugs target. *World J Virol* 2022; **11**: 57-72 [PMID: 35117971 DOI: 10.5501/wjv.v11.i1.57]
2 **Wedemeyer H**, Schöneweis K, Bogomolov PO, Voronkova N, Chulanov V, Stepanova T, B Bremer, L Allweiss, M Dandri, J Burhenne. GS-13-Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in cwith PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection. *J Hepatol* 2019; **70**: e81 [DOI: 10.1016/S0618-8278(19)30141-0]
3 **Blank A**, Eidam A, Haag M, Hohmann N, Burhenne J, Schwab M, van de Graaf S, Meyer MR, Maurer HH, Meier K, Weiss J, Bruckner T, Alexandrov A, Urban S, Mikus G, Haefeli WE. The NTCP-inhibitor Myrcludex B: Effects on Bile Acid Disposition and Tenofovir Pharmacokinetics. *Clin Pharmacol Ther* 2018; **103**: 341-348 [PMID: 28543042 DOI: 10.1002/cpt.744]
4 **Gilead Sciences**. Study to Assess Efficacy and Safety of Bulevirtide in Participants With Chronic Hepatitis Delta (CHD). [accessed 2022 May 15]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: http://clinicaltrials.gov/show/NCT03852719 ClinicalTrials.gov Identifier: NCT03852719
5 **Smith T**, Singh P, Chmielewski KO, Bloom K, Cathomen T, Arbuthnot P, Ely A. Improved Specificity and Safety of Anti-Hepatitis B Virus TALENs Using Obligate Heterodimeric *Fok*I Nuclease Domains. *Viruses* 2021; **13** [PMID: 34372550 DOI: 10.3390/v13071344]
6 **Zhang H**, Wang F, Zhu X, Chen Y, Chen H, Li X, Wu M, Li C, Liu J, Zhang Y, Ding Y, Niu J. Antiviral Activity and Pharmacokinetics of the Hepatitis B Virus (HBV) Capsid Assembly Modulator GLS4 in Patients With Chronic HBV Infection. *Clin Infect Dis* 2021; **73**: 175-182 [PMID: 32649736 DOI: 10.1093/cid/ciaa961]
7 **Arrowhead Pharmaceuticals**. A Multi-dose Study of ARC-520 in Patients With Hepatitis B 'e' Antigen (HBeAg) Negative, Chronic Hepatitis B Virus (HBV) Infection. [accessed 2022 May 15]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: http://clinicaltrials.gov/show/NCT02604199 ClinicalTrials.gov Identifier: NCT02604199
8 **Arrowhead Pharmaceuticals**. A Multi-dose Study of ARC-520 in Patients With Hepatitis B 'e' Antigen (HBeAg) Positive, Chronic Hepatitis B Virus Infection. [accessed 2022 May 15]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: http://clinicaltrials.gov/show/NCT02604212 ClinicalTrials.gov Identifier: NCT02604212
9 **Arrowhead Pharmaceuticals**. A Study of ARC-521 Injection in Normal Adult Volunteers and Patients With Chronic Hepatitis B (CHB). [accessed 2022 May 15]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: http://clinicaltrials.gov/show/NCT02797522 ClinicalTrials.gov Identifier: NCT02797522
10 **Calcedo R**, Morizono H, Wang L, McCarter R, He J, Jones D, Batshaw ML, Wilson JM. Adeno-associated virus antibody profiles in newborns, children, and adolescents. *Clin Vaccine Immunol* 2011; **18**: 1586-1588 [PMID: 21775517 DOI: 10.1128/CVI.05107-11]
11 **Bazinet M**, Pântea V, Placinta G, Moscalu I, Cebotarescu V, Cojuhari L, Jimbei P, Iarovoi L, Smesnoi V, Musteata T, Jucov A, Dittmer U, Krawczyk A, Vaillant A. Safety and Efficacy of 48 Weeks REP 2139 or REP 2165, Tenofovir Disoproxil, and Pegylated Interferon Alfa-2a in Patients With Chronic HBV Infection Naïve to Nucleos(t)ide Therapy. *Gastroenterology* 2020; **158**: 2180-2194 [PMID: 32147484 DOI: 10.1053/j.gastro.2020.02.058]
12 **Al-Mahtab M**, Bazinet M, Vaillant A. Safety and Efficacy of Nucleic Acid Polymers in Monotherapy and Combined with

Immunotherapy in Treatment-Naive Bangladeshi Patients with HBeAg+ Chronic Hepatitis B Infection. *PLoS One* 2016; **11**: e0156667 [PMID: 27257978 DOI: 10.1371/journal.pone.0156667]

13 **Sonneveld MJ**, Gehring AJ, Janssen HLA. Nucleic Acid Polymer Therapy for Hepatitis B Virus: Strong Hepatitis B Surface Antigen Decline But Many Unanswered Questions. *Gastroenterology* 2021; **160**: 966-967 [PMID: 32866506 DOI: 10.1053/j.gastro.2020.06.097]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 July 25; 11(4): 216-220

DOI: 10.5501/wjv.v11.i4.216

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

"Heart failure in COVID-19 patients: Critical care experience": A letter to the editor

Vasiliki Tsigkou, Gerasimos Siasos, Evangelos Oikonomou, Evanthia Bletsa, Manolis Vavuranakis, Dimitris Tousoulis

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Barone M, Italy; Lee S, South Korea; Papadopoulos K, Thailand; Wang MK, China

Received: March 7, 2022
Peer-review started: March 7, 2022
First decision: April 8, 2022
Revised: June 15, 2022
Accepted: July 6, 2022
Article in press: July 6, 2022
Published online: July 25, 2022

Vasiliki Tsigkou, Gerasimos Siasos, Evangelos Oikonomou, Evanthia Bletsa, Manolis Vavuranakis, Department of Cardiology, 'Sotiria' General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens 11527, Greece

Gerasimos Siasos, Division of Cardiovascular, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, United States

Dimitris Tousoulis, Department of Cardiology, 'Hippokration' General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens 11527, Greece

Corresponding author: Vasiliki Tsigkou, MD, MSc, Academic Research, Doctor, Department of Cardiology, 'Sotiria' General Hospital, National and Kapodistrian University of Athens, School of Medicine, Mesogeion 152, Athens 11527, Greece. bikytsigkoy@yahoo.gr

Abstract

Coronavirus disease 2019 (COVID-19) is associated with poor cardiovascular outcomes in patients with heart failure (HF) of all categories of ejection fraction (EF), but mainly in patients with HF with reduced EF. Moreover, cardiac transplant patients exhibit worse cardiovascular prognosis, high mortality, and more admissions to the intensive care unit. In general, COVID-19 seems to deteriorate the clinical status of HF and favors the development of acute respiratory distress syndrome and multiorgan failure, especially in the presence of cardiovascular comorbidities such as diabetes mellitus, kidney dysfunction, and older age. COVID-19 may induce new-onset HF with complex mechanisms that involve myocardial injury. Indeed, myocardial injury comprises a large category of detrimental effects for the myocardium, such as myocardial infarction type 1 or type 2, Takotsubo cardiomyopathy, microvascular dysfunction and myocarditis, which are not easily distinguished by HF. The pathophysiologic mechanisms mainly involve direct myocardial damage by severe acute respiratory syndrome coronavirus 2, cytokine storm, hypercoagulation, inflammation, and endothelial dysfunction. The proper management of patients with COVID-19 involves careful patient evaluation and ongoing monitoring for complications such as HF.

Key Words: Heart failure; COVID-19; Prognosis; Intensive care unit; New onset heart failure; Ejection fraction

Core Tip: Coronavirus disease 2019 poses a serious threat to patients with pre-existing heart failure (HF) and might induce new-onset HF in hospitalized patients, with complex mechanisms that involve myocardial injury. Cytokine storm, described as excessive inflammation and coagulation, results in microvascular dysfunction, myocardial ischemia and myocarditis, which might not be easily distinguishable from HF. Patients with advanced HF, such as those with reduced ejection fraction, exhibit worse cardiovascular outcomes. Treatment should take into consideration patient-specific characteristics and includes a thorough cardiologic assessment along with obtainment of evidence following published guidelines.

Citation: Tsigkou V, Siasos G, Oikonomou E, Bletsa E, Vavuranakis M, Tousoulis D. "Heart failure in COVID-19 patients: Critical care experience": A letter to the editor. *World J Virol* 2022; 11(4): 216-220
URL: https://www.wjgnet.com/2220-3249/full/v11/i4/216.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i4.216

TO THE EDITOR

We read with interest the systematic review of John *et al*[1], who presented the interaction between coronavirus disease 2019 (COVID-19) and heart failure (HF) from a critical care perspective. After discussing evidence from 26 observational studies, the authors concluded that patients with HF have higher mortality during hospitalization for COVID-19, as well as more complications and admissions to the intensive care unit (ICU)[1]. Furthermore, they found that patients with HF with reduced ejection fraction (HFrEF) exhibited worse outcomes in comparison to patients with HF with mildly reduced ejection fraction (HFmrEF) and with preserved EF (HFpEF)[1].

Patients with HF and COVID-19 develop serious complications, according to the literature; these include severe hypotension, acute respiratory distress syndrome (ARDS), and death[2]. This comes in accordance with the authors' conclusions that HF is a risk factor for COVID-19 and that patients with HF might require hospitalization or develop more complications post hospitalization in ICU, possibly due to an additional organ injury[1]. Patients with HF often need mechanical ventilation and develop venous thromboembolism, sepsis, acute kidney injury, and stroke[3]. In clinically unstable patients with COVID-19 recommendations suggest the discontinuation of chronic cardioprotective medications, such as angiotensin-converting enzyme (ACE) inhibitors or the angiotensin receptor-neprilysin inhibitor due to hypotension[4]. Among the literature there is uncertainty about the safety of these drugs in patients with HF since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE2 receptor and administration of these regimens increase the expression of ACE2 in the heart[5,6]. Several clinical trials are under progress, nevertheless, the current recommendation is to continue these drugs in clinically stable patients and in infected patients at risk of complications[6].

Heart transplant patients with comorbidities exhibit poorer cardiovascular outcomes and a need for ICU therapeutic modalities[7]. John *et al*[1] have also resulted in this conclusion, although the prognosis of critically ill heart transplant patients was, according to them, somewhat similar to the critically ill non-heart transplant patients. As mentioned by the authors, patients with HFrEF and COVID-19 have a poorer overall prognosis[1]. Indeed, COVID-19 is linked to poor prognosis of patients with advanced HFrEF, which is reflected by the need for inotropes and/or an intra-aortic balloon pump, increased incidence of lethal arrhythmias and/or cardiogenic or septic shock, and the need for transplantation[8]. However, evidence from the literature indicates that HFpEF might also be a risk factor for adverse complications, as well as a consequence of COVID-19 due to direct myocardial damage, which highlights the need for proper follow-up care of the infected patients[9,10].

COVID-19 may worsen myocardial injury in patients with HF due to the release of pro-inflammatory cytokines, the so-called 'cytokine storm'[11]. On the other hand, COVID-19 might ignite *de novo* left ventricular dysfunction posthospital admission[2]. Indeed, the risk of *de novo* HF post hospital admission, according to the authors, is greater, especially for patients who have been admitted to the ICU[1]. The diagnosis of *de novo* HF is challenging, since patients might suffer from subclinical myocarditis, sepsis-induced cardiomyopathy, Takotsubo cardiomyopathy, or subclinical ischemia[12,13]. According to the authors, in most of the studies cardiac injury was defined as the increase in cardiac troponin I > the 99th percentile upper reference limit or new electrocardiography/echocardiography findings; however, not all the studies reported strict definitions about chronic and *de novo* HF[1]. Actually, symptoms of COVID-19 might be similar to HF, and pneumonia and pulmonary edema might coexist, thereby complicating the diagnosis of both entities[14]. Interestingly, this comes in accordance with the authors conclusions about the diagnostic difficulties among patients with severe ARDS due to

COVID-19 and acute decompensation of HF[1].

COVID-19 induces direct and indirect injury in the myocardium *via* various mechanisms that involve excessive inflammation, hypercoagulation, endothelial dysfunction, and sympathetic system activation [15]. Myocardial injury in patients with COVID-19 is mediated by ischemic and non-ischemic mechanisms, which lead to different clinical consequences and therapeutic implications[16]. SARS-CoV-2 binds to human cells on the ACE2 receptor, which is overexpressed in patients with cardiovascular diseases and exerts harmful effects through direct inoculation of the myocardium[17]. Moreover, the virus stimulates an immune response, which involves T lymphocytes and cell-mediated cytotoxicity; these mechanisms may be associated with the induction of myocarditis post-infection[18]. Myocarditis might present as acute HF in serious cases and diagnosis must be carried out with considerations of findings from medical history-taking, laboratory examinations, electrocardiograms, echocardiography, and cardiovascular magnetic resonance studies; however, a definite diagnosis also involves endomyocardial biopsy, which is not routinely performed[13].

On the other hand, SARS-CoV-2 has been implicated in cardiac ischemia of several types[19]. The imbalance between oxygen supply and demand is reflected by the increase in cardiac troponins and reflects type 2 myocardial infarction (MI) ischemia, which is a common characteristic of pneumonia due to hypotension and blood hypoxemia, especially in patients with pre-existing coronary heart disease [19]. Also, type 1 MI might be the result of pre-existing coronary plaques that become unstable due to the proinflammatory and procoagulant states of the infection[20]. Additionally, the virus induces microvascular dysfunction in patients through endothelial dysfunction; in fact, proinflammatory biomarkers and the development of microthrombi may induce endothelial dysfunction at the level of microcirculation[21]. Lastly, there is evidence that acute coronary microvascular dysfunction may result in Takotsubo syndrome in patients with COVID-19 and especially among those with pre-existing comorbidities, but the specific mechanisms are under investigation[22].

Great effort is needed in order to improve our understanding of the therapeutic needs of patients with HF and COVID-19[23]. Lockdown policies might have reduced visits to general practitioners and have led to lower rates of diagnosis of heart disease, which could then result in more *de novo* HF diagnoses[24]. Targeting the cytokine storm with anti-inflammatory medications such as corticosteroids has been linked to decreased morbidity and mortality from virus infection[25]. On-going inflammation is also present in survivors of COVID-19 infection and poses a great risk for the development of HF, indicating the need for novel therapeutic advances[25]. The development of myocardial injury following COVID-19 infection and specifically of *de novo* HF might result in more hospitalizations and higher mortality; therefore, understanding the pathophysiology of COVID-19 is the cornerstone for therapeutic success[26]. This comes in accordance with the authors conclusions about the need of future studies in order to elucidate the pathophysiology of the complex effects of COVID-19 in the heart[1]. The management of patients with COVID-19 and prior or *de novo* acute HF should be similar and identify at an early stage possible complications, along with the treatment of oxygenation abnormalities, bleeding events and arrhythmias[27]. A detailed cardiac assessment of the structural and functional characteristics of the infected patients should be performed in order to identify the acute or worsening function of the heart[27]. Moreover, guideline-directed treatment should be continued in patients with HF according to their clinical status, irrespectively of COVID-19[26]. The increase of our knowledge from the on-going studies as well as the course of the pandemic might provide a more robust evidence for the management of the patients[26].

FOOTNOTES

Author contributions: Tsigkou V conceived and designed the study, acquired the data, and analyzed and interpreted the data; Bletsa E, Siasos G, Oikonomou E, Vavuranakis M, and Tousoulis D drafted and made critical revisions to the manuscript; all authors have read and gave final approval of the version of the article to be published.

Conflict-of-interest statement: All the authors state that they have no potential or real conflicts of interest to declare.

Country/Territory of origin: Greece

ORCID number: Vasiliki Tsigkou 0000-0002-2416-1461; Gerasimos Siasos 0000-0001-7601-8870; Evangelos Oikonomou 0000-0001-8079-0599; Evanthia Bletsa 0000-0003-3680-859X; Dimitris Tousoulis 0000-0001-7492-4984.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES

1 **John KJ**, Mishra AK, Ramasamy C, George AA, Selvaraj V, Lal A. Heart failure in COVID-19 patients: Critical care experience. *World J Virol* 2022; **11**: 1-19 [PMID: 35117968 DOI: 10.5501/wjv.v11.i1.1]

2 **Arentz M**, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; **323**: 1612-1614 [PMID: 32191259 DOI: 10.1001/jama.2020.4326]

3 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: 32217556 DOI: 10.1136/bmj.m1091]

4 **Inciardi RM**, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020; **41**: 1821-1829 [PMID: 32383763 DOI: 10.1093/eurheartj/ehaa388]

5 **Danser AHJ**, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. *Hypertension* 2020; **75**: 1382-1385 [PMID: 32208987 DOI: 10.1161/HYPERTENSIONAHA.120.15082]

6 **Vaduganathan M**, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* 2020; **382**: 1653-1659 [PMID: 32227760 DOI: 10.1056/NEJMsr2005760]

7 **Bottio T**, Bagozzi L, Fiocco A, Nadali M, Caraffa R, Bifulco O, Ponzoni M, Lombardi CM, Metra M, Russo CF, Frigerio M, Masciocco G, Potena L, Loforte A, Pacini D, Faggian G, Onorati F, Sponga S, Livi U, Iacovoni A, Terzi A, Senni M, Rinaldi M, Boffini M, Marro M, Jorgji V, Carrozzini M, Gerosa G. COVID-19 in Heart Transplant Recipients: A Multicenter Analysis of the Northern Italian Outbreak. *JACC Heart Fail* 2021; **9**: 52-61 [PMID: 33309578 DOI: 10.1016/j.jchf.2020.10.009]

8 **Bocchi EA**, Lima IGCV, Biselli B, Salemi VMC, Ferreira SMA, Chizzola PR, Munhoz RT, Pessoa RS, Cardoso FAM, Bello MVO, Hajjar LA, Gomes BR. Worsening of heart failure by coronavirus disease 2019 is associated with high mortality. *ESC Heart Fail* 2021; **8**: 943-952 [PMID: 33498096 DOI: 10.1002/ehf2.13199]

9 **Panagides V**, Vincent F, Weizman O, Jonveaux M, Trimaille A, Pommier T, Cellier J, Geneste L, Marsou W, Deney A, Attou S, Delmotte T, Fauvel C, Ezzouhairi N, Perin B, Zakine C, Levasseur T, Ma I, Chavignier D, Noirclerc N, Darmon A, Mevelec M, Karsenty C, Duceau B, Sutter W, Mika D, Pezel T, Waldmann V, Ternacle J, Cohen A, Bonnet G; Critical COVID-19 France Investigators. History of heart failure in patients with coronavirus disease 2019: Insights from a French registry. *Arch Cardiovasc Dis* 2021; **114**: 415-425 [PMID: 34099379 DOI: 10.1016/j.acvd.2021.04.003]

10 **Hadzibegovic S**, Lena A, Churchill TW, Ho JE, Potthoff S, Denecke C, Rösnick L, Heim KM, Kleinschmidt M, Sander LE, Witzenrath M, Suttorp N, Krannich A, Porthun J, Friede T, Butler J, Wilkenshoff U, Pieske B, Landmesser U, Anker SD, Lewis GD, Tschöpe C, Anker MS. Heart failure with preserved ejection fraction according to the HFA-PEFF score in COVID-19 patients: clinical correlates and echocardiographic findings. Eur J Heart Fail. 2021; 23: 1891-1902 [PMID: 33932255 DOI: 10.1002/ejhf.2210]

11 **Madjid M**, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol* 2020; **5**: 831-840 [PMID: 32219363 DOI: 10.1001/jamacardio.2020.1286]

12 **Mishra AK**, Lal A, Sahu KK, Sargent J. Cardiovascular factors predicting poor outcome in COVID-19 patients. *Cardiovasc Pathol* 2020; **49**: 107246 [PMID: 32640385 DOI: 10.1016/j.carpath.2020.107246]

13 **Siripanthong B**, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, Cooper LT Jr, Chahal CAA. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm* 2020; **17**: 1463-1471 [PMID: 32387246 DOI: 10.1016/j.hrthm.2020.05.001]

14 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

15 **Tomasoni D**, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020; **22**: 957-966 [PMID: 32412156 DOI: 10.1002/ejhf.1871]

16 **Shi S**, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802-810 [PMID: 32211816 DOI: 10.1001/jamacardio.2020.0950]

17 **Lindner D**, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Püschel K, Westermann D. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiol* 2020; **5**: 1281-1285 [PMID: 32730555 DOI: 10.1001/jamacardio.2020.3551]

18 **Abdelnabi M**, Eshak N, Saleh Y, Almaghraby A. Coronavirus Disease 2019 Myocarditis: Insights into Pathophysiology and Management. *Eur Cardiol* 2020; **15**: e51 [PMID: 32617120 DOI: 10.15420/ecr.2020.16]

19 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]

20 **Bikdeli B**, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y,

Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; **75**: 2950-2973 [PMID: 32311448 DOI: 10.1016/j.jacc.2020.04.031]

21 **Chen L**, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020; **116**: 1097-1100 [PMID: 32227090 DOI: 10.1093/cvr/cvaa078]

22 **Minhas AS**, Scheel P, Garibaldi B, Liu G, Horton M, Jennings M, Jones SR, Michos ED, Hays AG. Takotsubo Syndrome in the Setting of COVID-19. *JACC Case Rep* 2020; **2**: 1321-1325 [PMID: 32363351 DOI: 10.1016/j.jaccas.2020.04.023]

23 **Chieffo A**, Stefanini GG, Price S, Barbato E, Tarantini G, Karam N, Moreno R, Buchanan GL, Gilard M, Halvorsen S, Huber K, James S, Neumann FJ, Möllmann H, Roffi M, Tavazzi G, Ferré JM, Windecker S, Dudek D, Baumbach A. EAPCI Position Statement on Invasive Management of Acute Coronary Syndromes during the COVID-19 pandemic. *EuroIntervention* 2020; **16**: 233-246 [PMID: 32404302 DOI: 10.4244/EIJY20M05_01]

24 **Andersson C**, Gerds T, Fosbøl E, Phelps M, Andersen J, Lamberts M, Holt A, Butt JH, Madelaire C, Gislason G, Torp-Pedersen C, Køber L, Schou M. Incidence of New-Onset and Worsening Heart Failure Before and After the COVID-19 Epidemic Lockdown in Denmark: A Nationwide Cohort Study. *Circ Heart Fail* 2020; **13**: e007274 [PMID: 32482087 DOI: 10.1161/CIRCHEARTFAILURE.120.007274]

25 **Freaney PM**, Shah SJ, Khan SS. COVID-19 and Heart Failure With Preserved Ejection Fraction. *JAMA* 2020; **324**: 1499-1500 [PMID: 33001179 DOI: 10.1001/jama.2020.17445]

26 **Task Force for the management of COVID-19 of the European Society of Cardiology**. Corrigendum to: European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1-epidemiology, pathophysiology, and diagnosis; and ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2-care pathways, treatment, and follow-up. *Eur Heart J* 2022; **43**: 1776 [PMID: 34927669 DOI: 10.1093/eurheartj/ehab866]

27 **Zhang Y**, Coats AJS, Zheng Z, Adamo M, Ambrosio G, Anker SD, Butler J, Xu D, Mao J, Khan MS, Bai L, Mebazaa A, Ponikowski P, Tang Q, Ruschitzka F, Seferovic P, Tschöpe C, Zhang S, Gao C, Zhou S, Senni M, Zhang J, Metra M. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; **22**: 941-956 [PMID: 32463543 DOI: 10.1002/ejhf.1915]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2022 September 25; 11(5): 221-393

Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents

Bimonthly Volume 11 Number 5 September 25, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Virology

Bimonthly Volume 11 Number 5 September 25, 2022

Contents

SYSTEMATIC REVIEWS

LETTER TO THE EDITOR

World Journal of Virology

Bimonthly Volume 11 Number 5 September 25, 2022

Contents

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
September 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 221-236

DOI: 10.5501/wjv.v11.i5.221

ISSN 2220-3249 (online)

REVIEW

Mucosal COVID-19 vaccines: Risks, benefits and control of the pandemic

Dimitrina Miteva, Monika Peshevska-Sekulovska, Violeta Snegarova, Hristiana Batselova, Radostina Alexandrova, Tsvetelina Velikova

Specialty type: Immunology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tan JK, Malaysia; Wang CY, Taiwan

Received: March 13, 2022
Peer-review started: March 13, 2022
First decision: April 8, 2022
Revised: May 14, 2022
Accepted: August 10, 2022
Article in press: August 10, 2022
Published online: September 25, 2022

Dimitrina Miteva, Department of Genetics, Sofia University "St. Kliment Ohridski," Faculty of Biology, Sofia 1164, Bulgaria

Monika Peshevska-Sekulovska, Department of Gastroenterology, University Hospital Lozenetz, Sofia 1407, Bulgaria

Monika Peshevska-Sekulovska, Tsvetelina Velikova, Medical Faculty, Sofia University St. Kliment Ohridski, Sofia 1407, Bulgaria

Violeta Snegarova, Clinic of Internal Diseases, Naval Hospital - Varna, Military Medical Academy, Medical Faculty, Medical University, Varna 9000, Bulgaria

Hristiana Batselova, Department of Epidemiology and Disaster Medicine, Medical University, Plovdiv, University Hospital "St George", Plovdiv 6000, Bulgaria

Radostina Alexandrova, Department of Pathology, Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia 1000, Bulgaria

Tsvetelina Velikova, Department of Clinical Immunology, University Hospital Lozenetz, Sofia 1407, Bulgaria

Corresponding author: Tsvetelina Velikova, MD, PhD, Assistant Professor, Department of Clinical Immunology, University Hospital Lozenetz, Kozyak 1 Street, Sofia 1407, Bulgaria. tsvelikova@medfac.mu-sofia.bg

Abstract

Based on mucosal immunization to promote both mucosal and systemic immune responses, next-generation coronavirus disease 2019 (COVID-19) vaccines would be administered intranasally or orally. The goal of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is to provide adequate immune protection and avoid severe disease and death. Mucosal vaccine candidates for COVID-19 including vector vaccines, recombinant subunit vaccines and live attenuated vaccines are under development. Furthermore, subunit protein vaccines and virus-vectored vaccines have made substantial progress in preclinical and clinical settings, resulting in SARS-CoV-2 intranasal vaccines based on the previously successfully used nasal vaccines. Additional to their ability to trigger stable, protective immune responses at the sites of pathogenic infection, the

development of 'specific' mucosal vaccines targeting coronavirus antigens could be an excellent option for preventing future pandemics. However, their efficacy and safety should be confirmed.

Key Words: SARS-CoV-2; COVID-19 vaccine; Mucosal immunity; Intranasal vaccination; Oral vaccines; Resident memory T cells; Vaccine safety; Vaxart; OraPro-COVID-19 vaccine; RPS-vector system platform

Core Tip: Oral or nasal vaccination against coronavirus disease 2019 (COVID-19) would stimulate both the humoral and cellular immune responses and may exert many socioeconomic benefits. Mucosal vaccines are promising for preventing infections and reducing the transmission, morbidity and mortality of COVID-19. Mucosal vaccination may be used prophylactically in human populations at high risk for severe acute respiratory syndrome coronavirus 2. Currently, only a limited number of oral vaccines are approved for human use, and some others are included in preclinical and clinical trials to validate their efficacy and safety.

Citation: Miteva D, Peshevska-Sekulovska M, Snegarova V, Batselova H, Alexandrova R, Velikova T. Mucosal COVID-19 vaccines: Risks, benefits and control of the pandemic. *World J Virol* 2022; 11(5): 221-236
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/221.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.221

INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic, characterized by the ongoing rapid spread and high mutation rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emphasizes the need for more efficient vaccinations to avoid preventable illness and mortality. In addition, SARS-CoV-2 is a mucosal pathogen that spreads *via* person-to-person respiratory droplets[1] and infects human respiratory epithelial cells and gastrointestinal tract by attaching to angiotensin-converting enzyme 2 *via* the spike (S) receptor-binding domain[2]. Thus, mucosal immunity will be primary for adequate and long-term viral protection[3].

To date, there are over 300 potential anti-SARS-CoV-2 vaccines at various stages of preclinical and clinical trials and 24 vaccines approved for emergency use in humans[4-6], (https://covid19.trackvaccines.org/trials-vaccines-by-country/). Approved vaccines and most of the preparations under development are intended to be administered intramuscularly to provide high levels of antibodies against systemic viral infection[7]. This method of administration is the most common immunization method. While it is not the most efficient option to protect against pathogens entering through the mucous membranes, it is still an effective method.

Thus, current vaccines against COVID-19 fail to fully prevent viral infection, which is partly due to the lack of mucosal immune activation. On the other hand, mucosal immunization has the ability to promote both mucosal and systemic immune responses[8].

Over 10 different vaccines against SARS-CoV-2 are in various stages of development, including virus-based vaccines, recombinant subunit vaccines and live attenuated vaccines[9-13]. Their development and application are encouraging because of the expected efficacy of the mucosal and systemic immune response they will elicit.

Despite the emergence of SARS-CoV-2 variants, people will prefer the next generation COVID-19 vaccine (*i.e.* intranasal immunization). This vaccine is expected to be very effective in producing both mucosal and systemic immune responses[13].

Various intranasal vaccines against SARS-CoV-2 are now being studied, even though they are not yet approved, with 12 candidates advancing to multiple stages of clinical trials, including virus-vectored vaccines, recombinant subunit vaccines and live attenuated vaccines[14].

NATURAL AND VACCINE-INDUCED MUCOSAL IMMUNITY: PRINCIPLE OF MUCOSAL VACCINES

The rationale for the need for effective COVID-19 vaccines that elicit mucosal immunity is to use early mucosal immune responses against the virus to prevent the virus from entering mucosal layers and causing infection. This is also called "sterilizing immunity"[15]. So far, the data show that people naturally infected with SARS-CoV-2 produce mucosal immunoglobulin (Ig)A antibodies (*e.g.*, saliva,

nasal swab/wash or bronchoalveolar lavage fluid) and systemic IgG antibodies[16,17].

However, firstly, when SARS-CoV-2 infiltrates the nasal and/or oral cavities, nasopharynx-associated lymphoid tissue, bronchial-associated lymphoid tissue and mucosa-associated lymphoid tissue act as the first line of defense against viral infection[18]. In addition, all components of the innate immunity of the upper respiratory tract and/or the gastrointestinal tract (phagocytic neutrophils, macrophages, dendritic cells, resident microfolded M cells, innate lymphoid cells, natural killer cells and mast cells) [19] and immune molecules (*i.e.* galectins, collectins, cytokines and others) are involved in the immune response against the virus in various ways[20]. Additionally, T helper (Th)1- and Th2 cells, IgA-switched B cells are also rapidly activated after the initial interaction of SARS-CoV-2 with the innate immunity of the host[21].

These immune cells can work together to produce an integrated system that includes pattern-recognition receptors such as toll-like receptor 7 or toll-like receptor 8[22]. They identify molecular patterns (*i.e.* single-stranded RNA) associated with viral pathogens, resulting in increased production of proinflammatory cytokines such as type I interferon. Interferons have an essential role in the early stages of viral infection[23]. However, SARS-CoV-2 possesses the ability to suppress the production of interferons. The complement system is a vital part of innate immunity against SARS-CoV-2, which contributes to acute respiratory distress syndrome and cytokine storm[24]. Therefore, it is important to consider antibody-based treatments and vaccines when developing strategies to fight SARS-CoV-2.

After the innate immune system activation through dendritic cells, T and subsequent B cells specific to SARS-CoV-2 are recruited, mainly in the systemic bloodstream[25]. However, the simultaneous expansion of CD4+ T-helper cells, CD8+ cytotoxic T cells and plasma cells is crucial for viral elimination. Specific SIgA protects against SARS-CoV-2 by neutralizing it, suppressing its adhesion ability and agglutinating. This allows for a stronger anti-inflammatory response[26].

Traditional injectable vaccines are not very effective at inducing mucosal immunity. Furthermore, the benefits of such vaccination that leads to mucosal (SIgA) and circulating (IgG and IgA) antibody formation as well as SARS-specific effector and memory T cell responses have not been demonstrated in conventional vaccines[27,28].

However, a study showed induced S1-specific neutralizing IgA and IgG responses in the nasal mucosa following BNT162b2 but not after inactivated virus vaccine[29]. Additionally, it was shown that nasal immunization after an intramuscular vaccine could induce robust mucosal immunity to prevent mucosal pathogen entrance and development. A recent animal study showed promising results for using mucosal booster immunizations after mRNA priming to elicit mucosal immunity in addition to systemic responses[30].

There is evidence that SARS-CoV-2 nasal vaccination provides protection against both ancestral and mutant strains (*i.e.* variants of concern, B.1.1.7 and B.1.351)[31]. Furthermore, the authors suggest that adenovirus (Ad)-vectored multivalent vaccination delivered *via* the respiratory mucosa is a viable next-generation COVID-19 vaccine approach for inducing overall mucosal immunity against existing and future variants of concern[31].

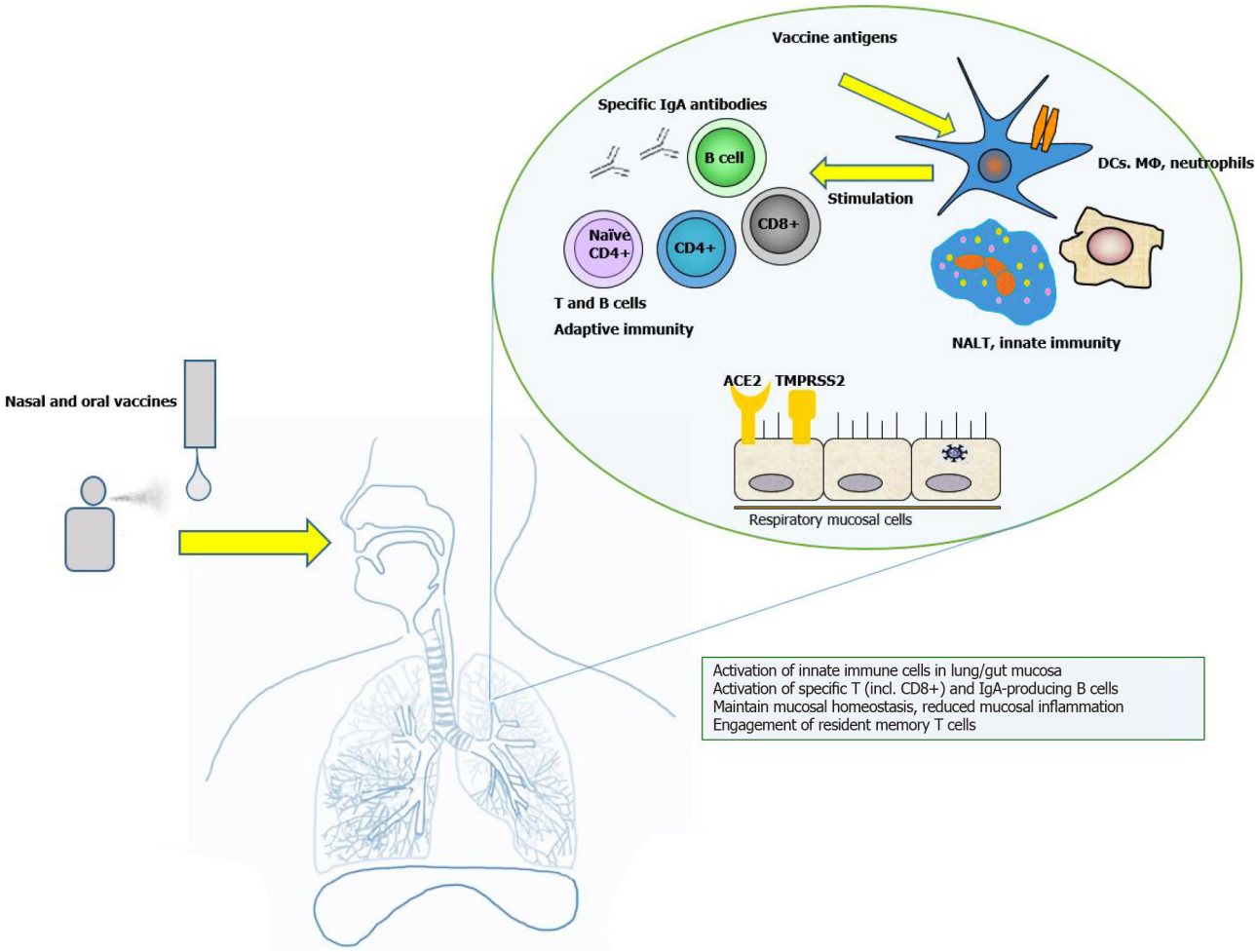
Similarly, a combination of mucosal prime and systemic booster vaccines has been shown to increase the lifespan of lung CD8+ resident memory T cells[32]. In addition, CD4+ resident memory T cells are essential to developing protective CD8+ memory cells and B lymphocytes[33,34]. The ability of nasal vaccinations to induce resident memory T cells in the respiratory and gastrointestinal tract considerably increases their effectiveness. The development of nasal vaccines also relies on the data that mucosal immunization can elicit a wide range of adaptive immune responses, including SIgA antibodies and resident memory T cells[35]. Nasopharynx-associated lymphoid tissue is an important location for the induction of mucosal immune responses. Th1- and Th2-polarized lymphocytes, as well as IgA-secreting B cells, proliferate there. SIgA antibodies neutralize toxins and pathogens *via* immunological exclusion, antigen excretion and intracellular neutralization[36-38].

Additionally, we must keep in mind that mucosal SIgA levels raise up rapidly in babies, and these levels reach adult levels early in the childhood[39]. This should be considered when developing vaccines for children[40]. Also, although the titers of protection are not known now, virus-neutralizing antibodies are needed to protect and control the infection[41].

Nasal vaccination successfully stimulates resident memory T cell production, and persistent antigens in the lungs and gut can support long-term memory cell maintenance[42]. Resident memory T cells (especially CD8+) in the mucosa may help protect the body against virus infection by producing cytokines that mediate tissue antiviral resistance and chemokines that attract additional immune cells [43]. It is known that resident memory T cells are more effective at protecting the lungs than circulating T cells[44]. Furthermore, these memory cells can move from the lungs to mediastinal lymph nodes *via* a mechanism known as "retrograde migration" to maintain the memory phenotype and provide long-term protection[45].

The principle of intranasal vaccines, the vaccine-induced immune responses, mucosal involvement and benefits are shown in Figure 1.

Intranasal and oral COVID-19 vaccines promise to generate both local and systemic immune responses. Fortunately, the local activation of innate antigen-presenting cells by viral antigens leads to the stimulation of adaptive immune cells and an efficient immune response against the virus. Once this occurs, this local immune response has the potential to spread to other mucosal surfaces in the



DOI: 10.5501/wjv.v11.i5.221

Figure 1 Intranasal and oral coronavirus disease 2019 vaccines promise to induce both local and systemic immune responses. ACE2: Angiotensin-converting enzyme 2; DCs: Dendritic cells; Mф: Macrophages; NALT: Nasopharynx-associated lymphoid tissue; Ig: Immunoglobulin; TMPRSS2: Transmembrane serine protease 2.

organism. It is assumed that local immunity will prevent virus entry and shedding and keep low levels of inflammation in the mucous membranes. Some adaptive cells remain in the mucosa and act as effector T cells or specific IgA-plasmacytes. Some of them exert systemic antiviral effects by going to the periphery. Additionally, activated innate and adaptive immune cells can clear the virus at the infection site, leading to undetectable viral RNA in airways and gut mucosa, leading to long-term immunity.

SUCCESSFUL MUCOSAL VACCINES IN HISTORY

Humans have been licensed to eight oral and one intranasal vaccines against various mucosal infections. All of these vaccines are complete viral vaccines[1,32]. These types of vaccines are exceptionally preferred since they do not involve needles. In addition, subunit protein vaccines and virus-vector vaccines have significant advantages. Therefore, using all the scientific data and knowledge gained over the years about these types of vaccines, the scientific community is trying to create nasal vaccines SARS-CoV-2 based on already used vaccines in human history[32].

Oral vaccination can be used prophylactically in human populations at high risk for SARS-CoV-2. Thus, it could be the most cost-effective and efficient way to reduce the transmission of infection and morbidity. As we already stated, a needle-free vaccine eliminates the risk of transmitting blood-borne infections. Another benefit is that healthcare staff can perform oral vaccination without medical training. Pain and discomfort from a needle stick are avoided, as is the need to monitor side effects[32].

Type 1 and 2 monovalent oral poliovirus (OPV) vaccines (serotypes 1 or 3) and bivalent containing serotypes 1 and 3 were approved and licensed in 1961 and type 3 monovalent OPV vaccine in 1962. A trivalent OPV vaccine was approved in 1963. The World Health Organization (WHO) has announced that types 2 and 3 have been eradicated in 2015 and 2019, respectively. It turns out that OPV is the most effective and successful polio vaccine by inducing poliovirus-specific mucosal immunity[46].

The OPV contains a live poliovirus strains (Sabin). The strains are derived from wild polioviruses and have been reduced in virulence. Poliovirus is a member of the enterovirus subgroup of the Picornaviridae family. Picornaviruses are small viruses with an RNA genome, characterized by three poliovirus serotypes (type1, type 2 and type 3). Scientists have proven that immunity to one serotype does not confer significant immunity to other serotypes[47,48]. The virus enters the mouth and spreads throughout the oropharynx and gastrointestinal tract. The poliovirus is usually present in the nasopharynx for 1 wk to 2 wk and can be excreted in the feces for several weeks after infection. Even people with mild symptoms or without illness can be sources of infection[49].

In 2020, a global campaign was launched to end OPV use and switch to inactivated polio vaccination. But the last reports show that the neutralizing antibodies found in the nasopharynx of patients treated with OPV were more than those treated with inactivated polio vaccination[50].

After being ingested, the OPV vaccine replicates in the intestinal mucosa and lymphoid cells in the oropharynx and intestine. It behaves similarly to wild poliovirus. Vaccine strains are excreted in the feces of the vaccinated individual up to 6 wk after a dose, with maximum excretion occurring in the first 1-2 wk.

The OPV vaccine is very effective in protecting people from poliovirus. Interference among serotypes was observed during replication in the gut. A single dose of trivalent OPV elicits immune responses to all three vaccine viruses in half of recipients[51].

It is crucial that the OPV vaccine produces localized immunity in the intestines. This decreases the amount of virus that is shed when someone is re-infected with the same poliovirus serotype and reduces the chance of potential transmission. Subsequent vaccine doses reduce interference during gut replication. In contrast, three doses of vaccine provide immunity to all three poliovirus serotypes in more than 95% of recipients in industrialized countries. The immunity from the OPV is probably lifelong[52,53].

The OPV vaccine has been proven to have many benefits over the years, including providing non-specific protection against other infections. In addition, various studies have been conducted to research the effects of OPV and live enterovirus vaccines on the induction of non-specific immune responses, which show the non-reactogenicity and safety of vaccines[54-57].

All these studies demonstrated that cytopathic agents in the gastrointestinal tract decrease and reduce isolated infections of influenza, Ad, parainfluenza, herpesviruses, *etc.* According to these findings, OPV may offer protection against other viral respiratory infections.

In 2015, another research group conducted a retrospective cohort study in Denmark. They studied how the incidence of infection among the children with various infections changes depending on the last vaccine children received: OPV, DTap- inactivated polio vaccination-Hib (diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemo type b) or measles, mumps, rubella (MMR)[58]. A similar study was conducted in the United States. The results show the most significant reduction in non-specific infections with live vaccines[59].

When COVID-19 cases began to rise worldwide, the researchers began studying the effects of OPV vaccines in symptomatic and asymptomatic patients because the SARS-CoV-2 virus suppresses the innate immune system, which affects adaptive immunity[60]. Suppose the damage to the innate immune system is crucial for the transmission and infection of SARS-CoV-2. In that case, it may be suggested that preparing the immune system before infection can alleviate the course of the COVID-19 disease. Furthermore, evidence suggests that the prophylactic use of OPV or other live vaccines prior to COVID-19 may activate innate immunity and strengthen the immune system for the subsequent SARS-CoV-2 infection[61-63]. Therefore, it is necessary to consider the potential benefits of the OPV vaccine and its application before or together with the available COVID-19 vaccines.

Since the start of the COVID-19 pandemic, scientists have been scrutinizing rotavirus vaccines. Rotavirus is a double-stranded RNA virus (Reoviridae family). The outer capsid contains two important proteins, VP7 (G-protein) and VP4 (P-protein), which stimulate neutralizing antibodies. It is believed that they play an important role in immune protection[64]. The scientists proved that up to 60%-70% of children with severe rotavirus gastroenteritis demonstrate rotavirus antigen and RNA in serum (antigenemia). However, the immune correlates of protection for rotavirus are still not fully understood [64].

The antibodies against VP7 and VP4 that are found in the serum and mucosa probably play a crucial role in protecting against disease. Cell-mediated immunity probably helps to protect from infection and recover from it. Unfortunately, immunity usually does not last long after a vaccine is given. Re-infection can happen at any age[64].

Two live oral rotavirus vaccines, RV5 (RotaTeq) and RV1 (Rotarix), are currently approved for use [65]. In Finland and the United States, Phase III clinical efficacy trials of the RV5 vaccine were conducted. The data proved 74% efficacy after a 3-dose series against G1-G4 rotavirus gastroenteritis and 98% against severe G1-G4 rotavirus gastroenteritis, during the first entire rotavirus season after vaccination. Furthermore, scientists observed children during the first 2 years of life in a large health care utilization study. Among them, the RV5 vaccine decreased the incidence of G1-G4 rotavirus gastroenteritis: medical visits by 86%, emergency department visits by 94% and hospitalizations by 96% [66].

In Latin America and Europe, phase III clinical efficacy trials of RV1 vaccine were conducted. This study found that the 2-dose series against severe rotavirus gastroenteritis is 85% effective to age 1 year. The European study estimated the vaccines efficacy against severe rotavirus gastroenteritis is 96% through the first rotavirus season and 87% against any rotavirus gastroenteritis. The trial data also showed that vaccinating against rotavirus resulted in a 96% reduction in the number of hospitalizations for rotavirus gastroenteritis in the second season after vaccination[67].

In the United States, several RV5 and RV1 case-control vaccine effectiveness evaluations have been conducted among children between 2 years or 3 years or younger. The scientists found that the vaccine effectiveness against the combined outcome of emergency department visits or hospital admission for rotavirus was estimated at 84% for the RV5 and 83% for the RV1 vaccine. Evaluations of vaccine effectiveness tends to increase as the severity of rotavirus disease. Both vaccines have been shown to be effective against a wide range of rotavirus genotypes[68].

The exact duration of immunity with rotavirus vaccine is still unknown. However, effectiveness has been demonstrated in the first 2 years to 3 years of life in the United States. Vaccine efficacy was generally lower in the 2nd year of life than in the 1st year in low-income countries[66,69,70].

In the last 2 years, two more vaccines have received much attention concerning COVID-19. These are the tuberculosis vaccine Bacille Calmette-Guerin (BCG) and MMR vaccine.

BCG vaccination is an effective intervention against tuberculosis, and the researchers could make an effort to create a novel BCG-based vaccine for COVID-19. However, many studies reported non-specific cross-protective effects of the vaccine against other infectious diseases. For example, in 1932 the BCG vaccine was introduced for tuberculosis prevention in Northern Sweden[71]. Later, two groups studied the protective effect of BCG and, for the first time, reported a 45% reduction in child mortality from respiratory infections in West Africa[72,73]. Other examples of BCG-mediated non-specific effects were also reported by Stensballe *et al*[74] and Wardhana *et al*[75].

Furthermore, the BCG vaccine has recently been found to protect against different virus infections such as influenza virus, herpes simplex virus, human papillomavirus, respiratory syncytial virus and virus for yellow fever[76].

With the worldwide occurrence of the SARS-CoV-2, different agencies, including the WHO, have called to explore every possible solution, even already approved therapies and vaccines, to slow transmission and reduce the effects of the COVID-19 pandemic. However, the obtained data suggest that BCG does not reduce COVID-19 mortality. Still, BCG vaccination may reduce the incidence of frequency during the COVID-19 crisis[77,78].

Only randomized controlled trials will show whether BCG reduces the frequency and severity of COVID-19. A recent study, a phase III ACTIVATE trial (NCT03296423), confirmed that adults over 65 years who have recently been vaccinated against BCG are less likely to get new virus infections. The study found that the incidence of new respiratory infections after receiving a placebo vaccine (42.3%) was different from the incidence of new respiratory infections after receiving BCG vaccine (25.0%)[78].

Another clinical trial in Brazil, BATTLE (NCT04369794), is designed to test BCG-like therapeutic vaccination. The aim is to show if it affects the elimination of SARS-CoV-2 and the degree of seroconversion and titration (IgA, IgG and IgM)[79]. In murine models, the new BCG:CoVac form, which combines BCG with the stable form of S protein, simultaneously stimulates SARS-CoV-2 and T-cell responses even at levels equivalent to or higher than expected by current vaccines[80].

In March 2020, with the rise of COVID-19 cases in the United Arab Emirates, the Emirates International Hospital Safety Committee decided to offer a BCG booster vaccination to hospital staff, which is 280 people. Seventy-one received the BCG vaccine. None of the 71 people who received the BCG booster vaccine tested positive for the SARS-CoV-2 virus. For the other 209 individuals that had not received booster BCG, there were 18 positive PCR cases of COVID-19. There were no available reports of complications with the BCG booster group[81]. In conclusion, BCG vaccination may protect medical staff who work or who are vulnerable to SARS-CoV-2 infection. Further studies are needed to determine if BCG vaccine is effective against COVID-19.

MMR (measles-mumps-rubella) vaccine is another childhood vaccine relevant to the COVID-19 pandemic. Homologies of the amino acid sequence between SARS-CoV-2 and measles, rubella and mumps viruses have been found[82,83]. A study found that there is a strong correlation between mumps IgG titers and the severity of COVID-19 in people vaccinated with the MMR vaccine in childhood[84]. There are also data that recently vaccinated MMR people had less severe COVID-19 and lower mortality rate[85].

Until the end of 2021, a placebo-controlled randomized clinical trial was conducted with 30000 individuals to investigate the protective effect of MMR vaccination after a positive test and symptomatic COVID-19[86]. A case-control study indicated that there may be a protective effect of the MMR vaccine against SARS-CoV-2 in males but not in females[87]. Several other studies have shown that recently receiving the MMR vaccine may protect against SARS-CoV-2 and/or the development of severe COVID-19[88-90]. They showed that the MMR vaccine can stimulate innate immunity inducing non-specific protection against other infections. Compared with those in the placebo group, participants who received at least one dose of MMR had a significantly decreased risk for symptomatic COVID-19 and need for treatment.

These data were used to make assumptions about the potential efficacy of COVID-19 vaccine administered live or nasal/oral. We summarize the information in Table 1.

MUCOSAL VACCINES FOR COVID-19: RISKS AND BENEFITS

Since the discovery of the first vaccine, it has always been a question about the benefits and risks of vaccines. However, over the years, vaccination programs that have been introduced and updated have managed to achieve their goals: Smallpox has been eradicated, polio and measles have been almost eradicated, and other diseases have been controlled[91].

The vaccines being administered now are given by injection. The mucosal vaccines can be superior to this process because they will elicit protective immune responses from the mucosa, blocking infection at the site of infection. The nature of the infection should be well known when developing mucosal vaccines: invasive (in intestinal pathogens), locally invasive (in shigellosis) or strictly mucosal (in cholera)[36,91,92]. This will affect the proper access of the circulating antibodies as well as the longevity of the immune response.

A large part of the population is willing to accept vaccines, but the claims about their risks have a greater impact than before. Therefore, the risks associated with a potential decision must be discussed in light of the best available scientific information.

When countries are faced with the decision to include a new vaccine in their national immunization programs, the relevant scientific, clinical, epidemiological and economic factors of the immunization program need to be considered.

Today, many vaccine production platforms vary in complexity and cost[93]. For example, the live attenuated OPV has a significantly lower cost of production. In contrast, the highly complex pneumococcal conjugate vaccine is much more expensive[94]. Financial cost-effectiveness is one of the most important factors when choosing a financial product or service. When a vaccine is cost-effective, it can help to manage both the health and financial consequences in a country. Oral vaccines offer great potential for preventing pandemics because they are very efficient, low cost, require no medical personnel and can elicit both systemic and mucosal immune responses. This type of vaccine is one of the most successful and cost-effective public health investments a country can make to improve people's health.

Oral vaccines require protection in the harsh environment of the gastrointestinal tract, where the pH is low and the proteases are present. Under normal circumstances, antigens that enter orally are treated as nutrients. If a vaccine does not trigger the appropriate danger signals, it is recognized as non-pathogenic by the intestinal tissue[95]. High doses are usually required for successful immunization, but this may increase the risk of tolerance[96]. These barriers are the main reasons there are so few effective oral vaccines.

Mucosal vaccines against SARS-CoV-2 are incredibly challenging to develop and confirm their safety. However, they will offer the ability to trigger stable, protective immune responses at the sites of pathogenic infection. Unfortunately, mortality and morbidity associated with various infectious diseases caused by mucosal pathogens have remained very high over the last 10 years.

Data so far demonstrated several attempts to develop intranasal vaccines against SARS-CoV and Middle East respiratory syndrome, based on viral vector, subunit, DNA, virus-like particle, inactivated and live-attenuated, described extensively elsewhere[97-101]. Based on our experience with mucosal vaccine platforms for SARS and Middle East respiratory syndrome, effective mucosal vaccines against SARS-CoV-2 could be developed. There are different types of correlates of protection, both humoral and cellular, that are associated with different goals of vaccination: prevention of infection at the mucosal or systemic level. However, until their efficacy and safety have been proven in clinical trials, their use is not recommended.

According to WHO data from 2020, lower respiratory tract infections are the fourth leading cause of death worldwide[102]. Developing an effective vaccine to protect against SARS-CoV-2 infection is a worthwhile endeavor. An extensive risk-benefit analysis of COVID-19 vaccines was published in 2021 [103]. The study was focused on thrombocytopenia and thromboembolism. It demonstrated that the risks of thrombocytopenia, venous or arterial thromboembolism, cerebral venous sinus thrombosis and ischemic stroke were much higher after SARS-CoV-2 infection than after vaccination.

The COVID-19 pandemic will continue and will hit low-income countries. Although there are already effective vaccines against SARS-CoV-2, mass production is still difficult, with no global coverage. The development of 'specific' mucosal vaccines targeting coronavirus antigens could be an excellent option for preventing future pandemics.

INTRANASAL AND ORAL COVID-19 VACCINES ON THE GO

As mentioned earlier, intramuscular injections are not effective at reducing viral replication or nasal secretions in the upper respiratory tract. This leads to asymptomatic or mild symptomatic disease,

Table 1 Approved vaccines that have received the attention of the scientific community concerning coronavirus disease 2019 as potential prototypes for developing mucosal coronavirus disease 2019 vaccines

Name of vaccine	Form	Immunity	Dosage	Route
OPV (oral poliovirus vaccine)	Live attenuated poliovirus (Sabin strain types 1, 2 or 3)	Poliovirus-specific mucosal immunity	2 doses	Oral
BCG (Bacille Calmette-Guerin)	Live attenuated bacteria *Mycobacterium bovis*	Mycobacterium-specific mucosal and systemic immunity	0.05 mL until 1 yr of age; 0.1 mL thereafter	Intradermal injection subcutaneous
MMR (measles, mumps and rubella vaccines)	Weakened forms of the measles, mumps and rubella viruses	Measles, mumps and rubella-specific systemic and mucosal immunity	2 doses	Subcutaneous injection
RV1 (Rotarix®)	Live-attenuated rotavirus	Rotavirus-specific mucosal immunity	2 doses	Oral
RV5 (RotaTeq®)	Live-attenuated rotavirus	Rotavirus-specific mucosal immunity	3 doses	Oral

which helps to spread the virus. On the other hand, intranasal vaccinations may generate sterilizing immunity against mucosal infections[104]. In addition, the principle of antigens exposed at the initial site of the viral infection will help to elicit a stable immune response in the mucosa[105]. The systemic immune response induced by intranasal vaccination is equivalent to or even stronger than the response caused by intramuscular immunization. This suggests that a lower dose will be needed to increase the efficacy and safety of vaccination.

Intranasal vaccination with chimpanzee Ad vector SARS-CoV-2 vaccine (ChAd-SARS-CoV-2-S) was shown to generate more significant levels of S-specific neutralizing antibodies in hamsters[106]. Such vaccination can produce pan-reactive antibodies[107], which is particularly attractive given the emergence of new SARS-CoV-2 mutants. The development of this type of vaccine would have a significant socioeconomic impact. A huge population could be vaccinated in a very short time in a global pandemic, such as COVID-19. The vaccines are supplied with nasal devices, which are preferred and convenient for patients. It is unnecessary from very low storage temperatures and a sterile environment that make them suitable for use. Furthermore, mucosal vaccination may hasten herd immunity, owing to its ease of delivery to impoverished individuals in low- and middle-income countries[98].

Because most clinical trial results have not yet been available, preclinical research is required to investigate the immunogenicity and safety of intranasal COVID-19 vaccines.

Preclinical studies of intranasal COVID-19 vaccines include a variety of mechanisms, which have been extensively described by Alu *et al*[8]. Studies on intranasal/mucosal COVID-19 vaccines, both preclinical and clinical trials[8], are shown schematically in Figure 2.

Oral mucosal COVID-19 vaccine: Vaxart

Vaxart's vaccine is an tablet vaccine that contains an adenoviral vector. The vector encodes the SARS-CoV-2 S and nucleocapsid proteins. The vaccine has progressed to a phase I trial (NCT04563702). Therefore, the film-coated tablets provide mucosal immunity by dissolving in the digestive tract. In addition, the active ingredient is protected from the aggressive action of the stomach's acidic environment by its enteric coating[7].

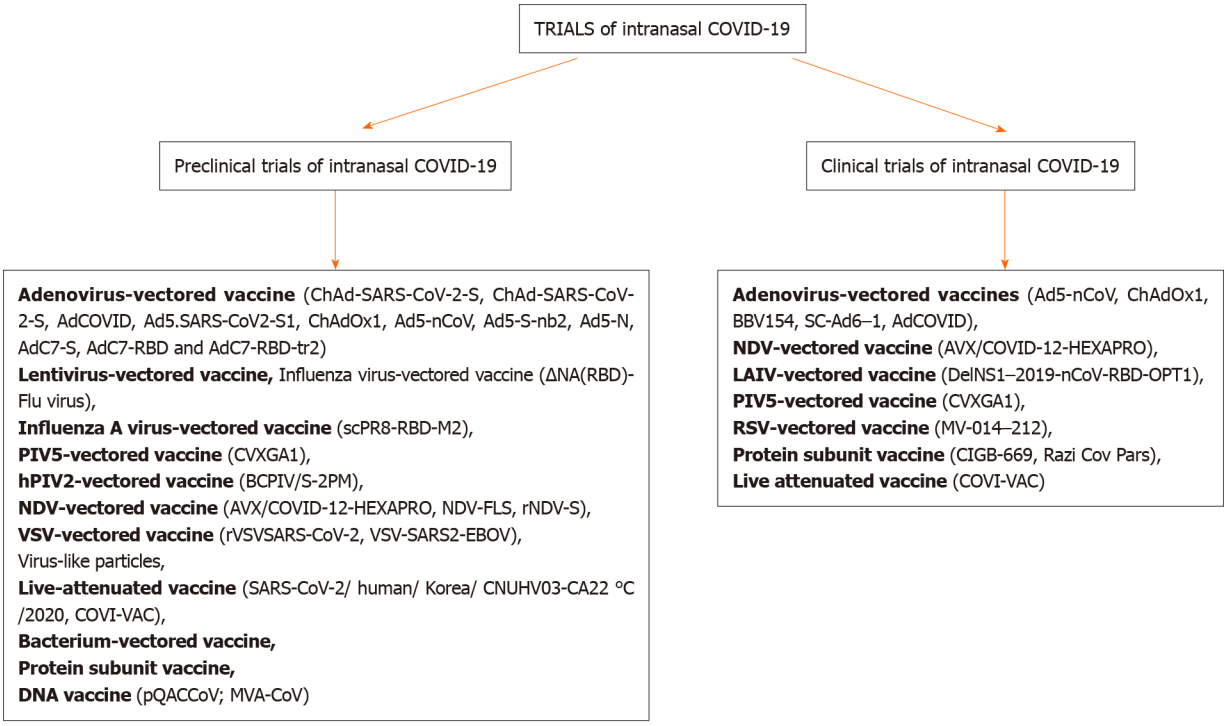
Studies show a significant increase in the titer of neutralizing antibodies against SARS-CoV-2 2 wk after the first vaccination in all animals that received the vaccine compared to the unvaccinated group [108]. Comparing the mucosal application of full-length wild-type S-protein antigens and those of the S1-domain or stabilized S-antigen, mucosal administration induced higher neutralizing antibody titers in the lungs and periphery.

Vaxart's tablet vaccine studies have shown that both low and high doses induce antigen-specific $CD4^+$ and $CD8^+$ cells. It is in the process of undergoing clinical phase evaluation[108].

OraPro-COVID-19™ vaccine - IosBio's (Sabilitech's)

Another interesting project underway is the IosBio Pharma's vaccine (United Kingdom). They also participated in the rat race for the golden choice SARS-CoV-2 vaccine by developing an oral dual-antigen COVID-19 vaccine in capsule form called OraPro-COVID-19[109]. This candidate is based on a human adenoviral vector (hAd5). It expresses modified SARS-CoV-2 S protein and nucleocapsid protein genes with enhanced T-cell stimulation domain, which is predicted to enhance major histocompatibility class II responses[110]. Gabitzsch *et al*[111] first investigated this adenoviral vector platform against various viral antigens such as influenza, HIV-1 and Lassa fever. Their previous and current results show that this immunization model both promotes humoral and cell-mediated immunity[111-114].

In investigating the role of T-cell-mediated immunity in SARS-CoV-2 infection, Sekine *et al*[115] highlighted its importance by detecting virus-specific T-cells in the serum of patients with SARS-CoV-2 negative antibodies, including asymptomatic individuals or exposed family members.



DOI: 10.5501/wjv.v11.i5.221

Figure 2 Preclinical and clinical trials on intranasal/mucosal coronavirus disease 2019 vaccines. PIV5: Parainfluenza Virus 5; hPIV2: Human parainfluenza virus 2; NDV: Newcastle disease virus; VSV: Vesicular stomatitis virus; LAIV: Live attenuated influenza vaccine; RSV: Respiratory syncytial virus; COVID-19: Coronavirus disease 2019.

Gabitzsch *et al*[116] also developed a dual vaccine model to ensure T-cell activation and more durative protective immunity. First, they studied a murine model using hAd5 S-Fusion + nucleocapsid protein genes with enhanced T-cell stimulation domain. They proved that this type of immunization elicits not only a protective humoral but also a Th1-dominant T-cell response. Furthermore, they found that if the vaccine was stored at room temperature, subcutaneous application followed by oral boost elicited both antibody-mediated and T-cell responses. In addition, they also demonstrated that applications of hAd5 S-Fusion + nucleocapsid protein genes with enhanced T-cell stimulation domain inhibited viral replication in both nasal and pulmonary mucosa within 24 h, with complete clearance 7 d after administration.

Human clinical trials are still underway to determine dose strengths and the number of vaccine applications. However, more research is needed to determine if this oral dual vaccine model is effective in managing COVID-19.

COVID-19 oral mucosal vaccine: Recombinant poliovirus Sabin 1-vector system platform

DNA vaccines have some limitations, such as the need for high doses, suitable adjuvants and unique technologies for delivering them to specific sites in the body[117,118]. So poliovirus has been used as a vaccine vector to overcome these barriers due to its safety, low cost and ability to be used orally.

One of the potential platforms for developing an effective vaccine against COVID-19 for oral mucosa is based on the Sabin-1 poliovirus cDNA-based recombinant poliovirus Sabin 1 (RPS) vector system. Sabin-1 is one of three attenuated poliovirus serotypes (OPV). The Sabin strains are safe and easy to store and manipulate experimentally. Therefore, they are ideal vaccine vectors for foreign antigen expression. There are two variants of this system: RPS-Vax and RPS-cytoplasmic transduction peptide (CTP). The RPS-Vax has the multiple cloning site and 3C-protease cutting site, which allow the cloning of a vaccine gene and the release of the vaccine protein from the viral particle during replication[119]. The RPS-CTP vector system is a modified version of the RPS-Vax vector system, which contains CTP right above the multiple cloning site.

Based on the RPS-CTP platform, the vaccine is designed to be used orally instead of parenterally or intramuscularly. In this regard, it has advantages that can make it convenient for patients with COVID-19: easy to apply and no loss during application[120]. In addition, it has also been well established that OPV can induce long T-cell and B-cell memory[121]. Therefore, OPV is an effective and preferred vaccine in most of the world because it has the potential to quickly halt viral transmission. Furthermore, it successfully mimics infection that is naturally acquired due to its oral application.

OPV also has the hypothetical ability to "vaccinate" indirectly through close contact of vaccine recipients, who spread OPV through nasopharyngeal secretions and feces[122]. These results suggest that the vector system RPS-CTP can be used to develop preventive or therapeutic mucosal vaccines against COVID-19 and other diseases.

NEXT-GENERATION RESPIRATORY MUCOSAL DELIVERY OF COVID-19 VACCINE CAN PROVIDE PROTECTION AGAINST SARS-COV-2 AND CONTROL THE PANDEMIC

Although challenging, oral vaccination has many socioeconomic benefits and stimulates both the humoral and cellular immune responses. They are easy to use, even in areas without medical staff, with relatively few side effects and lower cost. Although there are many oral vaccines currently undergoing clinical trials, only a limited number of these vaccines have been approved for human use. According to the WHO, most COVID-19 vaccines are designed to be administered by the intramuscular route[123] in order to produce high titers of neutralizing antibodies. It is well established that mucosal vaccines offer robust protective potential in pathogen infection sites. Additionally, the adaptive immunity induction at mucosal sites comprises secretory antibody production and T cell responses, preventing infection and developing disease symptoms[7]. These data support developing an oral or nasal mucosal vaccine against SARS-CoV-2, as this type of vaccine is known to activate the mucosal immune system and have been successful in protecting people from other infections in the past[124].

Identifying safe and effective mucosal adjuvants allied to innovative antigen delivery plays a crucial role in advancing mucosal COVID-19 vaccines. The complex mechanisms of innate and adaptive mucosal immunity regulation are not yet fully understood. But the significant progress that has been made in recent years will help create more effective oral vaccines. In addition, oral tablet versions of a COVID-19 vaccine will also reach regions without healthcare staff and healthcare infrastructure.

In addition, because the gut is already colonized with microorganisms, oral vaccines do not require extensive and expensive antigen purification. This simplifies the entire production process and reduces the cost. These benefits of oral vaccination may be preferred over conventional vaccination methods during pandemic situations like COVID-19.

The production of effective oral vaccines for COVID-19 must comply with high safety standards, stability and immunogenicity. When oral vaccines succeed in generating protective and therapeutic immune responses, we will be able to overcome the global COVID-19 pandemic that has changed people's lives worldwide[125].

CONCLUSION

A mucosal SARS-CoV-2 vaccine that targets the mucosal surfaces such as the nose or mouth would be ideal if it were shown to be safe. However, there are still major regulatory issues concerning stability and effectiveness. It is fascinating to see if the intranasal application of SARS-CoV-2 mRNA vaccines may induce resident memory T cells and B cells and protect the lungs and gut. Recent and ongoing studies highlight the importance of understanding local immune responses and suggest that mucosal, innate and vaccine-mediated immunity to SARS-CoV-2 has enormous therapeutic implication value.

FOOTNOTES

Author contributions: Miteva D and Velikova T were involved in conceptualizing the idea and writing the draft; Peshevska-Sekulovska M, Snegarova V and Batselova H wrote additional sections in the paper; Velikova T crafted the figure; Alexandrova R was responsible for the critical revision of the manuscript for relevant intellectual content; All of the authors approved the final version of the paper prior to submission.

Conflict-of-interest statement: All the authors declare no conflict of interest.

Country/Territory of origin: Bulgaria

ORCID number: Dimitrina Miteva 0000-0002-5931-2426; Monika Peshevska-Sekulovska 0000-0002-8468-0132; Violeta Snegarova 0000-0003-0754-6439; Hristiana Batselova 0000-0002-6201-848X; Radostina Alexandrova 0000-0002-7699-6479; Tsvetelina Velikova 0000-0002-0593-1272.

S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

REFERENCES

1 **Tiboni M**, Casettari L, Illum L. Nasal vaccination against SARS-CoV-2: Synergistic or alternative to intramuscular vaccines? *Int J Pharm* 2021; **603**: 120686 [PMID: 33964339 DOI: 10.1016/j.ijpharm.2021.120686]
2 **Hsieh CL**, Goldsmith JA, Schaub JM, DiVenere AM, Kuo HC, Javanmardi K, Le KC, Wrapp D, Lee AG, Liu Y, Chou CW, Byrne PO, Hjorth CK, Johnson NV, Ludes-Meyers J, Nguyen AW, Park J, Wang N, Amengor D, Maynard JA, Finkelstein IJ, McLellan JS. Structure-based Design of Prefusion-stabilized SARS-CoV-2 Spikes. *bioRxiv* 2020 [PMID: 32577660 DOI: 10.1101/2020.05.30.125484]
3 **Wang S**, Liu H, Zhang X, Qian F. Intranasal and oral vaccination with protein-based antigens: advantages, challenges and formulation strategies. *Protein Cell* 2015; **6**: 480-503 [PMID: 25944045 DOI: 10.1007/s13238-015-0164-2]
4 WHO's landscape of COVID-19 vaccine candidates. 24-November 2021. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines
5 Registry data of COVID-19 vaccine candidates. Last access 15-May-2022. Available from: https://covid19.trackvaccines.org/
6 **Kim JH**, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. *Nat Med* 2021; **27**: 205-211 [PMID: 33469205 DOI: 10.1038/s41591-021-01230-y]
7 **Ashraf MU**, Kim Y, Kumar S, Seo D, Ashraf M, Bae YS. COVID-19 Vaccines (Revisited) and Oral-Mucosal Vector System as a Potential Vaccine Platform. *Vaccines (Basel)* 2021; **9** [PMID: 33670630 DOI: 10.3390/vaccines9020171]
8 **Alu A**, Chen L, Lei H, Wei Y, Tian X, Wei X. Intranasal COVID-19 vaccines: From bench to bed. *EBioMedicine* 2022; **76**: 103841 [PMID: 35085851 DOI: 10.1016/j.ebiom.2022.103841]
9 **Ogra PL**, Faden H, Welliver RC. Vaccination strategies for mucosal immune responses. *Clin Microbiol Rev* 2001; **14**: 430-445 [PMID: 11292646 DOI: 10.1128/CMR.14.2.430-445.2001]
10 **Ella R**, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, Aileni VK, Kanungo S, Rai S, Reddy P, Verma S, Singh C, Redkar S, Mohapatra S, Pandey A, Ranganadin P, Gumashta R, Multani M, Mohammad S, Bhatt P, Kumari L, Sapkal G, Gupta N, Abraham P, Panda S, Prasad S, Bhargava B, Ella K, Vadrevu KM; COVAXIN Study Group. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet* 2021; **398**: 2173-2184 [PMID: 34774196 DOI: 10.1016/S0140-6736(21)02000-6]
11 **Karczmarzyk K**, Kęsik-Brodacka M. Attacking the Intruder at the Gate: Prospects of Mucosal Anti SARS-CoV-2 Vaccines. *Pathogens* 2022; **11** [PMID: 35215061 DOI: 10.3390/pathogens11020117]
12 WHO—COVID19 Vaccine Tracker. (accessed on 12 May 2022). Available from: https://covid19.trackvaccines.org/agency/who
13 **Matuchansky C**. Mucosal immunity to SARS-CoV-2: a clinically relevant key to deciphering natural and vaccine-induced defences. *Clin Microbiol Infect* 2021; **27**: 1724-1726 [PMID: 34391929 DOI: 10.1016/j.cmi.2021.08.008]
14 Clinical trials register. (accessed on 12 May 2022). Available from: https://clinicaltrials.gov/ct2/results?term=COVID-19+vaccine&recrs=a&cond=Covid19
15 **Kyei-Barffour I**, Addo SA, Aninagyei E, Ghartey-Kwansah G, Acheampong DO. Sterilizing Immunity against COVID-19: Developing Helper T cells I and II activating vaccines is imperative. *Biomed Pharmacother* 2021; **144**: 112282 [PMID: 34624675 DOI: 10.1016/j.biopha.2021.112282]
16 **Jeyanathan M**, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol* 2020; **20**: 615-632 [PMID: 32887954 DOI: 10.1038/s41577-020-00434-6]
17 **Velikova T**. Infection-acquired vs vaccine-induced immunity against COVID-19. *Cent Asian J Med Hypotheses Ethics* 2021; **2**: 29-35 [DOI: 10.47316/cajmhe.2021.2.1.05]
18 **Villena J**, Kitazawa H. The Modulation of Mucosal Antiviral Immunity by Immunobiotics: Could They Offer Any Benefit in the SARS-CoV-2 Pandemic? *Front Physiol* 2020; **11**: 699 [PMID: 32670091 DOI: 10.3389/fphys.2020.00699]
19 **Holmgren J**, Czerkinsky C. Mucosal immunity and vaccines. *Nat Med* 2005; **11**: S45-S53 [PMID: 15812489 DOI: 10.1038/nm1213]
20 **Yuan Q**, Walker WA. Innate immunity of the gut: mucosal defense in health and disease. *J Pediatr Gastroenterol Nutr* 2004; **38**: 463-473 [PMID: 15097431 DOI: 10.1097/00005176-200405000-00001]
21 **Velikova TV**, Kotsev SV, Georgiev DS, Batselova HM. Immunological aspects of COVID-19: What do we know? *World J Biol Chem* 2020; **11**: 14-29 [PMID: 33024515 DOI: 10.4331/wjbc.v11.i2.14]
22 **Akira S**, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell* 2006; **124**: 783-801 [PMID: 16497588 DOI: 10.1016/j.cell.2006.02.015]
23 **Bowie AG**, Unterholzner L. Viral evasion and subversion of pattern-recognition receptor signalling. *Nat Rev Immunol* 2008; **8**: 911-922 [PMID: 18989317 DOI: 10.1038/nri2436]
24 **Kurtovic L**, Beeson JG. Complement Factors in COVID-19 Therapeutics and Vaccines. *Trends Immunol* 2021; **42**: 94-103 [PMID: 33402318 DOI: 10.1016/j.it.2020.12.002]
25 **Velikova T**, Snegarova V, Kukov A, Batselova H, Mihova A, Nakov R. Gastrointestinal mucosal immunity and COVID-19. *World J Gastroenterol* 2021; **27**: 5047-5059 [PMID: 34497434 DOI: 10.3748/wjg.v27.i30.5047]
26 **Su F**, Patel GB, Hu S, Chen W. Induction of mucosal immunity through systemic immunization: Phantom or reality? *Hum Vaccin Immunother* 2016; **12**: 1070-1079 [PMID: 26752023 DOI: 10.1080/21645515.2015.1114195]
27 **Velikova T**, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. *Rheumatol Int*

2021; **41**: 509-518 [PMID: 33515320 DOI: 10.1007/s00296-021-04792-9]

28 **Azzi L**, Dalla Gasperina D, Veronesi G, Shallak M, Ietto G, Iovino D, Baj A, Gianfagna F, Maurino V, Focosi D, Maggi F, Ferrario MM, Dentali F, Carcano G, Tagliabue A, Maffioli LS, Accolla RS, Forlani G. Mucosal immune response in BNT162b2 COVID-19 vaccine recipients. *EBioMedicine* 2022; **75**: 103788 [PMID: 34954658 DOI: 10.1016/j.ebiom.2021.103788]

29 **Chan RWY**, Liu S, Cheung JY, Tsun JGS, Chan KC, Chan KYY, Fung GPG, Li AM, Lam HS. The Mucosal and Serological Immune Responses to the Novel Coronavirus (SARS-CoV-2) Vaccines. *Front Immunol* 2021; **12**: 744887 [PMID: 34712232 DOI: 10.3389/fimmu.2021.744887]

30 **Lapuente D**, Fuchs J, Willar J, Vieira Antão A, Eberlein V, Uhlig N, Issmail L, Schmidt A, Oltmanns F, Peter AS, Mueller-Schmucker S, Irrgang P, Fraedrich K, Cara A, Hoffmann M, Pöhlmann S, Ensser A, Pertl C, Willert T, Thirion C, Grunwald T, Überla K, Tenbusch M. Protective mucosal immunity against SARS-CoV-2 after heterologous systemic prime-mucosal boost immunization. *Nat Commun* 2021; **12**: 6871 [PMID: 34836955 DOI: 10.1038/s41467-021-27063-4]

31 **Afkhami S**, D'Agostino MR, Zhang A, Stacey HD, Marzok A, Kang A, Singh R, Bavananthasivam J, Ye G, Luo X, Wang F, Ang JC, Zganiacz A, Sankar U, Kazhdan N, Koenig JFE, Phelps A, Gameiro SF, Tang S, Jordana M, Wan Y, Mossman KL, Jeyanathan M, Gillgrass A, Medina MFC, Smaill F, Lichty BD, Miller MS, Xing Z. Respiratory mucosal delivery of next-generation COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2. *Cell* 2022; **185**: 896-915.e19 [PMID: 35180381 DOI: 10.1016/j.cell.2022.02.005]

32 **Lavelle EC**, Ward RW. Mucosal vaccines - fortifying the frontiers. *Nat Rev Immunol* 2022; **22**: 236-250 [PMID: 34312520 DOI: 10.1038/s41577-021-00583-2]

33 **Swarnalekha N**, Schreiner D, Litzler LC, Iftikhar S, Kirchmeier D, Künzli M, Son YM, Sun J, Moreira EA, King CG. T resident helper cells promote humoral responses in the lung. *Sci Immunol* 2021; **6** [PMID: 33419790 DOI: 10.1126/sciimmunol.abb6808]

34 **Son YM**, Cheon IS, Wu Y, Li C, Wang Z, Gao X, Chen Y, Takahashi Y, Fu YX, Dent AL, Kaplan MH, Taylor JJ, Cui W, Sun J. Tissue-resident $CD4^+$ T helper cells assist the development of protective respiratory B and $CD8^+$ T cell memory responses. *Sci Immunol* 2021; **6** [PMID: 33419791 DOI: 10.1126/sciimmunol.abb6852]

35 **Li Y**, Jin L, Chen T. The Effects of Secretory IgA in the Mucosal Immune System. *Biomed Res Int* 2020; **2020**: 2032057 [PMID: 31998782 DOI: 10.1155/2020/2032057]

36 **Strugnell RA**, Wijburg OL. The role of secretory antibodies in infection immunity. *Nat Rev Microbiol* 2010; **8**: 656-667 [PMID: 20694027 DOI: 10.1038/nrmicro2384]

37 **Corthésy B**. Multi-faceted functions of secretory IgA at mucosal surfaces. *Front Immunol* 2013; **4**: 185 [PMID: 23874333 DOI: 10.3389/fimmu.2013.00185]

38 **Rogier EW**, Frantz AL, Bruno ME, Kaetzel CS. Secretory IgA is Concentrated in the Outer Layer of Colonic Mucus along with Gut Bacteria. *Pathogens* 2014; **3**: 390-403 [PMID: 25437806 DOI: 10.3390/pathogens3020390]

39 **Nurkic J**, Numanovic F, Arnautalic L, Tihic N, Halilovic D, Jahic M. Diagnostic Significance of Reduced IgA in Children. *Med Arch* 2015; **69**: 236-239 [PMID: 26543309 DOI: 10.5455/medarh.2015.69.236-239]

40 **Fischer A**. Resistance of children to Covid-19. How? *Mucosal Immunol* 2020; **13**: 563-565 [PMID: 32467603 DOI: 10.1038/s41385-020-0303-9]

41 **Slabakova Y**, Gerenska D, Ivanov N, Velikova T. Immune titers of protection against severe acute respiratory syndrome coronavirus 2: are we there yet? *Explor Immunol* 2022; **2**: 9-24 [DOI: 10.37349/ei.2022.00033]

42 **Uddbäck I**, Cartwright EK, Schøller AS, Wein AN, Hayward SL, Lobby J, Takamura S, Thomsen AR, Kohlmeier JE, Christensen JP. Long-term maintenance of lung resident memory T cells is mediated by persistent antigen. *Mucosal Immunol* 2021; **14**: 92-99 [PMID: 32518368 DOI: 10.1038/s41385-020-0309-3]

43 **Rakhra K**, Abraham W, Wang C, Moynihan KD, Li N, Donahue N, Baldeon AD, Irvine DJ. Exploiting albumin as a mucosal vaccine chaperone for robust generation of lung-resident memory T cells. *Sci Immunol* 2021; **6** [PMID: 33741657 DOI: 10.1126/sciimmunol.abd8003]

44 **Slütter B**, Pewe LL, Kaech SM, Harty JT. Lung airway-surveilling CXCR3(hi) memory CD8(+) T cells are critical for protection against influenza A virus. *Immunity* 2013; **39**: 939-948 [PMID: 24238342 DOI: 10.1016/j.immuni.2013.09.013]

45 **Stolley JM**, Johnston TS, Soerens AG, Beura LK, Rosato PC, Joag V, Wijeyesinghe SP, Langlois RA, Osum KC, Mitchell JS, Masopust D. Retrograde migration supplies resident memory T cells to lung-draining LN after influenza infection. *J Exp Med* 2020; **217** [PMID: 32568362 DOI: 10.1084/jem.20192197]

46 **Zou X**, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020; **14**: 185-192 [PMID: 32170560 DOI: 10.1007/s11684-020-0754-0]

47 CDC. Poliomyelitis prevention in the United States: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000; **49**: 1-22

48 CDC. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. *MMWR* 2009; **58**: 829-830

49 **Chard AN**, Datta SD, Tallis G, Burns CC, Wassilak SGF, Vertefeuille JF, Zaffran M. Progress Toward Polio Eradication - Worldwide, January 2018-March 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 784-789 [PMID: 32584798 DOI: 10.15585/mmwr.mm6925a4]

50 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

51 **Vidor E**. Poliovirus vaccine—live. In Plotkin S, Orenstein W, Offit P, eds. Plotkin's Vaccines. 7th ed. Philadelphia, PA: Elsevier; 2018: 841-865.e10 [DOI: 10.1016/B978-0-323-35761-6.00047-X]

52 **Wallace GS**, Curns AT, Weldon WC, Oberste MS. Seroprevalence of Poliovirus Antibodies in the United States Population, 2009-2010. *BMC Public Health* 2016; **16**: 721 [PMID: 27492318 DOI: 10.1186/s12889-016-3386-1]

53 **Wattigney WA**, Mootrey GT, Braun MM, Chen RT. Surveillance for poliovirus vaccine adverse events, 1991 to 1998:

impact of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. *Pediatrics* 2001; **107**: E83 [PMID: 11331733 DOI: 10.1542/peds.107.5.e83]

54 **Voroshilova MK**. Potential use of nonpathogenic enteroviruses for control of human disease. *Prog Med Virol* 1989; **36**: 191-202 [PMID: 2555836]

55 **Terekhov SN**, Stepanchuk VA. Acute respiratory diseases. Materials of the Institute of Microbiology and Epidemiology 1971; 5: 62–6

56 **Prijmyagi LS**, Grinshpoon LE. Use of live enterovirus vaccines for urgent prophylaxis of influenza. In: Chumakov ed. Medical Virology 1973; 21:29–37

57 **Chumakov MP**, Voroshilova MK, Antsupova AS, Boĭko VM, Blinova MI, Priĭmiagi LS, Rodin VI, Seĭbil' VB, Siniak KM, Smorodintsev AA. Live enteroviral vaccines for the emergency non-specific prevention of mass respiratory diseases during fall-winter epidemics of influenza and acute respiratory diseases [in Russian]. *Zh Mikrobiol Epidemiol Immunobiol* 1992; 11-12: 37 [PMID: 1338742]

58 **Sørup S**, Stensballe LG, Krause TG, Aaby P, Benn CS, Ravn H. Oral Polio Vaccination and Hospital Admissions With Non-Polio Infections in Denmark: Nationwide Retrospective Cohort Study. *Open Forum Infect Dis* 2016; **3**: ofv204 [PMID: 26885538 DOI: 10.1093/ofid/ofv204]

59 **Bardenheier BH**, McNeil MM, Wodi AP, McNicholl JM, DeStefano F. Risk of Nontargeted Infectious Disease Hospitalizations Among US Children Following Inactivated and Live Vaccines, 2005-2014. *Clin Infect Dis* 2017; **65**: 729-737 [PMID: 28481979 DOI: 10.1093/cid/cix442]

60 **Sallenave JM**, Guillot L. Innate Immune Signaling and Proteolytic Pathways in the Resolution or Exacerbation of SARS-CoV-2 in Covid-19: Key Therapeutic Targets? *Front Immunol* 2020; **11**: 1229 [PMID: 32574272 DOI: 10.3389/fimmu.2020.01229]

61 **Benn CS**, Fisker AB, Rieckmann A, Sørup S, Aaby P. Vaccinology: time to change the paradigm? *Lancet Infect Dis* 2020; **20**: e274-e283 [PMID: 32645296 DOI: 10.1016/S1473-3099(19)30742-X]

62 **Chang AY**, Aaby P, Avidan MS, Benn CS, Bertozzi SM, Blatt L, Chumakov K, Khader SA, Kottilil S, Nekkar M, Netea MG, Sparrow A, Jamison DT. One vaccine to counter many diseases? Modelling the economics of oral polio vaccine against child mortality and COVID-19, medRxiv 2022.22269560 [DOI: 10.1101/2022.01.19.22269560]

63 **Comunale BA**, Engineer L, Jiang Y, Andrews JC, Liu Q, Ji L, Yurkovich JT, Comunale RA, Xie Q. Poliovirus Vaccination Induces a Humoral Immune Response That Cross Reacts With SARS-CoV-2. *Front Med (Lausanne)* 2021; **8**: 710010 [PMID: 34414206 DOI: 10.3389/fmed.2021.710010]

64 **Kimberlin D**, Brady M, Jackson M, eds. American Academy of Pediatrics. Rotavirus infections. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: 700–704 [DOI: 10.1542/9781610021470]

65 **Patel MM**, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012; **12**: 561-570 [PMID: 22742639 DOI: 10.1016/S1473-3099(12)70029-4]

66 **Pindyck T**, Tate JE, Parashar UD. A decade of experience with rotavirus vaccination in the United States - vaccine uptake, effectiveness, and impact. *Expert Rev Vaccines* 2018; **17**: 593-606 [PMID: 29909693 DOI: 10.1080/14760584.2018.1489724]

67 **Ruiz-Palacios GM**, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, Cheuvart B, Espinoza F, Gillard P, Innis BL, Cervantes Y, Linhares AC, López P, Macías-Parra M, Ortega-Barría E, Richardson V, Rivera-Medina DM, Rivera L, Salinas B, Pavía-Ruz N, Salmerón J, Rüttimann R, Tinoco JC, Rubio P, Nuñez E, Guerrero ML, Yarzábal JP, Damaso S, Tornieporth N, Sáez-Llorens X, Vergara RF, Vesikari T, Bouckenooghe A, Clemens R, De Vos B, O'Ryan M; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; **354**: 11-22 [PMID: 16394298 DOI: 10.1056/NEJMoa052434]

68 **CDC**. Prevention of rotavirus gastroenteritis among infants and children recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009; **58** (No.RR-2): 1-25

69 **Baker JM**, Tate JE, Steiner CA, Haber MJ, Parashar UD, Lopman BA. Longer-term Direct and Indirect Effects of Infant Rotavirus Vaccination Across All Ages in the United States in 2000-2013: Analysis of a Large Hospital Discharge Data Set. *Clin Infect Dis* 2019; **68**: 976-983 [PMID: 30020438 DOI: 10.1093/cid/ciy580]

70 **Bowen MD**, Mijatovic-Rustempasic S, Esona MD, Teel EN, Gautam R, Sturgeon M, Azimi PH, Baker CJ, Bernstein DI, Boom JA, Chappell J, Donauer S, Edwards KM, Englund JA, Halasa NB, Harrison CJ, Johnston SH, Klein EJ, McNeal MM, Moffatt ME, Rench MA, Sahni LC, Selvarangan R, Staat MA, Szilagyi PG, Weinberg GA, Wikswo ME, Parashar UD, Payne DC. Rotavirus Strain Trends During the Postlicensure Vaccine Era: United States, 2008-2013. *J Infect Dis* 2016; **214**: 732-738 [PMID: 27302190 DOI: 10.1093/infdis/jiw233]

71 Vaccination préventive de la tuberculose de l'homme et des animaux par le B C G. Rapports et documents provenant des divers pays (la France exceptée) transmis à l'Institut Pasteur en 1932. *JAMA* 1932; **99**: 940-941 [DOI: 10.1001/jama.1932.02740630066039]

72 **Kristensen I**, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000; **321**: 1435-1438 [PMID: 11110734 DOI: 10.1136/bmj.321.7274.1435]

73 **Garly ML**, Martins CL, Balé C, Baldé MA, Hedegaard KL, Gustafson P, Lisse IM, Whittle HC, Aaby P. BCG scar and positive tuberculin reaction associated with reduced child mortality in West Africa. A non-specific beneficial effect of BCG? *Vaccine* 2003; **21**: 2782-2790 [PMID: 12798618 DOI: 10.1016/s0264-410x(03)00181-6]

74 **Stensballe LG**, Nante E, Jensen IP, Kofoed PE, Poulsen A, Jensen H, Newport M, Marchant A, Aaby P. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls community based case-control study. *Vaccine* 2005; **23**: 1251-1257 [PMID: 15652667 DOI: 10.1016/j.vaccine.2004.09.006]

75 **Wardhana**, Datau EA, Sultana A, Mandang VV, Jim E. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. *Acta Med Indones* 2011; **43**: 185-190 [PMID: 21979284]

76 **Moorlag SJCFM**, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clin*

Microbiol Infect 2019; **25**: 1473-1478 [PMID: 31055165 DOI: 10.1016/j.cmi.2019.04.020]

77 **Moorlag SJCFM**, van Deuren RC, van Werkhoven CH, Jaeger M, Debisarun P, Taks E, Mourits VP, Koeken VACM, de Bree LCJ, Ten Doesschate T, Cleophas MC, Smeekens S, Oosting M, van de Veerdonk FL, Joosten LAB, Ten Oever J, van der Meer JWM, Curtis N, Aaby P, Stabell-Benn C, Giamarellos-Bourboulis EJ, Bonten M, van Crevel R, Netea MG. Safety and COVID-19 Symptoms in Individuals Recently Vaccinated with BCG: a Retrospective Cohort Study. *Cell Rep Med* 2020; **1**: 100073 [PMID: 32838341 DOI: 10.1016/j.xcrm.2020.100073]

78 **Giamarellos-Bourboulis EJ**, Tsilika M, Moorlag S, Antonakos N, Kotsaki A, Domínguez-Andrés J, Kyriazopoulou E, Gkavogianni T, Adami ME, Damoraki G, Koufargyris P, Karageorgos A, Bolanou A, Koenen H, van Crevel R, Droggiti DI, Renieris G, Papadopoulos A, Netea MG. Activate: Randomized Clinical Trial of BCG Vaccination against Infection in the Elderly. *Cell* 2020; **183**: 315-323.e9 [PMID: 32941801 DOI: 10.1016/j.cell.2020.08.051]

79 **Gonzalez-Perez M**, Sanchez-Tarjuelo R, Shor B, Nistal-Villan E, Ochando J. The BCG Vaccine for COVID-19: First Verdict and Future Directions. *Front Immunol* 2021; **12**: 632478 [PMID: 33763077 DOI: 10.3389/fimmu.2021.632478]

80 **Counoupas C**, Johansen MD, Stella AO, Nguyen DH, Ferguson AL, Aggarwal A, Bhattacharyya ND, Grey A, Hutchings O, Patel K, Siddiquee R, Stewart EL, Feng CG, Hansbro NG, Palendira U, Steain MC, Saunders BM, Low JKK, Mackay JP, Kelleher AD, Britton WJ, Turville SG, Hansbro PM, Triccas JA. A single dose, BCG-adjuvanted COVID-19 vaccine provides sterilising immunity against SARS-CoV-2 infection. *NPJ Vaccines* 2021; **6**: 143 [PMID: 34848711 DOI: 10.1038/s41541-021-00406-4]

81 **Amirlak L**, Haddad R, Hardy JD, Khaled NS, Chung MH, Amirlak B. Effectiveness of booster BCG vaccination in preventing Covid-19 infection. *Hum Vaccin Immunother* 2021; **17**: 3913-3915 [PMID: 34403297 DOI: 10.1080/21645515.2021.1956228]

82 **Sidiq KR**, Sabir DK, Ali SM, Kodzius R. Does Early Childhood Vaccination Protect Against COVID-19? *Front Mol Biosci* 2020; **7**: 120 [PMID: 32582766 DOI: 10.3389/fmolb.2020.00120]

83 **Young A**, Neumann B, Mendez RF, Reyahi A, Joannides A, Modis Y, Franklin RJM. Homologous protein domains in SARS-CoV-2 and measles, mumps and rubella viruses: preliminary evidence that MMR vaccine might provide protection against COVID-19. *medRxiv* 2020; 2005: 3207 [DOI: 10.1101/2020.04.10.20053207]

84 **Gold JE**, Baumgartl WH, Okyay RA, Licht WE, Fidel PL Jr, Noverr MC, Tilley LP, Hurley DJ, Rada B, Ashford JW. Analysis of Measles-Mumps-Rubella (MMR) Titers of Recovered COVID-19 Patients. *mBio* 2020; **11** [PMID: 33219096 DOI: 10.1128/mBio.02628-20]

85 **Ashford JW**, Gold JE, Huenergardt MA, Katz RBA, Strand SE, Bolanos J, Wheeler CJ, Perry G, Smith CJ, Steinman L, Chen MY, Wang JC, Ashford CB, Roth WT, Cheng JJ, Chao S, Jennings J, Sipple D, Yamamoto V, Kateb B, Earnest DL. MMR Vaccination: A Potential Strategy to Reduce Severity and Mortality of COVID-19 Illness. *Am J Med* 2021; **134**: 153-155 [PMID: 33198951 DOI: 10.1016/j.amjmed.2020.10.003]

86 **Avidan M**. An International, Multi-site, Bayesian Platform Adaptive, Randomized, Placebo-controlled Trial Assessing the Effectiveness of Candidate Agents in Mitigating COVID-19 Disease in Adults, 2021 Mar. Report No.: NCT04333732. Available from: https://clinicaltrials.gov/ct2/show/NCT04333732

87 **Lundberg L**, Bygdell M, Stukat von Feilitzen G, Woxenius S, Ohlsson C, Kindblom JM, Leach S. Recent MMR vaccination in health care workers and Covid-19: A test negative case-control study. *Vaccine* 2021; **39**: 4414-4418 [PMID: 34187707 DOI: 10.1016/j.vaccine.2021.06.045]

88 **De Serres G**, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro Surveill* 2013; **18** [PMID: 24079398 DOI: 10.2807/1560-7917.es2013.18.37.20585]

89 **Lopez Bernal J**, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, Simmons R, Cottrell S, Roberts R, O'Doherty M, Brown K, Cameron C, Stockton D, McMenamin J, Ramsay M. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021; **373**: n1088 [PMID: 33985964 DOI: 10.1136/bmj.n1088]

90 **Hyams C**, Marlow R, Maseko Z, King J, Ward L, Fox K, Heath R, Tuner A, Friedrich Z, Morrison L, Ruffino G, Antico R, Adegbite D, Szasz-Benczur Z, Garcia Gonzalez M, Oliver J, Danon L, Finn A. Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study. *Lancet Infect Dis* 2021; **21**: 1539-1548 [PMID: 34174190 DOI: 10.1016/S1473-3099(21)00330-3]

91 **Lycke N**. Recent progress in mucosal vaccine development: potential and limitations. *Nat Rev Immunol* 2012; **12**: 592-605 [PMID: 22828912 DOI: 10.1038/nri3251]

92 **Perez-Lopez A**, Behnsen J, Nuccio SP, Raffatellu M. Mucosal immunity to pathogenic intestinal bacteria. *Nat Rev Immunol* 2016; **16**: 135-148 [PMID: 26898110 DOI: 10.1038/nri.2015.17]

93 **Robinson JM**. Vaccine production: main steps and considerations. In: Bloom B, Lambert PH, editors. The vaccine book. 2nd ed. Academic Press; San Diego: 2016. pp. 77–96; Gomez PL, Robinson JM, Rogalewicz JA. Vaccine Manufacturing. Vaccines, 6th ed. In: Plotkin S, Orenstien W, Offit P. Orlando, editors. WB Saunders Company; 2013: 44–57

94 **Smith J**, Lipsitch M, Almond JW. Vaccine production, distribution, access, and uptake. *Lancet* 2011; **378**: 428-438 [PMID: 21664680 DOI: 10.1016/S0140-6736(11)60478-9]

95 **Tordesillas L**, Berin MC. Mechanisms of Oral Tolerance. *Clin Rev Allergy Immunol* 2018; **55**: 107-117 [PMID: 29488131 DOI: 10.1007/s12016-018-8680-5]

96 **Mestecky J**, Russell MW, Elson CO. Perspectives on mucosal vaccines: is mucosal tolerance a barrier? *J Immunol* 2007; **179**: 5633-5638 [PMID: 17947632 DOI: 10.4049/jimmunol.179.9.5633]

97 **Mudgal R**, Nehul S, Tomar S. Prospects for mucosal vaccine: shutting the door on SARS-CoV-2. *Hum Vaccin Immunother* 2020; **16**: 2921-2931 [PMID: 32931361 DOI: 10.1080/21645515.2020.1805992]

98 **Liu HL**, Yeh IJ, Phan NN, Wu YH, Yen MC, Hung JH, Chiao CC, Chen CF, Sun Z, Jiang JZ, Hsu HP, Wang CY, Lai MD. Gene signatures of SARS-CoV/SARS-CoV-2-infected ferret lungs in short- and long-term models. *Infect Genet Evol* 2020; **85**: 104438 [PMID: 32615317 DOI: 10.1016/j.meegid.2020.104438]

99 **Wu YH**, Yeh IJ, Phan NN, Yen MC, Hung JH, Chiao CC, Chen CF, Sun Z, Hsu HP, Wang CY, Lai MD. Gene signatures

and potential therapeutic targets of Middle East respiratory syndrome coronavirus (MERS-CoV)-infected human lung adenocarcinoma epithelial cells. *J Microbiol Immunol Infect* 2021; **54**: 845-857 [PMID: 34176764 DOI: 10.1016/j.jmii.2021.03.007]

100 **Ko M**, Chang SY, Byun SY, Ianevski A, Choi I, Pham Hung d'Alexandry d'Orengiani AL, Ravlo E, Wang W, Bjørås M, Kainov DE, Shum D, Min JY, Windisch MP. Screening of FDA-Approved Drugs Using a MERS-CoV Clinical Isolate from South Korea Identifies Potential Therapeutic Options for COVID-19. *Viruses* 2021; **13** [PMID: 33918958 DOI: 10.3390/v13040651]

101 **Pei H**, Liu J, Cheng Y, Sun C, Wang C, Lu Y, Ding J, Zhou J, Xiang H. Expression of SARS-coronavirus nucleocapsid protein in Escherichia coli and Lactococcus lactis for serodiagnosis and mucosal vaccination. *Appl Microbiol Biotechnol* 2005; **68**: 220-227 [PMID: 15660214 DOI: 10.1007/s00253-004-1869-y]

102 **WHO**. The top 10 causes of death. (2020). World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

103 **Hippisley-Cox J**, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, Zaccardi F, Watkinson P, Shankar-Hari M, Doidge J, Harrison DA, Griffin SJ, Sheikh A, Coupland CAC. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. *BMJ* 2021; **374**: n1931 [PMID: 34446426 DOI: 10.1136/bmj.n1931]

104 **Hassan AO**, Kafai NM, Dmitriev IP, Fox JM, Smith BK, Harvey IB, Chen RE, Winkler ES, Wessel AW, Case JB, Kashentseva E, McCune BT, Bailey AL, Zhao H, VanBlargan LA, Dai YN, Ma M, Adams LJ, Shrihari S, Danis JE, Gralinski LE, Hou YJ, Schäfer A, Kim AS, Keeler SP, Weiskopf D, Baric RS, Holtzman MJ, Fremont DH, Curiel DT, Diamond MS. A Single-Dose Intranasal ChAd Vaccine Protects Upper and Lower Respiratory Tracts against SARS-CoV-2. *Cell* 2020; **183**: 169-184.e13 [PMID: 32931734 DOI: 10.1016/j.cell.2020.08.026]

105 **Du Y**, Xu Y, Feng J, Hu L, Zhang Y, Zhang B, Guo W, Mai R, Chen L, Fang J, Zhang H, Peng T. Intranasal administration of a recombinant RBD vaccine induced protective immunity against SARS-CoV-2 in mouse. *Vaccine* 2021; **39**: 2280-2287 [PMID: 33731271 DOI: 10.1016/j.vaccine.2021.03.006]

106 **Bricker TL**, Darling TL, Hassan AO, Harastani HH, Soung A, Jiang X, Dai YN, Zhao H, Adams LJ, Holtzman MJ, Bailey AL, Case JB, Fremont DH, Klein R, Diamond MS, Boon ACM. A single intranasal or intramuscular immunization with chimpanzee adenovirus-vectored SARS-CoV-2 vaccine protects against pneumonia in hamsters. *Cell Rep* 2021; **36**: 109400 [PMID: 34245672 DOI: 10.1016/j.celrep.2021.109400]

107 **Lijek RS**, Luque SL, Liu Q, Parker D, Bae T, Weiser JN. Protection from the acquisition of Staphylococcus aureus nasal carriage by cross-reactive antibody to a pneumococcal dehydrogenase. *Proc Natl Acad Sci U S A* 2012; **109**: 13823-13828 [PMID: 22869727 DOI: 10.1073/pnas.1208075109]

108 Vaxart's Oral COVID-19 Tablet Vaccine to Enter Clinical Trials. [(accessed on 19 November 2020)]; Available from: https://www.biopharma-reporter.com/Article/2020/09/15/Vaxart-First-tablet-COVID-19-vaccine-to-enter-clinical-trials

109 Preclinical Studies of a Recombinant Adenoviral Mucosal Vaccine to Prevent SARS-CoV-2 Infection. [(accessed on 23 December 2020)]; Available from: https://www.biorxiv.org/content/10.1101/2020.09.04.283853v1

110 **Kumar A**, Kumar A. Mucosal and transdermal vaccine delivery strategies against COVID-19. *Drug Deliv Transl Res* 2022; **12**: 968-972 [PMID: 33993417 DOI: 10.1007/s13346-021-01001-9]

111 **Gabitzsch ES**, Xu Y, Yoshida LH, Balint J, Amalfitano A, Jones FR. Novel Adenovirus type 5 vaccine platform induces cellular immunity against HIV-1 Gag, Pol, Nef despite the presence of Ad5 immunity. *Vaccine* 2009; **27**: 6394-6398 [PMID: 19559110 DOI: 10.1016/j.vaccine.2009.06.028]

112 **Niazi KR**, Ochoa MT, Sieling PA, Rooke NE, Peter AK, Mollahan P, Dickey M, Rabizadeh S, Rea TH, Modlin RL. Activation of human CD4+ T cells by targeting MHC class II epitopes to endosomal compartments using human CD1 tail sequences. *Immunology* 2007; **122**: 522-531 [PMID: 17635609 DOI: 10.1111/j.1365-2567.2007.02666.x]

113 **Gabitzsch ES**, Xu Y, Yoshida LH, Balint J, Gayle RB, Amalfitano A, Jones FR. A preliminary and comparative evaluation of a novel Ad5 [E1-, E2b-] recombinant-based vaccine used to induce cell mediated immune responses. *Immunol Lett* 2009; **122**: 44-51 [PMID: 19073216 DOI: 10.1016/j.imlet.2008.11.003]

114 **Gabitzsch ES**, Xu Y, Balint JP Jr, Balcaitis S, Sanders-Beer B, Jones FR. Induction and comparison of SIV immunity in Ad5 naïve and Ad5 immune non-human primates using an Ad5 [E1-, E2b-] based vaccine. *Vaccine* 2011; **29**: 8101-8107 [PMID: 21864618 DOI: 10.1016/j.vaccine.2011.08.038]

115 **Sekine T**, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, Llewellyn-Lacey S, Kamal H, Bogdanovic G, Muschiol S, Wullimann DJ, Kammann T, Emgård J, Parrot T, Folkesson E; Karolinska COVID-19 Study Group, Rooyackers O, Eriksson LI, Henter JI, Sönnerborg A, Allander T, Albert J, Nielsen M, Klingström J, Gredmark-Russ S, Björkström NK, Sandberg JK, Price DA, Ljunggren HG, Aleman S, Buggert M. Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. *Cell* 2020; **183**: 158-168.e14 [PMID: 32979941 DOI: 10.1016/j.cell.2020.08.017]

116 **Gabitzsch E**, Safrit JT, Verma M, Rice A, Seiling P, Zakin L, Shin A, Morimoto B, Adisetiyo H, Wong R, Bezawada A, Dinkins K, Balint J, Peykov V, Garban H, Liu P, Bacon A, Drew J, Spilman P, Sender L, Rabizadeh S, Niazi K. Complete protection of nasal and lung airways against SARS-CoV-2 challenge by antibody plus Th1 dominant N- and S-specific T-cell responses to subcutaneous prime and thermally-stable oral boost bivalent hAd5 vaccination in an NHP study. *bioRxiv* 2021 [DOI: 10.1101/2020.12.08.416297]

117 **Ulaeto D**, Hruby DE. Uses of vaccinia virus in vaccine delivery. *Curr Opin Biotechnol* 1994; **5**: 501-504 [PMID: 7765463 DOI: 10.1016/0958-1669(94)90064-7]

118 **Wang Q**, Jiang W, Chen Y, Liu P, Sheng C, Chen S, Zhang H, Pan C, Gao S, Huang W. In vivo electroporation of minicircle DNA as a novel method of vaccine delivery to enhance HIV-1-specific immune responses. *J Virol* 2014; **88**: 1924-1934 [PMID: 24284319 DOI: 10.1128/JVI.02757-13]

119 **Han SS**, Lee J, Jung Y, Kang MH, Hong JH, Cha MS, Park YJ, Lee E, Yoon CH, Bae YS. Development of oral CTL vaccine using a CTP-integrated Sabin 1 poliovirus-based vector system. *Vaccine* 2015; **33**: 4827-4836 [PMID: 26241946 DOI: 10.1016/j.vaccine.2015.07.072]

120 **Xiao Y**, Daniell H. Long-term evaluation of mucosal and systemic immunity and protection conferred by different polio

booster vaccines. *Vaccine* 2017; **35**: 5418-5425 [PMID: 28111147 DOI: 10.1016/j.vaccine.2016.12.061]

121 **Okayasu H**, Sutter RW, Czerkinsky C, Ogra PL. Mucosal immunity and poliovirus vaccines: impact on wild poliovirus infection and transmission. *Vaccine* 2011; **29**: 8205-8214 [PMID: 21896299 DOI: 10.1016/j.vaccine.2011.08.059]

122 **Heymann DL**, Murphy K, Brigaud M, Aymard M, Tembon A, Maben GK. Oral poliovirus vaccine in tropical Africa: greater impact on incidence of paralytic disease than expected from coverage surveys and seroconversion rates. *Bull World Health Organ* 1987; **65**: 495-501 [PMID: 3500802]

123 **WHO**, Landscape of COVID-19 Candidate Vaccines; 2020. Last accessed on 15th of July. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

124 **Vela Ramirez JE**, Sharpe LA, Peppas NA. Current state and challenges in developing oral vaccines. *Adv Drug Deliv Rev* 2017; **114**: 116-131 [PMID: 28438674 DOI: 10.1016/j.addr.2017.04.008]

125 **Focosi D**, Maggi F, Casadevall A. Mucosal Vaccines, Sterilizing Immunity, and the Future of SARS-CoV-2 Virulence. *Viruses* 2022; **14** [PMID: 35215783 DOI: 10.3390/v14020187]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 237-251

DOI: 10.5501/wjv.v11.i5.237

ISSN 2220-3249 (online)

REVIEW

Association of COVID-19 with hepatic metabolic dysfunction

Ramesh Kumar, Vijay Kumar, Rahul Arya, Utpal Anand, Rajeev Nayan Priyadarshi

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Corrales FJ, Spain; Salim J, Indonesia

Received: March 13, 2022
Peer-review started: March 13, 2022
First decision: April 13, 2022
Revised: April 25, 2022
Accepted: June 20, 2022
Article in press: June 20, 2022
Published online: September 25, 2022

Ramesh Kumar, Rahul Arya, Department of Gastroenterology, All India Institute of Medical Sciences, Patna, Patna 801507, Bihar, India

Vijay Kumar, Department of Medicine, All India Institute of Medical Sciences, Patna, Patna 801507, Bihar, India

Utpal Anand, Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Patna, Patna 801507, Bihar, India

Rajeev Nayan Priyadarshi, Department of Radiodiagnosis, All India Institute of Medical Sciences, Patna, Patna 801507, Bihar, India

Corresponding author: Ramesh Kumar, MD, Associate Professor, Department of Gastroenterology, All India Institute of Medical Sciences, Phulwari Sharif, Patna 801507, Bihar, India. docrameshkr@gmail.com

Abstract

The coronavirus disease 2019 (COVID-19) pandemic continues to be a global problem with over 438 million cases reported so far. Although it mostly affects the respiratory system, the involvement of extrapulmonary organs, including the liver, is not uncommon. Since the beginning of the pandemic, metabolic comorbidities, such as obesity, diabetes, hypertension, and dyslipidemia, have been identified as poor prognostic indicators. Subsequent metabolic and lipidomic studies have identified several metabolic dysfunctions in patients with COVID-19. The metabolic alterations appear to be linked to the course of the disease and inflammatory reaction in the body. The liver is an important organ with high metabolic activity, and a significant proportion of COVID-19 patients have metabolic comorbidities; thus, this factor could play a key role in orchestrating systemic metabolic changes during infection. Evidence suggests that metabolic dysregulation in COVID-19 has both short- and long-term metabolic implications. Furthermore, COVID-19 has adverse associations with metabolic-associated fatty liver disease. Due to the ensuing effects on the renin-angiotensin-aldosterone system and ammonia metabolism, COVID-19 can have significant implications in patients with advanced chronic liver disease. A thorough understanding of COVID-19-associated metabolic dysfunction could lead to the identification of important plasma biomarkers and novel treatment targets. In this review, we discuss the current understanding of metabolic dysfunction in COVID-19, focusing on the liver and exploring the underlying mechanistic pathogenesis and clinical implications.

Key Words: COVID-19; Coronavirus; Metabolism; Metabolic syndrome; Metabolic inflammation; Hepatic dysfunction

Core Tip: In coronavirus disease 2019 (COVID-19) patients, the virus induces a complex viral-host interaction that leads to metabolic reprogramming, altered immunological responses, and a variety of clinical consequences. In metabolomic and lipidomic studies, a variety of alterations in amino acids, lipids, carbohydrates, and energy metabolism have been identified in such patients. The liver is the primary metabolic organ; thus, these metabolic alterations may have a major impact on patients with liver diseases and metabolic comorbidities that are common in COVID-19 patients. Therefore, this review article discusses the pathophysiological aspects and clinical implications of metabolic dysfunction in COVID-19 patients with a focus on the liver.

Citation: Kumar R, Kumar V, Arya R, Anand U, Priyadarshi RN. Association of COVID-19 with hepatic metabolic dysfunction. *World J Virol* 2022; 11(5): 237-251
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/237.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.237

INTRODUCTION

Patients with metabolic disorders such as obesity, hypertension, diabetes mellitus (DM), and non-alcoholic fatty liver disease (NAFLD) are more likely to develop a severe case of coronavirus disease 2019 (COVID-19)[1-5]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection *per se* is linked to the changes in numerous metabolic pathways involving glucose, lipids, and amino acids[6-8]. The metabolic reprogramming that occurs in COVID-19 patients performs several roles, including providing energy and substrates for viral replication and modulating the immunological response. Pre-existing metabolic comorbidities may fire up metabolic reprogramming more strongly due to the varying amounts of metabolites and their influence on the immune response. Untargeted metabolomic and lipidomic methods provide new insight into the host's response to COVID-19 infection. Hyperglycemia, new-onset DM, dyslipidemia, and worsening of pre-existing metabolic abnormalities have all been described in COVID-19 patients[9-11]. As the liver is a primary metabolic hub, it is crucial in orchestrating systemic metabolic alterations during infection. The angiotensin-converting enzyme 2 (ACE2) that allows SARS-CoV-2 to enter the body is normally present in the liver and is overexpressed in patients with chronic liver disease (CLD)[12,13]. Additionally, ACE2 is an integral part of the renin-angiotensin-aldosterone system (RAAS), which plays a major role in the pathophysiology of liver cirrhosis[14].

Obesity and DM have been associated with a poor disease prognosis since the outset of the COVID-19 pandemic[15,16]. As these metabolic conditions are still among the world's most common public health issues, a sizable section of the population is at risk of severe COVID-19 infection. Compelling evidence suggests that patients with metabolic comorbidities also have a higher risk of post-infection sequels[17,18]. Furthermore, NAFLD is common in subjects with obesity and DM. When compared to non-NAFLD COVID-19 patients, those with NAFLD have a higher risk of disease progression (6.6% *vs* 44.7%), a higher likelihood of impaired liver function (70% *vs* 11.1%), and a longer viral shedding period (17.5 *vs* 12.1 d)[19]. Moreover, patients with COVID-19 frequently have elevated liver enzyme levels, and this has been linked to poor clinical outcomes[20,21]. Similarly, COVID-19 has been proven to have a negative impact on the complications and outcomes of CLD patients[21].

Infections trigger a wide range of responses in the host, including inflammation, tissue injury, and healing. In this context, evidence suggests that COVID-19 has both immediate and long-term metabolic consequences associated with inflammation[4,7,17,22,23]. Immunometabolism, which is the direct link between metabolic diseases and inflammation, has recently emerged as a key study subject. Correlation analyses reveal strong links between metabolites and proinflammatory cytokines and chemokines[22,23]. In this sense, studies have found that arginine, tryptophan, and purine metabolism have a regulatory interaction with inflammation. Therefore, targeting metabolism to modulate the release of proinflammatory cytokines could be a viable method for treating cytokine storms in COVID-19 patients. This review article discusses the spectrum of metabolic dysfunctions in COVID-19 patients, their pathophysiological aspects, and clinical implications in patients with underlying metabolic comorbidities and liver disorders.

ALTERATIONS IN METABOLIC AND BIOSYNTHETIC PATHWAYS IN COVID-19

In patients with severe COVID-19, considerable changes in hepatic metabolic and biosynthetic pathways have been discovered[6-8,24-28]. Lipids, glycoproteins, amines, aromatic compounds, amino acids, steroids, and flavone metabolism were all found to be altered (Table 1). A study on liver autopsy samples of COVID-19 patients has demonstrated a significant downregulation of transcripts implicated in the metabolic pathways. The most downregulated genes were acyl-CoA dehydrogenases 11 (involved in mitochondrial β-oxidation and metabolism of long-chain fatty acyl-CoAs), *CIDEB* (a liver-specific regulator of lipids metabolism), glycine N-methyltransferase (contributes to liver steatosis and fibrosis), and glycerol-3-phosphate acyltransferase (implicated in triglyceride biosynthesis)[6,24-26]. The suppression of lipid and amino acid metabolism has resulted in the accumulation of amino acids and steroids in the sera of COVID-19 patients[7]. More than 100 Lipids were discovered to be downregulated in COVID-19 patient sera, including sphingolipids, glycerophospholipid, and fatty acids, most likely due to liver damage. Many steroid hormones, such as progesterone, androgens, and estrogens, have been found to accumulate, which can enhance immune cell activation. Increased levels of 21-hydroxypregnenolone could imply that corticosterone is protective against COVID-19[7].

In this context, many such metabolic changes aid SARS-CoV-2 replication and have been linked to the severity of COVID-19 cases. Glycolysis and glutaminolysis were found to be required for virus replication[8,27]. In this regard, glutaminolysis is a process that converts glutamine to tricarboxylic acid (TCA) cycle intermediates and is required for protein, lipid, and nucleic acid production. Inhibiting glutaminolysis has been shown to impede viral replication and production. Furthermore, patients with severe COVID-19 disease had higher glucose and mannose levels in their blood[8], and mannose was found to be a reliable biomarker for the severity of COVID-19 disease. Chen YM found that the TCA cycle and glycolytic pathways were significantly dysregulated in COVID-19 patients[28]. Significant suppression of cytochrome P450 enzymes has been observed in COVID-19 patients, suggesting a compromised hepatic detoxification capacity[6]. In a metabolomic study, Shen *et al*[7] have detected elevated levels of glucuronate, which is a bilirubin degradation product, and bile acid derivatives in severe COVID-19 patients, also indicating a decline in the liver's detoxification function. It is noteworthy that the suppressed hepatic metabolic pathways in COVID-19 patients are consistent with mitochondrial dysfunction[6]. In this regard, Scozzi *et al*[29] have reported that circulating levels of mitochondrial DNA (MT-DNA), inflammatory nucleic acids released by injured tissues, were highly elevated in patients who eventually died or required ICU admission. Thus, MT-DNA in blood could be a potential early prognostic marker for poor outcomes in COVID-19 cases. Moreover, mitochondrial dysfunction also appears to play a role in COVID-19-induced porphyrin accumulation occurring due to interference with the heme biosynthetic pathway[30]. Heme synthesis is dependent on the sequential action of eight enzymes, which are mainly expressed in the liver and erythroid cells.

ALTERATIONS IN AMINO ACIDS, LIPIDS, AND SUGAR

Amino acids

Amino acids (AAs), which are mostly synthesized in the liver, are essential for metabolism, immunological function, and redox balance[31]. The potential effects of glutamine, arginine, methionine, and cysteine on immunological function have been well documented[32]. Branched-chain amino acids (BCAAs) play an important role in metabolism and inflammation. In this sense, BCAAs stimulate the synthesis of glycogen and proteins such as albumin *via* activating the mammalian target of rapamycin complex 1 (mTORC1) signaling[33]. Serine and glycine are important components of the one-carbon cycle, which aids redox balance and several biosynthetic activities[34].

BCAA levels in the blood increase in severe COVID-19 patients[35]. Through the transcription factor NF-kB, elevated levels of BCAA increase reactive oxygen species generation and proinflammatory responses in endothelial cells[33]. Additionally, BCAAs also cause insulin resistance (IR) *via* activating mTORC1[36]. Furthermore, increased BCAA levels in the blood are linked to a higher risk of metabolic diseases, including DM. On the other hand, a decrease in the BCAA/aromatic amino acids ratio, also known as Fischer's ratio, has been linked to hepatic impairment in COVID-19 patients[37]. A metabolomics study has linked the severity of COVID-19 to a reduction in serotonin and increased plasma levels of aspartate, glutamate, phenylalanine, and succinic acid[38]. The rise in such amino acids and succinic acid could be related to a dysregulation of central carbon metabolism in the liver as well as metabolic and oxidative stress.

On another note, changes in tryptophan metabolism along the kynurenine pathway have been reported in COVID-19 patients[39]. This pathway is activated by proinflammatory cytokines such as interleukin-6 (IL-6) in response to diverse situations. Indeed, the kynurenine and tryptophan ratio (KTR) is frequently used to assess inflammation and immunological responses in a variety of disorders. In COVID-19 patients, an increased KTR was also indicative of the disease severity and progression[40]. Other alterations indicative of hepatic dysfunction in COVID-19 patients include elevated levels of taurine and ethanolamine[37]. Increased taurine levels in the blood have been identified as indicators of

Table 1 Metabolic alterations in coronavirus disease 2019 with implications

Metabolite alteration	Implications/association
Increased branched chain amino-acids	Insulin resistance, reactive oxygen species production, and pro-inflammatory responses
Decreased tryptophan; Increased kynurenine	Increased kynurenine tryptophan ratio indicates inflammatory response
Increased glutamic acid; Decreased glutamine	Lower glutamine level is associated with insulin resistance and an increased risk of diabetes
Decrease arginine; Increased ornithine	Attempt to suppress virus-specific $CD8^+$ T cell. Delayed interferon response or metabolic syndrome tend to increase arginine/ornithine ratio, causing tissues damage
Increased spermidine and spermine	Help structural assembling and genome replication
Increased serum triglycerides and VLDL; Decreased total cholesterol, HDL and LDL; Upregulation of fatty acid synthesis	Viral replication, inflammation, atherogenic risk, hepatic steatosis
Increased ketone bodies and 2-hydroxybutyric acid	Altered energy metabolism and oxidative stress
Decreased glycerophospholipid; Increased lysophospholipids	Indicates inflammation and tissue damage
increased levels of pyruvate, pyruvate kinase and lactate dehydrogenase	Indicates enhanced glucose metabolism. Increased glycolysis promotes replication of SARS-CoV-2 and cytokine storm
Increased methionine sulfoxide levels; Decreased glutathione levels	Indicative of increased oxidative stress

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; VLDL: Very-low-density lipoprotein.

liver failure. Furthermore, glutamate and glutamine are important in energy metabolism. In this regard, glutamic acid levels are higher in COVID-19 patients; however, glutamine levels are much lower, and this is linked to IR and an increased risk of DM[41]. Low glutamine levels in COVID-19 patients may be due to an abnormal cysteine catabolism secondary to increased hepatic glutathione biosynthesis, induced by proinflammatory cytokines[42]. On another note, the hepatic urea cycle is dysregulated in severe COVID-19 patients[40]. The urea cycle, which converts ammonia to urea, is the principal metabolic pathway implicated in detoxification processes, with a fumarate shunt connecting the urea cycle and the TCA cycle[43]. In moderate and severe COVID-19 patients, an increased level of ornithine, the main metabolite of the urea cycle, is observed. This, along with increased levels of aspartate and glutamate, which are also linked to the cycle, suggests that SARS-CoV-2 disturbs the hepatic urea cycle. Moreover, ornithine and glutamate demonstrate a positive correlation with lactic acid in severe COVID-19[38].

In viral infections, modification of liver metabolism and the urea cycle may be an endogenous immunoregulatory mechanism to minimize tissue damage[44]. The reprogramming of liver metabolism that occurs after a viral infection is correlated with type I interferon (IFN-I) responses. In this sense, the IFN-I response modifies the urea cycle, resulting in lower arginine and higher ornithine concentrations in the blood, thus suppressing virus-specific CD8+ T-cell responses and reducing the liver damage[45]. However, in COVID-19 patients, the IFN-I response is frequently delayed, and this may weaken the protective response. Metabolic syndrome, which is common in COVID-19 patients, causes decreased arginine availability and an elevated arginine/ornithine ratio, which may further worsen tissue damage [46]. Furthermore, the synthesis of polyamines may be increased if ornithine metabolism is dysregulated. Metabolomics analysis has reported increased levels of spermidine and spermine in the serum of COVID-19 patients[47]. As polyamines are involved in various viral activities, including viral assembly and genome replication, blocking polyamine synthesis could be a useful antiviral strategy.

Lipids

Lipids play an important role throughout the viral life cycle, and viruses exploit host lipid metabolism to facilitate their replication. Several studies have looked at lipidomic profiling in COVID-19 patients. Even though these studies are heterogeneous, several consistent findings have been reported[48]. COVID-19 patients exhibited downregulation of several serum lipids, including sphingolipids, glycerophospholipids, and fatty acids[49]. The liver damage caused by SARS-CoV-2 infection has been linked to dyslipidemia and oxidative stress[50]. In this regard, the levels of blood triglycerides and very-low-density lipoprotein are significantly elevated, whereas the levels of high-density lipoprotein and low-density lipoprotein are much lower[37,50,51]. Notably, COVID-19-related dyslipidemia occurs primarily in patients with high severity and not in those who recover from a mild uneventful infection. Bruzzone *et al*[50] used nuclear magnetic resonance spectroscopy to determine the lipidomic serum profile of 389 COVID-19 patients, revealing a pathogenic redistribution of lipoprotein particle size and composition with atherosclerosis risk. In the same study, the metabolomics analysis revealed unusually high levels of

ketone bodies, which are produced in the liver from free fatty acids, and 2-hydroxybutyric acid, which is a marker of oxidative stress and a consequence of glutathione synthesis in the liver. Ketosis in COVID-19 patients has been associated with a longer hospitalization and increased mortality rates[52]. Furthermore, a shift to fatty acid oxidation is a common metabolic response observed during many severe illnesses, and COVID-19 is no exception[49,53]. In this regard, a reduction in sphingosine-1-phosphate (S1P), which is a sphingosine molecule that regulates a variety of biological processes such as inflammation and apoptosis, is observed in COVID-19 patients[7,54]. In a study, serum level of S1P was found to be inversely associated with COVID-19 severity[55]. Additionally, glycerophospholipid levels are also reduced, whereas the levels of the corresponding lysophospholipids are increased, indicating increased phospholipase A_2 activation[7,54,56]. Elevated levels of phospholipase A2 may be an early marker of severe COVID-19.

Glucose

On another note, SARS-CoV-2 infection is also associated with dysregulated glucose metabolism. Regardless of previous diabetes status, hyperglycemia frequently develops in COVID-19 patients, and many develop new-onset DM and diabetes ketoacidosis[9-11,57]. Furthermore, the abnormal glucose metabolism has been reported to persist even after recovery from COVID-19. In a hospitalized sample of 551 COVID-19 patients, 46% were hyperglycemic, and glycemic abnormalities were detected for at least 2 mo following COVID-19 recovery[58]. In several observational studies, more severe hyperglycemia has been linked to a worse prognosis in COVID-19 patients[2,8,9,10,59]. IR and/or decreased insulin production are the primary causes of abnormal glucose metabolism in COVID-19 patients, and proinflammatory cytokines play an essential role in this process. The increased glucose metabolism due to sustained hyperglycemia may further enhance entry of SARS-CoV-2, with exacerbated immune response[60]. In this sense, elevated glucose levels and glycolysis lead to an increase in SARS-CoV-2 replication[27,61]. Furthermore, COVID-19 causes glycemic control to deteriorate in patients with pre-existing DM, and new-onset hyperglycemia is an independent predictor of mortality in such patients[11, 62,63]. As glycemic control deteriorates, the severity of illness and the risk of mortality increases.

PATHOPHYSIOLOGY OF METABOLIC DYSFUNCTIONS IN COVID-19

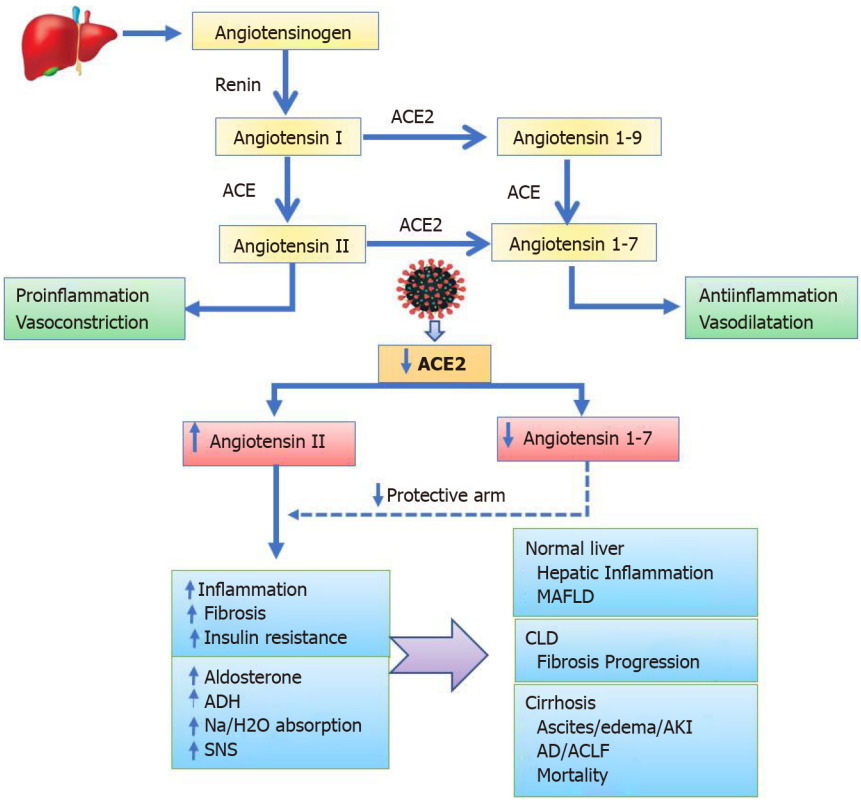
The occurrence of metabolic dysfunction in COVID-19 has been well documented; however, the molecular mechanisms behind these dysfunctions are sparsely known. Infection with SARS-CoV-2 can affect several metabolic organs such as the liver, pancreas, adipose tissue, and muscles, either directly or indirectly. Proinflammatory cytokines, oxidative stress, and IR all appear to contribute to metabolic dysregulation in COVID-19, and the association between metabolism and inflammation is well-known and still being investigated. The by-products of glycolysis increase cytokine maturation and, as a result, T-cell proliferation[64]. One such glycolytic metabolite necessary for IL-1β synthesis is 3-phosphoglycerate. Moreover, alterations in the levels of fatty acids and tryptophan metabolites have been associated with inflammatory markers in COVID-19 patients[40]. A study found high-affinity interactions between the viral spike protein and toll-like receptors (TLRs), particularly TLR4[65]. TLR4 activation is known to cause inflammation and cellular metabolic alterations[66]. Additionally, hyperglycemia has been linked to delayed IFN response and cytokine storm in COVID-19 patients[67,68].

Entry of SARS-CoV-2 into host cells

The interaction between the spike protein and ACE2 allows SARS-CoV-2 to enter host cells. Virus entry is facilitated through the priming of spike proteins by specific proteases such as transmembrane serine protease 2 (TMPRSS2) and furin protease. At first, SARS-CoV-2 targets epithelial cells in the lungs; however, viral RNA has been found in a variety of organs, including the liver, suggesting that other organs could be targeted as well. ACE2 is expressed by many cells, and its expression is further upregulated in a variety of conditions, including inflammatory and liver diseases[12,69]. As a result, increased ACE2 expression could be a risk factor as well as an effect of SARS-CoV-2 infection. In particular, the delta and omicron variants of SARS-CoV-2 have an even higher affinity for ACE2 than other variants[70]. While ACE2 expression is low in healthy livers, cirrhotic livers exhibit higher levels of ACE2 expression[12]. As a result, patients with liver cirrhosis may be more susceptible to SARS-CoV-2 infection.

Alterations in the RAAS

SARS-CoV-2 infection significantly influences the RAAS since ACE2 is a key part of it[71]. The discovery of functional local RAAS in several organs, including the liver, has changed our knowledge of the RAAS[14]. Alternative RAAS pathways mediated by ACE2 in the local RAAS result in the opposite effects of classic RAAS (Figure 1). ACE2 is a major regulator in the alternative RAAS pathways, regulating the production of angiotensin 1–7 (Ang 1-7) from angiotensin II (Ang II). Additionally, ACE2 converts angiotensin I to angiotensin 1–9 (Ang 1-9), which can be further converted to Ang 1–7 by the angiotensin-converting enzyme. Importantly, the protective arm of the RAAS is made up of ACE2, Ang



DOI: 10.5501/wjv.v11.i5.237

Figure 1 Interaction between severe acute respiratory syndrome coronavirus 2 and renin–angiotensin–aldosterone system system *via* angiotensin converting enzymes 2 as receptor. The interaction between the cellular spike protein and angiotensin converting enzymes 2 (ACE2) allows severe acute respiratory syndrome coronavirus 2 to enter host cells. ACE2 mediates alternative renin–angiotensin–aldosterone system (RAAS) pathways in the local RAAS system. ACE2 regulates the production of angiotensin 1–7 from angiotensin II (Ang II) and angiotensin 1–9. ACE2 after binding to virions is internalised, reducing its availability on the cellular surface. Once ACE2 is downregulated, Ang II gets upregulated which upon binding to the Ang II receptors, causes proinflammatory, profibrotic, vasoconstrictive, and antidiuretic responses. Overactivation of the RAAS has been linked to the development of refractory ascites, hepatorenal syndrome, and circulatory dysfunction in cirrhosis. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RAAS: renin-angiotensin-aldosterone system; ACE2: Angiotensin converting enzymes 2, CLD: Chronic liver disease, MAFLD: metabolic associated fatty liver disease, ADH: Antidiuretic hormone; Na: Sodium; H2O: Water; SNS: Sympathetic nervous system, AD: Acute decompensation, ACLF: Acute-on-chronic liver failure.

1–7, and its Mas receptor, and this results in anti-inflammatory and antifibrotic responses (Figure 1). However, when ACE2 is downregulated, Ang II gets upregulated, and upon binding to the Ang II receptors, it causes proinflammatory, profibrotic, vasoconstrictive, and antidiuretic responses that can lead to end-organ damage[71]. The plasma level Ang II rises in COVID-19 patients and is linearly associated with viral load[72]. Ultimately, SARS-CoV-2 infection causes inflammatory reactions due to the downregulation of ACE2[71-73]. Generally, ACE2 coupled to virions is internalized, reducing its availability on the cellular surface. Moreover, some unknown mechanism induces the gene expression of disintegrins and metalloproteinase domain-17 (ADAM-17)[74]. ADAM-17 is a membrane sheddase protease that releases ACE2, IL-4, and IFN from cell membranes. Finally, free IFN-γ and IL-4 suppress membrane-bound ACE2, further shifting the RAAS to a higher Ang II and lower Ang1-7 tone[71,74].

Alterations in one-carbon pathways

The one-carbon pathway is a metabolic network that include the methionine and folate cycles and is involved in many biological functions such as synthesis of amino acids, polyamines, nucleic acids, adenosine triphosphate, phospholipids and glutathione[75]. In particular, the metabolic pathways of methionine, folate, and choline have been implicated in the pathogenesis of hepatic steatosis[76]. One-carbon metabolism appears to have a crucial role in COVID-19[78-83]. In this regard, SARS-CoV-2 uses folate and one-carbon metabolism to gain a competitive advantage in replication[77]. It modifies host folate metabolism at the post-transcriptional level to enhance de novo purine synthesis. Several observational studies on COVID-19 patients have linked one-carbon metabolism to the disease severity, although mechanistic insights are still being developed[78]. The results of various studies on the link between one-carbon metabolism and COVID-19 have been varied and conflicting, except for a few metabolites such as glutathione, choline, and methionine sulfoxide, which were consistently altered by COVID-19[78]. These discrepancies could be related to the confounding effects of non-matched study subjects, variances in disease severity, and the time points at which samples were collected in different

studies.

Furthermore, metabolomic studies have ascertained that S-adenosylmethionine (SAM), the universal methyl donor, is significantly increased in severe and fatal cases of COVID-19[79,80]. As the generation of SAM requires vitamin B12-dependent methionine synthase, many symptoms of long COVID-19 are similar to those of vitamin B12 deficiency, a condition in which methylation is disturbed[81]. Multiple independent metabolic studies have reported higher serum levels of methionine sulfoxide in COVID-19 patients, implying increased oxidative stress[82,83]. Moreover, glutathione, the most important antioxidant, is consistently depleted in COVID-19 patients and is often associated with increased lipid peroxidation markers[84]. In children with mild COVID-19, higher levels of methylmalonic acid (MMA), which is a catabolic product of certain amino acids, have been found[83]. A vitamin B12-dependent enzyme further metabolizes MMA to succinic acid, which is a TCA cycle substrate. The antiviral and anti-inflammatory properties of MMA are thought to protect children from severe infection. Polyamines, including as spermidine and spermine, have been found to have a role in the replication and attachment of SARS-CoV-2, with serum levels of these compounds being greater in COVID-19 patients[47]. Overall, it appears that the virus exploits one-carbon metabolism pathways for its replicative advantages, producing metabolic disturbance in the host cells.

Pathogenesis of hyperglycemia

The pathophysiological basis of hyperglycemia in COVID-19 patients appears to be the development of IR and pancreatic β-cell dysfunction (Figure 2). Peripheral IR is caused by SARS-CoV-2-induced hyperinflammation and cytokine storm. Metaflammation, defined as a rise in TNF, IL-6, and IL-1 Levels in patients with metabolic syndrome, can further increase IR[85]. Furthermore, pancreatic damage with subsequent impairment of insulin secretion is evident in COVID-19 patients[10,86]. However, SARS-CoV-2 does not appear to infect β-cells. directly, as ACE2 and TMPRSS2 have only been detected in pancreatic microvasculature and ducts, not in β-cells[87]. Pancreatic injury caused by SARS-CoV-2 increases the release of pancreatic lipase, resulting in lipolysis and the release of unsaturated fatty acids, thus causing mitochondrial damage and inflammation[86,88]. When ACE2 is downregulated in the intestinal epithelium, SGLT1 is upregulated, resulting in hyperglycemia[89]. The unopposed action of Ang II leads to oxidative stress that triggers β-cell damage and further impairment of insulin secretion. Hyperglycemia *per se* can cause β-cell dysfunction by upregulating the Ang II receptor on β-cells and causing glucolipotoxicity[11]. Furthermore, persistent hyperglycemia may exacerbate COVID-19 by glycating ACE2, which facilitates the entry of SARS-CoV-2[10]. Recently, a circulating protein GP73, which is a glucogenic hormone that enhances hepatic gluconeogenesis, has been found in COVID-19 patients, and it appears to modulate SARS-CoV-2-induced glucose metabolic alteration[90].

CLINICAL IMPLICATIONS OF METABOLIC ALTERATIONS IN COVID-19

COVID-19 and metabolic diseases

Multiple studies have found that metabolic comorbidities are more common in COVID-19 patients and are associated with poorer outcomes. However, the pathophysiologic mechanisms that underpin this adverse metabolic interaction are still poorly understood. The proinflammatory environment in patients with metabolic disorders may aggravate immune dysregulation, inflammation, microvascular dysfunction, and thrombosis, which may intensify the essential interaction between virus and host components. Additionally, patients with metabolic illnesses are more likely to respond to infection in a proinflammatory rather than protective manner, which could contribute to increased cytokines in COVID-19 infection. Obesity[91,92], DM[2,59], hypertension[93], dyslipidemia[94,95], and metabolic-associated fatty liver (MAFLD)[5,96] have all been shown to be associated with a more severe disease course and increased mortality in COVID-19 (Table 2). A pooled data analysis of 20 studies determined that obese individuals had a 46% (Odds ratio [OR]: 1.46) higher chance of testing positive for COVID-19 than non-obese people[97]. Moreover, a history of prior bariatric surgery is associated with a reduced severity in COVID-19 patients[98]. In severe COVID-19 patients, the prevalence of DM (OR: 3.5) and hypertension (OR: 2.6) is higher than that in non-severe patients[99]. In a meta-analysis of 33 studies, including 16003 COVID-19 patients, the pooled odds ratio of mortality or severity in presence of DM was 2.16 (95%; CI: 1.74-2.68; $P < 0.01$)[59]. Poor outcome of COVID-19 associated with DM or hyperglycemia may be attributed to higher glucose levels that provide huge substrates for increased glycolysis thus producing energy and substrates for SARS-CoV-2 replication. On the other hand, improved glycemic control is associated with better outcomes in COVID-19 patients with DM[62]. Lactic acidosis has been documented frequently in severe COVID-19 patients with DM treated with metformin [100]. A meta-analysis of 7 studies (n = 6922) showed that dyslipidemia is associated with severe COVID-19 infections [RR 1.39][95].

COVID-19 and liver diseases

SARS-CoV-2 produces steatosis and lobular and portal inflammation in the liver[101]. Microthrombi have been found in the hepatic sinusoids in fatal cases due to coagulopathy and endothelial

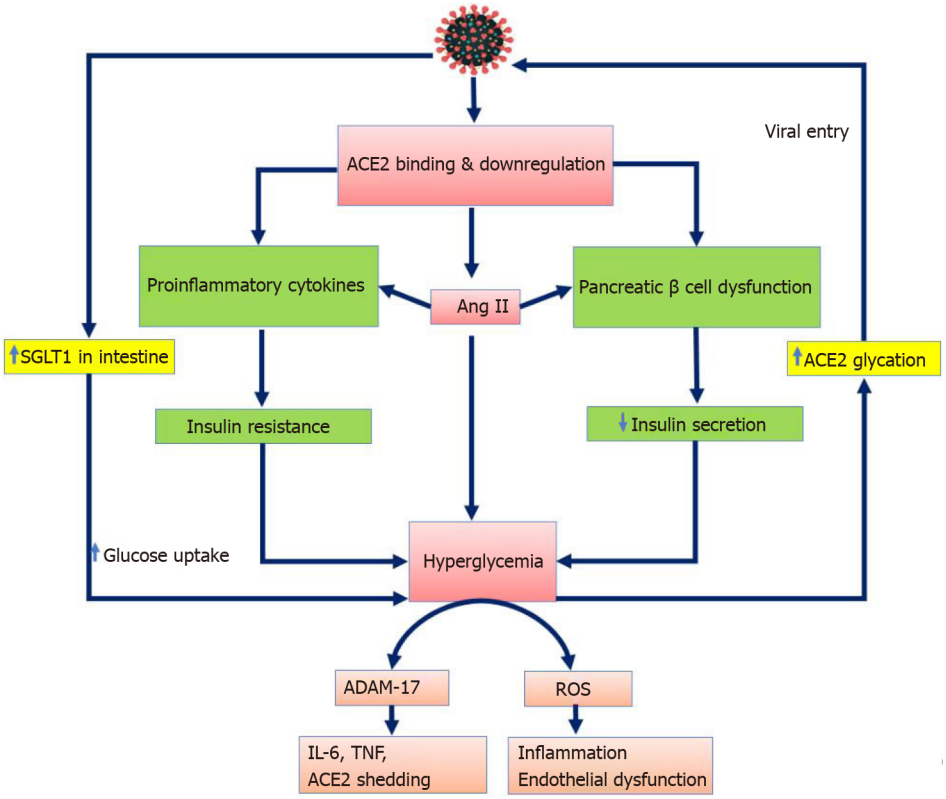
Table 2 Meta-analyses of associations between coronavirus disease 2019 and metabolic diseases

Ref.	Metabolic condition	COVID-19 (N); Studies/Patients	Main results
Ho *et al*[91]	Obesity	61/270241	Obesity was associated with more severe disease (OR 3.13, 95%CI: 1.41-6.92) and mortality (OR 1.36, 95%CI: 1.09-1.69)
Yang *et al*[92]	Obesity	50/18 260 378	Obesity was associated with a higher risk of SARS-CoV2 infection (OR: 1.39, 95%CI: 1.25-1.54), increased disease severity (OR: 3.74, 95%CI: 1.18-11.87) and mortality (OR: 1.65, 95%CI: 1.21-2.25)
Huang *et al*[2]	DM	30/6452	DM was associated with composite poor outcome (RR 2.38 [1.88, 3.03], $P < 0.001$)
Kumar *et al*[59]	DM	33/16003	The combined corrected pooled OR of mortality or severity was 2.16 (95%CI: 1.74-2.68; $P < 0.01$)
Atmosudigdo *et al*[94]	Dyslipidemia	09/3663	Dyslipidemia was associated with poor outcome (RR 1.39 [1.02, 1.88], more so in patients with older age, male, and hypertension
Hariyanto *et al*[95]	Dyslipidemia	07/6922	Dyslipidemia was associated with severe disease (RR 1.39 (95%CI: 1.03-1.87)
Du *et al*[93]	Hypertension	24/99918	Patients with hypertension had a 1.82-fold higher risk for critical COVID-19 (OR: 1.82; 95%CI: 1.19-2.77; $P = 0.005$) and a 2.17-fold higher risk for COVID-19 mortality (OR: 2.17; 95% CI: 1.67-2.82; $P < 0.001$)
Zuin *et al*[4]	Metabolic syndrome	06/209.569	Pre-existing metabolic syndrome was associated with higher risk of mortality (OR: 2.30, 95%CI: 1.52-3.45). Meta-regression showed a direct correlation with hypertension, DM and hyperlipidaemia
Tao *et al*[5]	MAFLD	07/2141	MAFLD increased the risk of severe COVID-19 (OR: 1.80, 95%Cl: 1.53-2.13)
Pan *et al*[96]	MAFLD	06/1293	MAFLD increased the risk of disease severity, with a pooled OR of 2.93 (95%CI: 1.87, 4.60)

COVID-19: Coronavirus disease 2019; CI: Confidence interval; DM: Diabetes mellitus; RR: Relative risk, OR: Odds ratio; MAFLD: Metabolic associated fatty liver disease.

dysfunction. Despite the preponderance of ACE2 on the biliary epithelium, significant cholestasis is rare. In a histological study of patients who died of complications of COVID-19, macrovesicular steatosis was the most common finding as it was observed in 75% of patients, and PCR for viral ribonucleic acid in liver tissue was positive in 55% of patients tested[102]. Such a high frequency of hepatic steatosis suggests a role of some metabolic derangements associated with COVID infection, which in turn lead to fatty liver disease. In this regard, COVID-19 patients with NAFLD have a higher risk of developing liver injury[103], a higher risk of disease progression (44.7% *vs* 6.6%), more likelihood of impaired liver function, and a longer viral shedding time compared to those without NAFLD[19]. It is noteworthy that NAFLD is now known as MAFLD, which refers to the hepatic manifestation of metabolic health. In two meta-analyses, MAFLD was found to increase the risk of severe COVID-19 (OR: 1.8 and 2.9, respectively)[4,5]. After adjusting for confounders, the pooled OR for severe COVID-19 in NAFLD was 2.358, demonstrating that NAFLD alone, without confounding factors, may contribute to worse COVID-19 outcomes; however, the exact explanation is still unknown[104]. Therefore, further research on the impact of NAFLD in COVID-19 patients is needed.

In patients with liver cirrhosis, the RAAS plays a key role in the development of portal hypertension and ascites[14,105,106]. The hyperdynamic circulation seen in portal hypertension is caused by overexpression of ACE2 and enhanced Ang1-7 production in the mesenteric arterioles[105,106]. As per the combined SECURE-liver and COVID-Hep registries, 38% of patients with cirrhosis and COVID-19 had worsening ascites, acute kidney injury (AKI), or encephalopathy[107]. In cirrhosis, RAAS activation occurs as a compensatory response to the systemic and splanchnic arterial vasodilation, resulting in renal water and sodium retention, which contributes to the development of the complications of cirrhosis such as ascites and AKI[14,108,109]. COVID-19 can increase the risk of these complications by interacting with the RAAS. On another note, hyperammonemia has been reported in COVID-19 patients, and it could be linked to hepatic dysfunction and urea cycle interference[110]. Ammonia is a neurotoxin that affects astrocytes and plays a role in the development of cerebral edema and hepatic encephalopathy. By causing IR and pancreatic dysfunction, COVID-19 can increase the risk of hepatogenous diabetes in patients with liver cirrhosis, and it can aggravate pre-existing gut dysbiosis in cirrhosis. On the one hand, gut dysbiosis can result in the translocation of endotoxins and bacteria leading to inflammation; on the other hand, it reduces the anti-inflammatory effects by reducing the production of commensal bacterial metabolites such as butyrate, bile acid derivatives, and indole[111]. Overall, the proinflammatory environment with metabolic alterations in COVID-19 patients with liver cirrhosis leads to the development of acute decompensation, acute-on-chronic liver failure, and increased mortality[109,112].



DOI: 10.5501/wjv.v11.i5.237

Figure 2 The pathophysiological mechanism linking coronavirus disease 2019 with hyperglycemia. The pathophysiological basis of hyperglycaemia in coronavirus disease 2019 patients is still poorly understood but appears to be due to the development of insulin resistance and pancreatic β-cell dysfunction in which upregulation of angiotensin II, inflammation, and oxidative stress play important role. ACE2: Angiotensin converting enzymes 2; Ang II: Angiotensin II; SGLT1: Sodium glucose transport protein1; ROS: Reactive oxygen species; ADAM-17: Disintegrin and metalloproteinase domain-17; IL-6: Interleukin-6, TNF: Tumour necrosis factor.

METABOLIC CHANGES DURING AND FOLLOWING RECOVERY FROM COVID-19

During the early convalescence of COVID-19 patients, distinct profiles of metabolites and cytokines have been observed. One study reported a reduction in saturated fat palmitic acid while unsaturated fatty acids such as docosapentaenoic acid and docosahexaenoic acid were elevated[29]. These changes correspond to the prevention of hepatocyte apoptosis and facilitation of liver repair. Furthermore, a rise in tryptophan levels was observed, and this could aid in the reversal of liver injury by preserving protein synthesis activity[113]. On another note, the glycemic abnormalities persist for at least 2 mo following recovery from COVID-19[58]. A long-term follow-up study on patients who had recovered from the original SARS-CoV-1 infection found a significant prevalence of hyperlipidemia (68%) and glycemic abnormalities (60%)[114]. Given the structural similarity of the SARS-CoV-2 virus to the original SARS-CoV-1 virus, comparable outcomes can be expected; however, this remains to be seen. The metabolic abnormality appears to persist more in patients with metabolic comorbidities. In this sense, a study with 1-year follow-up following discharge reported significant abnormalities in metabolic indicators such as blood lipids, uric acid, and liver function in obese COVID-19 patients compared to non-obese ones[18]. Another study demonstrated incomplete metabolic phenorversion in post-COVID patients. Even though most metabolic markers showed a high level of normalization, plasma taurine, and lower glutamine/glutamate ratios indicated little normalization in the majority of patients, indicating probable liver and muscle injury[17]. Further research is needed to determine the long-term clinical implications of these findings. In a study published recently, MAFLD was highly prevalent after hospital discharge, indicating potential long-term metabolic health implications. The prevalence of MAFLD was 55.3% at follow-up, while it was 37.3% on admission[115]. As metabolic alterations such as dysglycemia, hyperlipidemia, and inflammation are important in the progression of MAFLD, a high prevalence of MAFLD-induced advanced CLD may be expected in the years to come.

CONCLUSION

Human SARS-CoV-2 infection triggers a complex viral-host interaction that results in metabolic

reprogramming, altered immunological response, and a variety of clinical consequences. As the liver is the metabolic hub of the body, it is targeted in this process. In metabolomics and lipidomic studies on COVID-19 patients, a variety of alterations in amino acids, lipids, carbohydrates, and energy metabolism have been identified. Although the impact of each metabolic change remains to be determined, pathophysiological alterations in the RAAS, insulin sensitivity, pancreatic functions, biosynthesis pathways, and ammonia metabolism can be used to make various extrapolations in the clinical setting. Furthermore, evidence suggests a direct link between metabolic changes and inflammatory responses in the body. Patients with underlying low-grade chronic inflammation, such as metabolic syndrome or CLD, may be particularly affected by COVID-19-induced metabolic changes. Therefore, obesity, DM, hypertension, dyslipidemia, and MAFLD in COVID-19 patients have all been associated with a more severe disease course and higher mortality. Moreover, preliminary data suggest that metabolic changes in COVID-19 can also have long-term health implications. Improved metabolic parameters such as blood glucose, blood pressure, and body weight may help control the systemic inflammatory response and reduce the severity of COVID-19 disease. Furthermore, metabolic changes may reflect the molecular profile of SARS-CoV-2-infected individuals, opening up new avenues for targeted therapeutic interventions.

FOOTNOTES

Author contributions: Kumar R, Kumar V, and Arya R contributed in concept and design of manuscript, data collection and manuscript writing; Anand U and Priyadarshi RN contributed in data collection, critical inputs and manuscript revision.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest for this article.

Country/Territory of origin: India

ORCID number: Ramesh Kumar 0000-0001-5136-4865; Vijay Kumar 0000-0001-6042-7784; Rahul Arya 0000-0003-3714-0990; Utpal Anand 0000-0003-0653-4129; Rajeev Nayan Priyadarshi 0000-0003-2890-8910.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Yang J**, Hu J, Zhu C. Obesity aggravates COVID-19: A systematic review and meta-analysis. *J Med Virol* 2021; **93**: 257-261 [PMID: 32603481 DOI: 10.1002/jmv.26237]
2 **Huang I**, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 2020; **14**: 395-403 [PMID: 32334395 DOI: 10.1016/j.dsx.2020.04.018]
3 **Zheng KI**, Gao F, Wang XB, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, Liu WY, George J, Zheng MH. Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism* 2020; **108**: 154244 [PMID: 32320741 DOI: 10.1016/j.metabol.2020.154244]
4 **Zuin M**, Rigatelli G, Bilato C, Cervellati C, Zuliani G, Roncon L. Prognostic Role of Metabolic Syndrome in COVID-19 Patients: A Systematic Review Meta-Analysis. *Viruses* 2021; **13** [PMID: 34696368 DOI: 10.3390/v13101938]
5 **Tao Z**, Li Y, Cheng B, Zhou T, Gao Y. Risk of Severe COVID-19 Increased by Metabolic Dysfunction-associated Fatty Liver Disease: A Meta-analysis. *J Clin Gastroenterol* 2021; **55**: 830-835 [PMID: 34406175 DOI: 10.1097/MCG.0000000000001605]
6 **Hammoudeh SM**, Hammoudeh AM, Bhamidimarri PM, Mahboub B, Halwani R, Hamid Q, Rahmani M, Hamoudi R. Insight into molecular mechanisms underlying hepatic dysfunction in severe COVID-19 patients using systems biology. *World J Gastroenterol* 2021; **27**: 2850-2870 [PMID: 34135558 DOI: 10.3748/wjg.v27.i21.2850]
7 **Shen B**, Yi X, Sun Y, Bi X, Du J, Zhang C, Quan S, Zhang F, Sun R, Qian L, Ge W, Liu W, Liang S, Chen H, Zhang Y, Li J, Xu J, He Z, Chen B, Wang J, Yan H, Zheng Y, Wang D, Zhu J, Kong Z, Kang Z, Liang X, Ding X, Ruan G, Xiang N, Cai X, Gao H, Li L, Li S, Xiao Q, Lu T, Zhu Y, Liu H, Guo T. Proteomic and Metabolomic Characterization of COVID-19 Patient Sera. *Cell* 2020; **182**: 59-72.e15 [PMID: 32492406 DOI: 10.1016/j.cell.2020.05.032]
8 **Krishnan S**, Nordqvist H, Ambikan AT, Gupta S, Sperk M, Svensson-Akusjärvi S, Mikaeloff F, Benfeitas R, Saccon E, Ponnan SM, Rodriguez JE, Nikouyan N, Odeh A, Ahlén G, Asghar M, Sällberg M, Vesterbacka J, Nowak P, Végvári Á,

Sönnerborg A, Treutiger CJ, Neogi U. Metabolic Perturbation Associated With COVID-19 Disease Severity and SARS-CoV-2 Replication. *Mol Cell Proteomics* 2021; **20**: 100159 [PMID: 34619366 DOI: 10.1016/j.mcpro.2021.100159]

9 **Wang A**, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. *Diabetes Res Clin Pract* 2020; **162**: 108118 [PMID: 32179126 DOI: 10.1016/j.diabres.2020.108118]

10 **Albulescu R**, Dima SO, Florea IR, Lixandru D, Serban AM, Aspritoiu VM, Tanase C, Popescu I, Ferber S. COVID-19 and diabetes mellitus: Unraveling the hypotheses that worsen the prognosis (Review). *Exp Ther Med* 2020; **20**: 194 [PMID: 33101484 DOI: 10.3892/etm.2020.9324]

11 **Singh AK**, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. *Diabetes Res Clin Pract* 2020; **167**: 108382 [PMID: 32853686 DOI: 10.1016/j.diabres.2020.108382]

12 **Paizis G**, Tikellis C, Cooper ME, Schembri JM, Lew RA, Smith AI, Shaw T, Warner FJ, Zuilli A, Burrell LM, Angus PW. Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. *Gut* 2005; **54**: 1790-1796 [PMID: 16166274 DOI: 10.1136/gut.2004.062398]

13 **Brojakowska A**, Narula J, Shimony R, Bander J. Clinical Implications of SARS-CoV-2 Interaction With Renin Angiotensin System: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020; **75**: 3085-3095 [PMID: 32305401 DOI: 10.1016/j.jacc.2020.04.028]

14 **Di Pascoli M**, La Mura V. Renin-angiotensin-aldosterone system in cirrhosis: There's room to try! *Dig Liver Dis* 2019; **51**: 297-298 [PMID: 30220630 DOI: 10.1016/j.dld.2018.07.038]

15 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

16 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

17 **Holmes E**, Wist J, Masuda R, Lodge S, Nitschke P, Kimhofer T, Loo RL, Begum S, Boughton B, Yang R, Morillon AC, Chin ST, Hall D, Ryan M, Bong SH, Gay M, Edgar DW, Lindon JC, Richards T, Yeap BB, Pettersson S, Spraul M, Schaefer H, Lawler NG, Gray N, Whiley L, Nicholson JK. Incomplete Systemic Recovery and Metabolic Phenoreversion in Post-Acute-Phase Nonhospitalized COVID-19 Patients: Implications for Assessment of Post-Acute COVID-19 Syndrome. *J Proteome Res* 2021; **20**: 3315-3329 [PMID: 34009992 DOI: 10.1021/acs.jproteome.1c00224]

18 **Shang L**, Wang L, Zhou F, Li J, Liu Y, Yang S. Long-term effects of obesity on COVID-19 patients discharged from hospital. *Immun Inflamm Dis* 2021; **9**: 1678-1685 [PMID: 34499804 DOI: 10.1002/iid3.522]

19 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]

20 **Nasa P**, Alexander G. COVID-19 and the liver: What do we know so far? *World J Hepatol* 2021; **13**: 522-532 [PMID: 34131467 DOI: 10.4254/wjh.v13.i5.522]

21 **Saviano A**, Wrensch F, Ghany MG, Baumert TF. Liver Disease and Coronavirus Disease 2019: From Pathogenesis to Clinical Care. *Hepatology* 2021; **74**: 1088-1100 [PMID: 33332624 DOI: 10.1002/hep.31684]

22 **Batabyal R**, Freishtat N, Hill E, Rehman M, Freishtat R, Koutroulis I. Metabolic dysfunction and immunometabolism in COVID-19 pathophysiology and therapeutics. *Int J Obes (Lond)* 2021; **45**: 1163-1169 [PMID: 33727631 DOI: 10.1038/s41366-021-00804-7]

23 **Sathish T**, Tapp RJ, Cooper ME, Zimmet P. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. *Diabetes Metab* 2021; **47**: 101204 [PMID: 33129968 DOI: 10.1016/j.diabet.2020.10.002]

24 **Li JZ**, Ye J, Xue B, Qi J, Zhang J, Zhou Z, Li Q, Wen Z, Li P. Cideb regulates diet-induced obesity, liver steatosis, and insulin sensitivity by controlling lipogenesis and fatty acid oxidation. *Diabetes* 2007; **56**: 2523-2532 [PMID: 17646209 DOI: 10.2337/db07-0040]

25 **He M**, Pei Z, Mohsen AW, Watkins P, Murdoch G, Van Veldhoven PP, Ensenauer R, Vockley J. Identification and characterization of new long chain acyl-CoA dehydrogenases. *Mol Genet Metab* 2011; **102**: 418-429 [PMID: 21237683 DOI: 10.1016/j.ymgme.2010.12.005]

26 **Varela-Rey M**, Martínez-López N, Fernández-Ramos D, Embade N, Calvisi DF, Woodhoo A, Rodríguez J, Fraga MF, Julve J, Rodríguez-Millán E, Frades I, Torres L, Luka Z, Wagner C, Esteller M, Lu SC, Martínez-Chantar ML, Mato JM. Fatty liver and fibrosis in glycine N-methyltransferase knockout mice is prevented by nicotinamide. *Hepatology* 2010; **52**: 105-114 [PMID: 20578266 DOI: 10.1002/hep.23639]

27 **Codo AC**, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoff JS, Carregari VC, de Biagi Junior CAO, Crunfli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira FB, Velloso LA, Vinolo MAR, Damasio A, Proença-Módena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis. *Cell Metab* 2020; **32**: 498-499 [PMID: 32877692 DOI: 10.1016/j.cmet.2020.07.015]

28 **Chen YM**, Zheng Y, Yu Y, Wang Y, Huang Q, Qian F, Sun L, Song ZG, Chen Z, Feng J, An Y, Yang J, Su Z, Sun S, Dai F, Chen Q, Lu Q, Li P, Ling Y, Yang Z, Tang H, Shi L, Jin L, Holmes EC, Ding C, Zhu TY, Zhang YZ. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. *EMBO J* 2020; **39**: e105896 [PMID: 33140861 DOI: 10.15252/embj.2020105896]

29 **Scozzi D**, Cano M, Ma L, Zhou D, Zhu JH, O'Halloran JA, Goss C, Rauseo AM, Liu Z, Sahu SK, Peritore V, Rocco M, Ricci A, Amodeo R, Aimati L, Ibrahim M, Hachem R, Kreisel D, Mudd PA, Kulkarni HS, Gelman AE. Circulating mitochondrial DNA is an early indicator of severe illness and mortality from COVID-19. *JCI Insight* 2021; **6** [PMID: 33444289 DOI: 10.1172/jci.insight.143299]

30 **San Juan I**, Bruzzone C, Bizkarguenaga M, Bernardo-Seisdedos G, Laín A, Gil-Redondo R, Diercks T, Gil-Martínez J, Urquiza P, Arana E, Seco M, García de Vicuña A, Embade N, Mato JM, Millet O. Abnormal concentration of porphyrins in serum from COVID-19 patients. *Br J Haematol* 2020; **190**: e265-e267 [PMID: 32745239 DOI: 10.1111/bjh.17060]

31 **Miyajima M**. Amino acids: key sources for immunometabolites and immunotransmitters. *Int Immunol* 2020; **32**: 435-446 [PMID: 32383454 DOI: 10.1093/intimm/dxaa019]

32 **Li P**, Yin YL, Li D, Kim SW, Wu G. Amino acids and immune function. *Br J Nutr* 2007; **98**: 237-252 [PMID: 17403271 DOI: 10.1017/S000711450769936X]

33 **Zhenyukh O**, Civantos E, Ruiz-Ortega M, Sánchez MS, Vázquez C, Peiró C, Egido J, Mas S. High concentration of branched-chain amino acids promotes oxidative stress, inflammation and migration of human peripheral blood mononuclear cells *via* mTORC1 activation. *Free Radic Biol Med* 2017; **104**: 165-177 [PMID: 28089725 DOI: 10.1016/j.freeradbiomed.2017.01.009]

34 **Locasale JW**. Serine, glycine and one-carbon units: cancer metabolism in full circle. *Nat Rev Cancer* 2013; **13**: 572-583 [PMID: 23822983 DOI: 10.1038/nrc3557]

35 **Wu J**, Zhao M, Li C, Zhang Y, Wang DW. The SARS-CoV-2 induced targeted amino acid profiling in patients at hospitalized and convalescent stage. *Biosci Rep* 2021; **41** [PMID: 33625490 DOI: 10.1042/BSR20204201]

36 **Lynch CJ**, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. *Nat Rev Endocrinol* 2014; **10**: 723-736 [PMID: 25287287 DOI: 10.1038/nrendo.2014.171]

37 **Kimhofer T**, Lodge S, Whiley L, Gray N, Loo RL, Lawler NG, Nitschke P, Bong SH, Morrison DL, Begum S, Richards T, Yeap BB, Smith C, Smith KGC, Holmes E, Nicholson JK. Integrative Modeling of Quantitative Plasma Lipoprotein, Metabolic, and Amino Acid Data Reveals a Multiorgan Pathological Signature of SARS-CoV-2 Infection. *J Proteome Res* 2020; **19**: 4442-4454 [PMID: 32806897 DOI: 10.1021/acs.jproteome.0c00519]

38 **Caterino M**, Costanzo M, Fedele R, Cevenini A, Gelzo M, Di Minno A, Andolfo I, Capasso M, Russo R, Annunziata A, Calabrese C, Fiorentino G, D'Abbraccio M, Dell'Isola C, Fusco FM, Parrella R, Fabbrocini G, Gentile I, Castaldo G, Ruoppolo M. The Serum Metabolome of Moderate and Severe COVID-19 Patients Reflects Possible Liver Alterations Involving Carbon and Nitrogen Metabolism. *Int J Mol Sci* 2021; **22** [PMID: 34502454 DOI: 10.3390/ijms22179548]

39 **Essa MM**, Hamdan H, Chidambaram SB, Al-Balushi B, Guillemin GJ, Ojcius DM, Qoronfleh MW. Possible role of tryptophan and melatonin in COVID-19. *Int J Tryptophan Res* 2020; **13**: 1178646920951832 [PMID: 32913393 DOI: 10.1177/1178646920951832]

40 **Thomas T**, Stefanoni D, Reisz JA, Nemkov T, Bertolone L, Francis RO, Hudson KE, Zimring JC, Hansen KC, Hod EA, Spitalnik SL, D'Alessandro A. COVID-19 infection alters kynurenine and fatty acid metabolism, correlating with IL-6 levels and renal status. *JCI Insight* 2020; **5** [PMID: 32559180 DOI: 10.1172/jci.insight.140327]

41 **Liu X**, Zheng Y, Guasch-Ferré M, Ruiz-Canela M, Toledo E, Clish C, Liang L, Razquin C, Corella D, Estruch R, Fito M, Gómez-Gracia E, Arós F, Ros E, Lapetra J, Fiol M, Serra-Majem L, Papandreou C, Martínez-González MA, Hu FB, Salas-Salvadó J. High plasma glutamate and low glutamine-to-glutamate ratio are associated with type 2 diabetes: Case-cohort study within the PREDIMED trial. *Nutr Metab Cardiovasc Dis* 2019; **29**: 1040-1049 [PMID: 31377179 DOI: 10.1016/j.numecd.2019.06.005]

42 **Bilinsky LM**, Reed MC, Nijhout HF. The role of skeletal muscle in liver glutathione metabolism during acetaminophen overdose. *J Theor Biol* 2015; **376**: 118-133 [PMID: 25890031 DOI: 10.1016/j.jtbi.2015.04.006]

43 **Shambaugh GE 3rd**. Urea biosynthesis I. The urea cycle and relationships to the citric acid cycle. *Am J Clin Nutr* 1977; **30**: 2083-2087 [PMID: 337792 DOI: 10.1093/ajcn/30.12.2083]

44 **Lercher A**, Bhattacharya A, Popa AM, Caldera M, Schlapansky MF, Baazim H, Agerer B, Gürtl B, Kosack L, Májek P, Brunner JS, Vitko D, Pinter T, Genger JW, Orlova A, Pikor N, Reil D, Ozsvár-Kozma M, Kalinke U, Ludewig B, Moriggl R, Bennett KL, Menche J, Cheng PN, Schabbauer G, Trauner M, Klavins K, Bergthaler A. Type I Interferon Signaling Disrupts the Hepatic Urea Cycle and Alters Systemic Metabolism to Suppress T Cell Function. *Immunity* 2019; **51**: 1074-1087.e9 [PMID: 31784108 DOI: 10.1016/j.immuni.2019.10.014]

45 **Nishio A**, Rehermann B. Virus-Induced Interferon Regulates the Urea Cycle. *Immunity* 2019; **51**: 975-977 [PMID: 31951542 DOI: 10.1016/j.immuni.2019.11.012]

46 **Moon J**, Kim OY, Jo G, Shin MJ. Alterations in Circulating Amino Acid Metabolite Ratio Associated with Arginase Activity Are Potential Indicators of Metabolic Syndrome: The Korean Genome and Epidemiology Study. *Nutrients* 2017; **9** [PMID: 28704931 DOI: 10.3390/nu9070740]

47 **Firpo MR**, Mastrodomenico V, Hawkins GM, Prot M, Levillayer L, Gallagher T, Simon-Loriere E, Mounce BC. Targeting Polyamines Inhibits Coronavirus Infection by Reducing Cellular Attachment and Entry. *ACS Infect Dis* 2021; **7**: 1423-1432 [PMID: 32966040 DOI: 10.1021/acsinfecdis.0c00491]

48 **Theken KN**, Tang SY, Sengupta S, FitzGerald GA. The roles of lipids in SARS-CoV-2 viral replication and the host immune response. *J Lipid Res* 2021; **62**: 100129 [PMID: 34599996 DOI: 10.1016/j.jlr.2021.100129]

49 **Casari I**, Manfredi M, Metharom P, Falasca M. Dissecting lipid metabolism alterations in SARS-CoV-2. *Prog Lipid Res* 2021; **82**: 101092 [PMID: 33571544 DOI: 10.1016/j.plipres.2021.101092]

50 **Bruzzone C**, Bizkarguenaga M, Gil-Redondo R, Diercks T, Arana E, García de Vicuña A, Seco M, Bosch A, Palazón A, San Juan I, Laín A, Gil-Martínez J, Bernardo-Seisdedos G, Fernández-Ramos D, Lopitz-Otsoa F, Embade N, Lu S, Mato JM, Millet O. SARS-CoV-2 Infection Dysregulates the Metabolomic and Lipidomic Profiles of Serum. *iScience* 2020; **23**: 101645 [PMID: 33043283 DOI: 10.1016/j.isci.2020.101645]

51 **Meoni G**, Ghini V, Maggi L, Vignoli A, Mazzoni A, Salvati L, Capone M, Vanni A, Tenori L, Fontanari P, Lavorini F, Peris A, Bartoloni A, Liotta F, Cosmi L, Luchinat C, Annunziato F, Turano P. Metabolomic/lipidomic profiling of COVID-19 and individual response to tocilizumab. *PLoS Pathog* 2021; **17**: e1009243 [PMID: 33524041 DOI: 10.1371/journal.ppat.1009243]

52 **Li J**, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab* 2020; **22**: 1935-1941 [PMID: 32314455 DOI: 10.1111/dom.14057]

53 **Nie X**, Qian L, Sun R, Huang B, Dong X, Xiao Q, Zhang Q, Lu T, Yue L, Chen S, Li X, Sun Y, Li L, Xu L, Li Y, Yang M, Xue Z, Liang S, Ding X, Yuan C, Peng L, Liu W, Yi X, Lyu M, Xiao G, Xu X, Ge W, He J, Fan J, Wu J, Luo M, Chang X, Pan H, Cai X, Zhou J, Yu J, Gao H, Xie M, Wang S, Ruan G, Chen H, Su H, Mei H, Luo D, Zhao D, Xu F, Zhu Y, Xia J, Hu Y, Guo T. Multi-organ proteomic landscape of COVID-19 autopsies. *Cell* 2021; **184**: 775-791.e14 [PMID: 33503446 DOI: 10.1016/j.cell.2021.01.004]

54 **Hao Y**, Zhang Z, Feng G, Chen M, Wan Q, Lin J, Wu L, Nie W, Chen S. Distinct lipid metabolic dysregulation in asymptomatic COVID-19. *iScience* 2021; **24**: 102974 [PMID: 34396083 DOI: 10.1016/j.isci.2021.102974]

55 **Marfia G**, Navone S, Guarnaccia L, Campanella R, Mondoni M, Locatelli M, Barassi A, Fontana L, Palumbo F, Garzia E, Ciniglio Appiani G, Chiumello D, Miozzo M, Centanni S, Riboni L. Decreased serum level of sphingosine-1-phosphate: a novel predictor of clinical severity in COVID-19. *EMBO Mol Med* 2021; **13**: e13424 [PMID: 33190411 DOI: 10.15252/emmm.202013424]

56 **Barberis E**, Timo S, Amede E, Vanella VV, Puricelli C, Cappellano G, Raineri D, Cittone MG, Rizzi E, Pedrinelli AR, Vassia V, Casciaro FG, Priora S, Nerici I, Galbiati A, Hayden E, Falasca M, Vaschetto R, Sainaghi PP, Dianzani U, Rolla R, Chiocchetti A, Baldanzi G, Marengo E, Manfredi M. Large-Scale Plasma Analysis Revealed New Mechanisms and Molecules Associated with the Host Response to SARS-CoV-2. *Int J Mol Sci* 2020; **21** [PMID: 33207699 DOI: 10.3390/ijms21228623]

57 **Smith SM**, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, Dobesh DP, Brufsky A, Connor RI. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol* 2021; **93**: 409-415 [PMID: 32589756 DOI: 10.1002/jmv.26227]

58 **Montefusco L**, Ben Nasr M, D'Addio F, Loretelli C, Rossi A, Pastore I, Daniele G, Abdelsalam A, Maestroni A, Dell'Acqua M, Ippolito E, Assi E, Usuelli V, Seelam AJ, Fiorina RM, Chebat E, Morpurgo P, Lunati ME, Bolla AM, Finzi G, Abdi R, Bonventre JV, Rusconi S, Riva A, Corradi D, Santus P, Nebuloni M, Folli F, Zuccotti GV, Galli M, Fiorina P. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab* 2021; **3**: 774-785 [PMID: 34035524 DOI: 10.1038/s42255-021-00407-6]

59 **Kumar A**, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, Khare S, Srivastava A. Is diabetes mellitus associated with mortality and severity of COVID-19? *Diabetes Metab Syndr* 2020; **14**: 535-545 [PMID: 32408118 DOI: 10.1016/j.dsx.2020.04.044]

60 **Ardestani A**, Azizi Z. Targeting glucose metabolism for treatment of COVID-19. *Signal Transduct Target Ther* 2021; **6**: 112 [PMID: 33677470 DOI: 10.1038/s41392-021-00532-4]

61 **Wu L**, Girgis CM, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. *Clin Endocrinol (Oxf)* 2020; **93**: 390-393 [PMID: 32683745 DOI: 10.1111/cen.14288]

62 **Zhu L**, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab* 2020; **31**: 1068-1077.e3 [PMID: 32369736 DOI: 10.1016/j.cmet.2020.04.021]

63 **Barron E**, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; **8**: 813-822 [PMID: 32798472 DOI: 10.1016/S2213-8587(20)30272-2]

64 **Buck MD**, O'Sullivan D, Pearce EL. T cell metabolism drives immunity. *J Exp Med* 2015; **212**: 1345-1360 [PMID: 26261266 DOI: 10.1084/jem.20151159]

65 **Choudhury A**, Mukherjee S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. *J Med Virol* 2020; **92**: 2105-2113 [PMID: 32383269 DOI: 10.1002/jmv.25987]

66 **Andrade Silva M**, da Silva ARPA, do Amaral MA, Fragas MG, Câmara NOS. Metabolic Alterations in SARS-CoV-2 Infection and Its Implication in Kidney Dysfunction. *Front Physiol* 2021; **12**: 624698 [PMID: 33716771 DOI: 10.3389/fphys.2021.624698]

67 **Acharya D**, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. *Nat Rev Immunol* 2020; **20**: 397-398 [PMID: 32457522 DOI: 10.1038/s41577-020-0346-x]

68 **Berbudi A**, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. *Curr Diabetes Rev* 2020; **16**: 442-449 [PMID: 31657690 DOI: 10.2174/1573399815666191024085838]

69 **Beyerstedt S**, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis* 2021; **40**: 905-919 [PMID: 33389262 DOI: 10.1007/s10096-020-04138-6]

70 **Candido KL**, Eich CR, de Fariña LO, Kadowaki MK, da Conceição Silva JL, Maller A, Simão RCG. Spike protein of SARS-CoV-2 variants: a brief review and practical implications. *Braz J Microbiol* 2022 [PMID: 35397075 DOI: 10.1007/s42770-022-00743-z]

71 **Steenblock C**, Schwarz PEH, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, Tkachuk VA, Markov AG, Lehnert H, de Angelis MH, Rietzsch H, Rodionov RN, Khunti K, Hopkins D, Birkenfeld AL, Boehm B, Holt RIG, Skyler JS, DeVries JH, Renard E, Eckel RH, Alberti KGMM, Geloneze B, Chan JC, Mbanya JC, Onyegbutulem HC, Ramachandran A, Basit A, Hassanein M, Bewick G, Spinas GA, Beuschlein F, Landgraf R, Rubino F, Mingrone G, Bornstein SR. COVID-19 and metabolic disease: mechanisms and clinical management. *Lancet Diabetes Endocrinol* 2021; **9**: 786-798 [PMID: 34619105 DOI: 10.1016/S2213-8587(21)00244-8]

72 **Ni W**, Yang X, Yang D, Bao J, Li R, Xiao Y, Hou C, Wang H, Liu J, Xu Y, Cao Z, Gao Z. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care* 2020; **24**: 422 [PMID: 32660650 DOI: 10.1186/s13054-020-03120-0]

73 **Iwasaki M**, Saito J, Zhao H, Sakamoto A, Hirota K, Ma D. Inflammation Triggered by SARS-CoV-2 and ACE2 Augment

Drives Multiple Organ Failure of Severe COVID-19: Molecular Mechanisms and Implications. *Inflammation* 2021; **44**: 13-34 [PMID: 33029758 DOI: 10.1007/s10753-020-01337-3]

74 **Healy EF**, Lilic M. A model for COVID-19-induced dysregulation of ACE2 shedding by ADAM17. *Biochem Biophys Res Commun* 2021; **573**: 158-163 [PMID: 34416436 DOI: 10.1016/j.bbrc.2021.08.040]

75 **Clare CE**, Brassington AH, Kwong WY, Sinclair KD. One-Carbon Metabolism: Linking Nutritional Biochemistry to Epigenetic Programming of Long-Term Development. *Annu Rev Anim Biosci* 2019; **7**: 263-287 [PMID: 30412672 DOI: 10.1146/annurev-animal-020518-115206]

76 **Radziejewska A**, Muzsik A, Milagro FI, Martínez JA, Chmurzynska A. One-Carbon Metabolism and Nonalcoholic Fatty Liver Disease: The Crosstalk between Nutrients, Microbiota, and Genetics. *Lifestyle Genom* 2020; **13**: 53-63 [PMID: 31846961 DOI: 10.1159/000504602]

77 **Zhang Y**, Guo R, Kim SH, Shah H, Zhang S, Liang JH, Fang Y, Gentili M, Leary CNO, Elledge SJ, Hung DT, Mootha VK, Gewurz BE. SARS-CoV-2 hijacks folate and one-carbon metabolism for viral replication. *Nat Commun* 2021; **12**: 1676 [PMID: 33723254 DOI: 10.1038/s41467-021-21903-z]

78 **Perła-Kaján J**, Jakubowski H. COVID-19 and One-Carbon Metabolism. *Int J Mol Sci* 2022; **23** [PMID: 35456998 DOI: 10.3390/ijms23084181]

79 **Danlos FX**, Grajeda-Iglesias C, Durand S, Sauvat A, Roumier M, Cantin D, Colomba E, Rohmer J, Pommeret F, Baciarello G, Willekens C, Vasse M, Griscelli F, Fahrner JE, Goubet AG, Dubuisson A, Derosa L, Nirmalathasan N, Bredel D, Mouraud S, Pradon C, Stoclin A, Rozenberg F, Duchemin J, Jourdi G, Ellouze S, Levavasseur F, Albigès L, Soria JC, Barlesi F, Solary E, André F, Pène F, Ackerman F, Mouthon L, Zitvogel L, Marabelle A, Michot JM, Fontenay M, Kroemer G. Metabolomic analyses of COVID-19 patients unravel stage-dependent and prognostic biomarkers. *Cell Death Dis* 2021; **12**: 258 [PMID: 33707411 DOI: 10.1038/s41419-021-03540-y]

80 **Roberts I**, Wright Muelas M, Taylor JM, Davison AS, Xu Y, Grixti JM, Gotts N, Sorokin A, Goodacre R, Kell DB. Untargeted metabolomics of COVID-19 patient serum reveals potential prognostic markers of both severity and outcome. *Metabolomics* 2021; **18**: 6 [PMID: 34928464 DOI: 10.1007/s11306-021-01859-3]

81 **McCaddon A**, Regland B. COVID-19: A methyl-group assault? *Med Hypotheses* 2021; **149**: 110543 [PMID: 33657459 DOI: 10.1016/j.mehy.2021.110543]

82 **Su Y**, Chen D, Yuan D, Lausted C, Choi J, Dai CL, Voillet V, Duvvuri VR, Scherler K, Troisch P, Baloni P, Qin G, Smith B, Kornilov SA, Rostomily C, Xu A, Li J, Dong S, Rothchild A, Zhou J, Murray K, Edmark R, Hong S, Heath JE, Earls J, Zhang R, Xie J, Li S, Roper R, Jones L, Zhou Y, Rowen L, Liu R, Mackay S, O'Mahony DS, Dale CR, Wallick JA, Algren HA, Zager MA; ISB-Swedish COVID19 Biobanking Unit, Wei W, Price ND, Huang S, Subramanian N, Wang K, Magis AT, Hadlock JJ, Hood L, Aderem A, Bluestone JA, Lanier LL, Greenberg PD, Gottardo R, Davis MM, Goldman JD, Heath JR. Multi-Omics Resolves a Sharp Disease-State Shift between Mild and Moderate COVID-19. *Cell* 2020; **183**: 1479-1495.e20 [PMID: 33171100 DOI: 10.1016/j.cell.2020.10.037]

83 **Wang C**, Li X, Ning W, Gong S, Yang F, Fang C, Gong Y, Wu D, Huang M, Gou Y, Fu S, Ren Y, Yang R, Qiu Y, Xue Y, Xu Y, Zhou X. Multi-omic profiling of plasma reveals molecular alterations in children with COVID-19. *Theranostics* 2021; **11**: 8008-8026 [PMID: 34335977 DOI: 10.7150/thno.61832]

84 **Kumar P**, Osahon O, Vides DB, Hanania N, Minard CG, Sekhar RV. Severe Glutathione Deficiency, Oxidative Stress and Oxidant Damage in Adults Hospitalized with COVID-19: Implications for GlyNAC (Glycine and *N*-Acetylcysteine) Supplementation. *Antioxidants (Basel)* 2021; **11** [PMID: 35052554 DOI: 10.3390/antiox11010050]

85 **Boucher J**, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harb Perspect Biol* 2014; **6** [PMID: 24384568 DOI: 10.1101/cshperspect.a009191]

86 **Goyal H**, Kopel J, Ristić B, Perisetti A, Anastasiou J, Chandan S, Tharian B, Inamdar S. The pancreas and COVID-19: a clinical conundrum. *Am J Transl Res* 2021; **13**: 11004-11013 [PMID: 34786039]

87 **Coate KC**, Cha J, Shrestha S, Wang W, Gonçalves LM, Almaça J, Kapp ME, Fasolino M, Morgan A, Dai C, Saunders DC, Bottino R, Aramandla R, Jenkins R, Stein R, Kaestner KH, Vahedi G; HPAP Consortium, Brissova M, Powers AC. SARS-CoV-2 Cell Entry Factors ACE2 and TMPRSS2 Are Expressed in the Microvasculature and Ducts of Human Pancreas but Are Not Enriched in β Cells. *Cell Metab* 2020; **32**: 1028-1040.e4 [PMID: 33207245 DOI: 10.1016/j.cmet.2020.11.006]

88 **Taneera J**, El-Huneidi W, Hamad M, Mohammed AK, Elaraby E, Hachim MY. Expression Profile of SARS-CoV-2 Host Receptors in Human Pancreatic Islets Revealed Upregulation of *ACE2* in Diabetic Donors. *Biology (Basel)* 2020; **9** [PMID: 32784802 DOI: 10.3390/biology9080215]

89 **Koufakis T**, Metallidis S, Zebekakis P, Kotsa K. Intestinal SGLT1 as a therapeutic target in COVID-19-related diabetes: A "two-edged sword" hypothesis. *Br J Clin Pharmacol* 2021; **87**: 3643-3646 [PMID: 33684969 DOI: 10.1111/bcp.14800]

90 **Wan L**, Gao Q, Deng Y, Ke Y, Ma E, Yang H, Lin H, Li H, Yang Y, Gong J, Li J, Xu Y, Liu J, Zhang X, Huang L, Feng J, Zhang Y, Huang H, Wang H, Wang C, Chen Q, Huang X, Ye Q, Li D, Yan Q, Liu M, Wei M, Mo Y, Tang K, Lin C, Zheng F, Xu L, Cheng G, Wang P, Yang X, Wu F, Sun Z, Qin C, Wei C, Zhong H. GP73 is a glucogenic hormone contributing to SARS-CoV-2-induced hyperglycemia. *Nat Metab* 2022; **4**: 29-43 [PMID: 34992299 DOI: 10.1038/s42255-021-00508-2]

91 **Ho JSY**, Fernando DI, Chan MY, Sia CH. Obesity in COVID-19: A Systematic Review and Meta-analysis. *Ann Acad Med Singap* 2020; **49**: 996-1008 [PMID: 33463658 DOI: 10.47102/annals-acadmedsg.2020299]

92 **Yang J**, Ma Z, Lei Y. A meta-analysis of the association between obesity and COVID-19. *Epidemiol Infect* 2020; **149**: e11 [PMID: 33349290 DOI: 10.1017/S0950268820003027]

93 **Du Y**, Zhou N, Zha W, Lv Y. Hypertension is a clinically important risk factor for critical illness and mortality in COVID-19: A meta-analysis. *Nutr Metab Cardiovasc Dis* 2021; **31**: 745-755 [PMID: 33549450 DOI: 10.1016/j.numecd.2020.12.009]

94 **Atmosudigdo IS**, Pranata R, Lim MA, Henrina J, Yonas E, Vania R, Radi B. Dyslipidemia Increases the Risk of Severe COVID-19: A Systematic Review, Meta-analysis, and Meta-regression. *J Clin Exp Hepatol* 2021 [PMID: 33584063 DOI: 10.1016/j.jceh.2021.01.007]

95 **Hariyanto TI**, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection.

Diabetes Metab Syndr 2020; **14**: 1463-1465 [PMID: 32771919 DOI: 10.1016/j.dsx.2020.07.054]

96 **Pan L**, Huang P, Xie X, Xu J, Guo D, Jiang Y. Metabolic associated fatty liver disease increases the severity of COVID-19: A meta-analysis. *Dig Liver Dis* 2021; **53**: 153-157 [PMID: 33011088 DOI: 10.1016/j.dld.2020.09.007]

97 **Popkin BM**, Du S, Green WD, Beck MA, Algaith T, Herbst CH, Alsukait RF, Alluhidan M, Alazemi N, Shekar M. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. *Obes Rev* 2020; **21**: e13128 [PMID: 32845580 DOI: 10.1111/obr.13128]

98 **Aminian A**, Fathalizadeh A, Tu C, Butsch WS, Pantalone KM, Griebeler ML, Kashyap SR, Rosenthal RJ, Burguera B, Nissen SE. Association of prior metabolic and bariatric surgery with severity of coronavirus disease 2019 (COVID-19) in patients with obesity. *Surg Obes Relat Dis* 2021; **17**: 208-214 [PMID: 33243670 DOI: 10.1016/j.soard.2020.10.026]

99 **Yanai H**. Adiposity is the Crucial Enhancer of COVID-19. *Cardiol Res* 2020; **11**: 353-354 [PMID: 32849972 DOI: 10.14740/cr1118]

100 **Lui DTW**, Lee CH, Tan KCB. One year into the clash of pandemics of diabetes and COVID-19: Lessons learnt and future perspectives. *J Diabetes Investig* 2022; **13**: 19-21 [PMID: 34375500 DOI: 10.1111/jdi.13644]

101 **Bourgonje AR**, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, Bolling MC, Dijkstra G, Voors AA, Osterhaus AD, van der Voort PH, Mulder DJ, van Goor H. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol* 2020; **251**: 228-248 [PMID: 32418199 DOI: 10.1002/path.5471]

102 **Lagana SM**, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, Del Portillo A, De Michele S, de Gonzalez AK, Saqi A, Khairallah P, Chong AM, Park H, Uhlemann AC, Lefkowitch JH, Verna EC. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol* 2020; **33**: 2147-2155 [PMID: 32792598 DOI: 10.1038/s41379-020-00649-x]

103 **Huang R**, Zhu L, Wang J, Xue L, Liu L, Yan X, Huang S, Li Y, Zhang B, Xu T, Li C, Ji F, Ming F, Zhao Y, Cheng J, Wang Y, Zhao H, Hong S, Chen K, Zhao XA, Zou L, Sang D, Shao H, Guan X, Chen X, Chen Y, Wei J, Zhu C, Wu C. Clinical features of COVID-19 patients with non-alcoholic fatty liver disease. *Hepatol Commun* 2020 [PMID: 32838108 DOI: 10.1002/hep4.1592]

104 **Sachdeva S**, Khandait H, Kopel J, Aloysius MM, Desai R, Goyal H. NAFLD and COVID-19: a Pooled Analysis. *SN Compr Clin Med* 2020; **2**: 2726-2729 [PMID: 33173850 DOI: 10.1007/s42399-020-00631-3]

105 **Grace JA**, Klein S, Herath CB, Granzow M, Schierwagen R, Masing N, Walther T, Sauerbruch T, Burrell LM, Angus PW, Trebicka J. Activation of the MAS receptor by angiotensin-(1-7) in the renin-angiotensin system mediates mesenteric vasodilatation in cirrhosis. *Gastroenterology* 2013; **145**: 874-884.e5 [PMID: 23796456 DOI: 10.1053/j.gastro.2013.06.036]

106 **Casey S**, Schierwagen R, Mak KY, Klein S, Uschner F, Jansen C, Praktiknjo M, Meyer C, Thomas D, Herath C, Jones R, Trebicka J, Angus P. Activation of the Alternate Renin-Angiotensin System Correlates with the Clinical Status in Human Cirrhosis and Corrects Post Liver Transplantation. *J Clin Med* 2019; **8** [PMID: 30934723 DOI: 10.3390/jcm8040419]

107 **Kushner T**, Cafardi J. Chronic Liver Disease and COVID-19: Alcohol Use Disorder/Alcohol-Associated Liver Disease, Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Autoimmune Liver Disease, and Compensated Cirrhosis. *Clin Liver Dis (Hoboken)* 2020; **15**: 195-199 [PMID: 32537135 DOI: 10.1002/cld.974]

108 **Lubel JS**, Herath CB, Burrell LM, Angus PW. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. *J Gastroenterol Hepatol* 2008; **23**: 1327-1338 [PMID: 18557800 DOI: 10.1111/j.1440-1746.2008.05461.x]

109 **Singh V**, Kumar R, Nain CK, Singh B, Sharma AK. Terlipressin versus albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized study. *J Gastroenterol Hepatol* 2006; **21**: 303-307 [PMID: 16460491 DOI: 10.1111/j.1440-1746.2006.04182.x]

110 **Bobermin LD**, Quincozes-Santos A. COVID-19 and hyperammonemia: Potential interplay between liver and brain dysfunctions. *Brain Behav Immun Health* 2021; **14**: 100257 [PMID: 33870235 DOI: 10.1016/j.bbih.2021.100257]

111 **Chen J**, Vitetta L. The gut-liver axis in chronic liver disease associated with severe COVID-19. *Eur J Gastroenterol Hepatol* 2021; **33**: e1103 [PMID: 34560696 DOI: 10.1097/MEG.0000000000002290]

112 **Shalimar**, Elhence A, Vaishnav M, Kumar R, Pathak P, Soni KD, Aggarwal R, Soneja M, Jorwal P, Kumar A, Khanna P, Singh AK, Biswas A, Nischal N, Dar L, Choudhary A, Rangarajan K, Mohan A, Acharya P, Nayak B, Gunjan D, Saraya A, Mahapatra S, Makharia G, Trikha A, Garg P. Poor outcomes in patients with cirrhosis and Corona Virus Disease-19. *Indian J Gastroenterol* 2020; **39**: 285-291 [PMID: 32803716 DOI: 10.1007/s12664-020-01074-3]

113 **Koike S**, Kabuyama Y, Obeng KA, Sugahara K, Sato Y, Yoshizawa F. An Increase in Liver Polyamine Concentration Contributes to the Tryptophan-Induced Acute Stimulation of Rat Hepatic Protein Synthesis. *Nutrients* 2020; **12** [PMID: 32882842 DOI: 10.3390/nu12092665]

114 **Wu Q**, Zhou L, Sun X, Yan Z, Hu C, Wu J, Xu L, Li X, Liu H, Yin P, Li K, Zhao J, Li Y, Wang X, Zhang Q, Xu G, Chen H. Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. *Sci Rep* 2017; **7**: 9110 [PMID: 28831119 DOI: 10.1038/s41598-017-09536-z]

115 **Milic J**, Barbieri S, Gozzi L, Brigo A, Beghé B, Verduri A, Bacca E, Iadisernia V, Cuomo G, Dolci G, Yaacoub D, Aprile E, Belli M, Venuta M, Meschiari M, Sebastiani G, Clini E, Mussini C, Lonardo A, Guaraldi G, Raggi P. Metabolic-Associated Fatty Liver Disease Is Highly Prevalent in the Postacute COVID Syndrome. *Open Forum Infect Dis* 2022; **9**: ofac003 [PMID: 35146047 DOI: 10.1093/ofid/ofac003]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 252-274

DOI: 10.5501/wjv.v11.i5.252

ISSN 2220-3249 (online)

REVIEW

SARS-CoV-2 infection and diabetes: Pathophysiological mechanism of multi-system organ failure

Bipradas Roy, Sadia Afrin Runa

Specialty type: Pathology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single-blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mukhopadhyay A, India; Munteanu C, Romania

Received: May 18, 2022
Peer-review started: May 18, 2022
First decision: June 16, 2022
Revised: June 25, 2022
Accepted: August 1, 2022
Article in press: August 1, 2022
Published online: September 25, 2022

Bipradas Roy, Department of Physiology, Wayne State University, Detroit, MI 48201, United States

Bipradas Roy, Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, MI 48202, United States

Sadia Afrin Runa, Department of Biotechnology and Genetic Engineering, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh

Corresponding author: Bipradas Roy, MSc, PhD, Research Assistant, Department of Physiology, Wayne State University, 5374 Scott Hall, 540 E. Canfield, Detroit, MI 48201, United States. biroy@med.wayne.edu

Abstract

Since the discovery of the coronavirus disease 2019 outbreak, a vast majority of studies have been carried out that confirmed the worst outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with preexisting health conditions, including diabetes, obesity, hypertension, cancer, and cardiovascular diseases. Likewise, diabetes itself is one of the leading causes of global public health concerns that impose a heavy global burden on public health as well as socio-economic development. Both diabetes and SARS-CoV-2 infection have their independent ability to induce the pathogenesis and severity of multi-system organ failure, while the co-existence of these two culprits can accelerate the rate of disease progression and magnify the severity of the disease. However, the exact pathophysiology of multi-system organ failure in diabetic patients after SARS-CoV-2 infection is still obscure. This review summarized the organ-specific possible molecular mechanisms of SARS-CoV-2 and diabetes-induced pathophysiology of several diseases of multiple organs, including the lungs, heart, kidneys, brain, eyes, gastrointestinal system, and bones, and subsequent manifestation of multi-system organ failure.

Key Words: SARS-CoV-2; Diabetes; Neurological dysfunction; Cardiovascular complications; Renal dysfunction; Bone loss

Core Tip: There is no therapeutic approach yet that can eradicate diabetes and its complications from human life, as the etiopathology of diabetes is very complex. Before the outbreak of coronavirus disease 2019, it was almost unknown that diabetes is a leading risk factor that could fuel the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced multi-organ dysfunction and subsequent mortality. Additionally, SARS-CoV-2-infected children and young people have been shown to develop diabetes. Therefore, identifying the precise molecular mechanisms of diabetes-induced SARS-CoV-2 susceptibility and subsequent manifestation of multi-organ dysfunction may help us to develop drugs that prevent millions of human lives.

Citation: Roy B, Runa SA. SARS-CoV-2 infection and diabetes: Pathophysiological mechanism of multi-system organ failure. *World J Virol* 2022; 11(5): 252-274
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/252.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.252

INTRODUCTION

Diabetes mellitus (DM) is a multi-faceted metabolic syndrome that induces or exacerbates the pathophysiology of several complications, including neuropathy, nephropathy, retinopathy, cardiovascular diseases, pulmonary dysfunction, gastrointestinal (GI) dysfunction, and osteoporosis[1]. DM and its complications are increasing day by day while decreasing life expectancy and increasing the cost of diagnosis and treatment. According to the most recent Centers for Disease Control and Prevention (CDC) report, 37.3 million Americans have diabetes, and another 96 million US population have prediabetes[2].

Recently, coronavirus disease 2019 (COVID-19) has been the most discussed topic worldwide due to its devastating physiological and socioeconomic impacts since its discovery in December 2019 in Wuhan, China. As of 21 June 2022, the World Health Organization has reported 539119771 globally diagnosed COVID-19 cases, including 6322311 COVID-19-associated mortalities (WHO Coronavirus Dashboard. Available online: https://covid19.who.int). Although the overall COVID-19 positive case numbers declined from the previous years, the post-COVID-19 impact is still increasing. As time goes by, the trend of the pathogenicity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shifted from acute to long-term. Many studies determined the physiological consequences of the acute phase of SARS-CoV-2 infection and the post-COVID-19 effects on human health and diseases, including diabetes. However, few studies have been carried out to characterize the long-term risks and burden of diabetes in the post-acute phase of COVID-19. A recent study in a cohort that recruited 181280 participants who tested positive for SARS-CoV-2 and a contemporary control that recruited 4118441 participants showed that people with COVID-19 exhibited an increased risk and excess burden of incident diabetes as well as increased risk of antihyperglycemic use compared with the contemporary control group[3]. Another retrospective cohort study that recruited 126710 participants with one or more nasal swabs positive for SARS-CoV-2 and 2651058 participants with no positive swab showed that SARS-CoV-2 was associated with a higher risk of incident diabetes in men but not in women, compared with no positive tests. This study further demonstrated that among hospitalized COVID-19 patients, SARS-CoV-2 was associated with a higher risk of diabetes at 120 d and the end of follow-up in men but not in women[4]. However, the exact mechanism of SARS-CoV-2-induced increase in diabetic incidence and subsequent multiorgan dysfunction is unknown. This review provides ideas about the organ-specific cellular mechanism through which SARS-CoV-2 and diabetes mellitus results in multi-system organ dysfunction.

METHODS

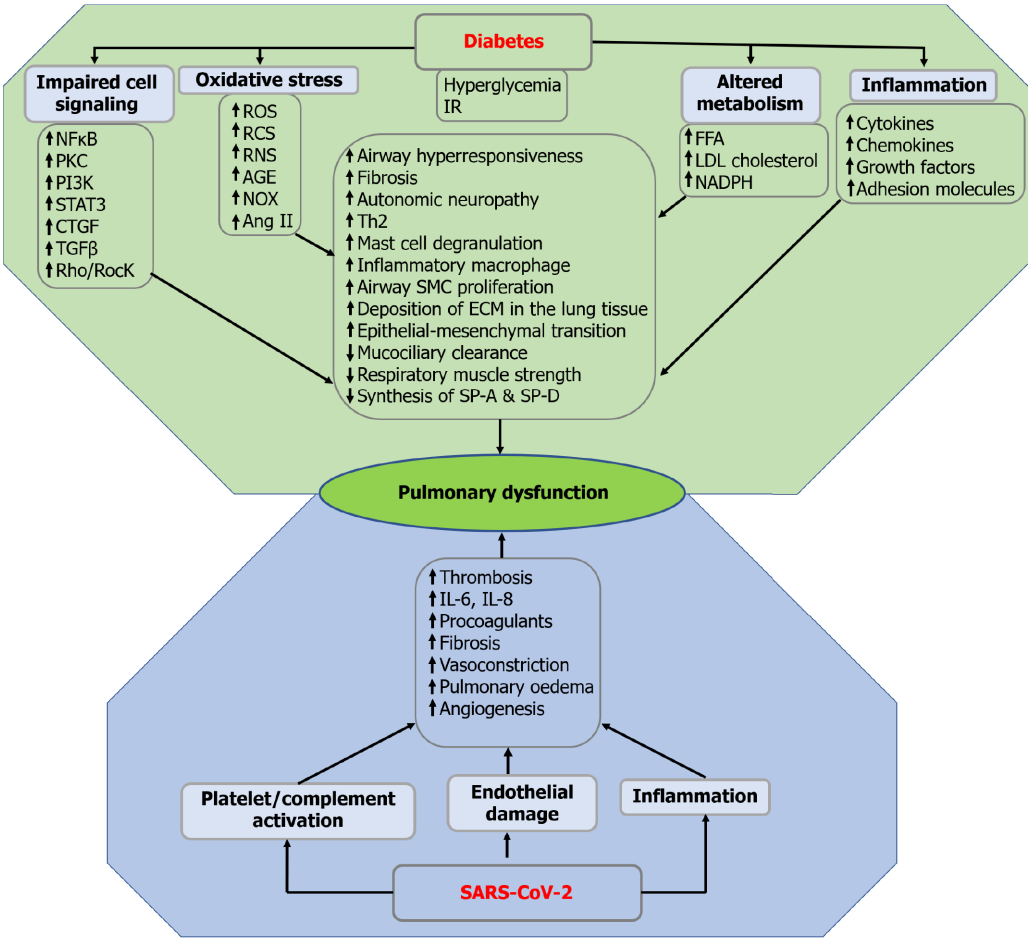
We searched our queries using Google Scholar, PubMed Central, ResearchGate, and the CDC databases. For this manuscript, we used articles published recently in standard peer-reviewed journals. We tried to avoid using review articles as much as possible; instead, we used research articles and case studies. We recruited research articles based on the following hierarchy: studies in humans > studies in animals > and studies in cell culture models. We thoroughly read the selected articles and picked the findings supporting our query.

SARS-CoV-2 INFECTION EXACERBATES DIABETES-INDUCED MULTI-SYSTEM ORGAN FAILURE

SARS-CoV-2 infection exacerbates diabetes-induced pulmonary dysfunction

Many studies have been carried out to determine the pathophysiology of diabetes-induced pulmonary dysfunction. For instance, a retrospective, longitudinal cohort study on 1811228 subjects showed that the prevalence of asthma, chronic obstructive pulmonary disease (COPD), fibrosis, and pneumonia was significantly higher in diabetic patients relative to their age and sex-matched non-diabetic controls[5]. Another retrospective cohort study with 1332 patients with concomitant asthma and diabetes showed that the use of metformin, a well-known diabetic drug, significantly reduced the risk of asthma[6]. Findings from this study suggest that diabetes induces the development of asthma in humans. A prospective multicenter study that employed 5334 COPD patients with or without diabetes showed that COPD patients with comorbid diabetes had a more severe profile and higher hospitalization costs[7]. A study in 162 T2DM patients without diabetes complications and 55 healthy control subjects showed that pulmonary function in T2DM patients is negatively correlated with vascular endothelial functional index, *e.g.*, flow-mediated dilation and nitric oxide (NO), whereas positively correlated with endothelin-1 (ET-1) and glycosylated hemoglobinA1c (HbA1c)[8]. This study suggests that T2DM-induced vascular EC dysfunction is an important biomarker of pulmonary dysfunction. Hyperglycemia or insulin resistance (IR)-induced diabetic ketoacidosis (DKA) is associated with reduced serum potassium levels that subsequently cause respiratory muscle weakness and culmination of acute respiratory failure[9]. Additionally, DKA may contribute to the pathogenesis of pulmonary edema results from an acute shift of a large volume of fluid into the extracellular compartment and subsequent elevation of pulmonary venous pressure (hydrostatic pulmonary edema) as well as increased pulmonary capillary permeability (non-hydrostatic pulmonary edema) due to pulmonary microangiopathy[9]. A study in 26 diabetic patients showed a significant increase in angiotensin converting enzyme-2 (ACE2) protein levels in both alveolar tissue and bronchial epithelium compared to the control subjects, independent of smoking, chronic obstructive pulmonary disease, body mass index (BMI), renin-angiotensin-aldosterone system (RAAS) inhibitor use, and other potential confounders[10]. A study in 34239 patients (with or without diabetes) with a pneumonia-related hospitalization and 342390 healthy control subjects showed that poor long-term glycemic control in T1DM and T2DM increases the risk of hospitalization with pneumonia[11]. In addition to humans, a vast majority of studies have been carried out in rodents to determine the role of diabetes in pulmonary dysfunction. For instance, streptozotocin (STZ)-induced diabetic rats showed increased pulmonary basal membrane thickness, increased inflammatory reaction due to mononuclear cell infiltration in their lungs, and increased levels of protein carbonyl content, a by-product of oxidative stress, relative to their age-matched controls[12]. Likewise, myocardial ischemia-reperfusion in STZ-induced diabetic rats demonstrated an increase in alveolar wall thickness and lung tissue damage along with increased infiltration or aggregation of neutrophils in lung tissue compared with their age-matched wild-type controls[13]. Another study in STZ-induced diabetic rats showed that the lung tissue and lamellar bodies were significantly collapsed along with a significant reduction in SOD activity and the mRNA expression and protein levels of aldehyde dehydrogenase 2, an alcohol detoxifying mitochondrial enzyme in the lung tissue of diabetic rats[14]. STZ-induced diabetic rats developed pulmonary fibrosis along with increased inflammation in the lung tissue as evaluated by increased expression and levels of several profibrotic and proinflammatory biomarkers, including fibronectin, connective tissue growth factor (CTGF), plasminogen activator inhibitor-1 and tumor necrosis factor (TNF)-α[15]. Additionally, the expression of NADPH oxidase (NOX), an important mediator of oxidative and nitrative stress, significantly increased along with increased protein nitration and upregulation of angiotensin II (Ang II) and its receptor angiotensin II type 1 (AT1) in diabetic lung tissue. This study again reported that chronic administration of Ang II in normal mice induced diabetes-like lung fibrosis and inflammation (Figure 1), and the effects of Ang II were completely abrogated with losartan treatment, a potential AT1 inhibitor[15]. All the studies I stated so far revealed mostly the association between diabetes and different types of lung dysfunction. However, the precise underlying mechanism of diabetes-induced pathophysiology of lung disease is not well understood. Hyperglycemia and hyperinsulinemia in diabetes increase oxidative stress, non-enzymatic glycation of tissue proteins, activation of protein kinase C (PKC), nuclear factor-κB (NF-κB), and polyol pathways, and eventually lead to the development of pulmonary dysfunction through autonomic neuropathy, micro/macroangiopathy in the lung, impairment in pulmonary elastin and collagen content, alteration of pulmonary connective tissue, surfactant dysfunction and malfunctioning of respiratory muscles (Figure 1)[16].

It is well established that ACE-2 is predominantly expressed in pulmonary endothelial cells and airway epithelial cells (AECs), the main cellular entry of SARS-CoV-2 to start the pathogenesis of COVID-19 manifestation. A *phenome-wide* Mendelian randomization study in 898130 T2DM subjects showed an increase in ACE2 expression in their lung tissue compared with non-diabetic healthy controls[17]. Another study in humans showed an increased expression of ACE2 and transmembrane serine protease 2 (TMPRSS2) in the upper and lower airway tissue in adults than in children. This study further showed an elevated expression of ACE2 and TMPRSS2 in the airway tissue of smokers and



DOI: 10.5501/wjv.v11.i5.252

Figure 1 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced pulmonary dysfunction. Hyperglycemia and insulin resistance in diabetes is associated with impaired cell signaling, oxidative stress, inflammation, and altered metabolism and subsequently lead to the manifestation of pulmonary dysfunction due to increased airway hyperresponsiveness, fibrosis, autonomic neuropathy, T helper 2, mast cell degranulation, Inflammatory macrophage, airway smooth muscle cell proliferation, deposition of extracellular matrix in the lung tissue, epithelial-mesenchymal transition, whereas reduced mucociliary clearance, respiratory muscle strength and synthesis of SP-A and SP-D. On the other hand, platelet or complement activation, endothelial damage, and inflammation in severe acute respiratory syndrome coronavirus 2 infection lead to the pathogenesis of pulmonary dysfunction due to elevated thrombosis, IL-6, IL-8, procoagulants, fibrosis, vasoconstriction, pulmonary edema, and angiogenesis. IR: Insulin resistance; NFκB: Nuclear factor-κB; PKC: Protein kinase C; PI3K: Phosphoinositide 3-kinases; STAT3: Signal transducer and activator of transcription 3; CTGF: Connective tissue growth factor; TGFβ: Transforming growth factor beta; Rho/RocK: Ras homologous/Rho-associated coiled-coil kinase; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; RCS: Reactive carbonyl species; AGE: Advanced glycation end products; NOX: Nitrogen oxides; Ang II: Angiotensin II; Th2: T helper 2; SMC: Smooth muscle cell; ECM: Extracellular matrix; SP-A: Surfactant proteins A; SP-D: Surfactant proteins D; FFA: Free fatty acid; LDL: low-density lipoprotein; NADPH: Reduced nicotinamide adenine dinucleotide phosphate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

COPD patients[18]. A study in 55, 44 COVID-19 post-mortem lung samples showed increased expression of ACE2 along with increased diffuse alveolar damage, acute bronchopneumonia, and acute lung injury in severe COVID-19 patients relative to the lung samples from healthy subjects[19]. There are contradictory findings regarding the prevalence of ACE2 expression in pulmonary vascular endothelial cells *vs* airway epithelial cells/pneumocytes. Findings from a vast majority of studies confirmed that ACE2 is predominantly expressed in airway epithelial cells. For instance, a study in two cohorts in Australia showed that gene expression and protein levels of ACE2 in the lower AECs were significantly higher in older age and male sex compared with younger age and females, respectively [20]. However, another study in humans suggests that pulmonary endothelial cells express twice as many ACE2 receptors for viral entry than pneumocytes[21].

A study in lungs from patients who died from COVID-19 as well as patients who died from acute respiratory distress syndrome secondary to influenza A (H1N1) infection showed alveolar damage with perivascular T-cell infiltration along with severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Additionally, pulmonary vessels in patients with Covid-19 showed widespread thrombosis with microangiopathy. This study further demonstrated that the prevalence of alveolar-capillary microthrombi was nine times higher in the Covid-19 patients relative to patients with influenza[21]. Another study in the lung tissue from 11 Covid-19 deaths showed an increased loss of alveolar wall integrity, detachment of lung tissue pieces, fibroblast prolif-

eration, and extensive fibrosis[22]. SARS-CoV-2 infected human AECs showed an increased cytopathic effect which was determined through a lack of cilium beating on the surface of AECs after 96 h of inoculation. However, SARS-CoV-2 infected Vero E6, and Huh-7 cell lines did not show any cytopathic effect[23]. Another case series study employing ultrasound-guided minimally invasive autopsy (MIA-US) in 10 fatal cases of COVID-19 showed exudative/proliferative diffuse alveolar damage, intense pleomorphic cytopathic effects on the respiratory epithelium, including airway and alveolar cells, increased fibrinous thrombi in alveolar arterioles and elevation of alveolar megakaryocyte numbers. This study further showed that small thrombi formation was less frequent in other tissues, including the glomeruli, spleen, heart, dermis, testis, and liver sinusoids, compared to the lungs[24]. Findings from this study suggest that COVID-19 is a systemic disease that predominantly infects the lungs through severe epithelial injury and microthrombotic vascular phenomena, along with damage to other organs and tissues. Immunohistochemistry of the lung tissue biopsy from a 72-year-old man with a history of diabetes and hypertension showed denuded alveolar lining cells, increased reactive type II pneumocyte hyperplasia, and increased intra-alveolar fibrinous exudates, along with loose interstitial fibrosis, and chronic inflammatory infiltrates. This study further confirmed the presence of SARS-Cov-2 in alveolar epithelial cells due to the presence of SARS-CoV-2 Rp3 NP protein[25]. A study in 108 individuals showed increased alveolar type II-pneumocyte injury as confirmed by elevated plasma levels of surfactant protein D, a biomarker of alveolar type II-pneumocyte injury, along with increased interleukin (IL)-6 serum levels in critically ill COVID-19 patients[26].

Other studies also showed that the use of ET-1 receptor antagonist, Bosentan has been approved as a drug to treat pulmonary arterial hypertension in New York Heart Association functional classification II-IV and in scleroderma patients, as it decreases the systemic levels of profibrotic and proinflammatory cytokines including IL-2, IL-6, IL-8 and interferon (IFN)-γ in scleroderma patients, as well as slows down the progression of fibrosis and vascular damage[27]. The possible mechanisms of diabetes and SARS-CoV-2-induced pulmonary dysfunction are stated in Figure 1.

SARS-CoV-2 infection exacerbates diabetes-induced immune dysfunction

The complement system, a complex innate immune surveillance system, contributes to the destruction/neutralization of pathogens, including viruses and bacteria, that invade our body[28]. The complement system is composed of plasma proteins synthesized mainly by the liver or membrane proteins expressed on the cell surface, whose main functions are to promote the opsonization and phagocytosis of microorganisms and apoptotic cells through macrophages and neutrophils to induce their degradation[28,29]. A study showed that hyperglycemia inhibited complement-mediated opsonization of *S. aureus* in diabetic rats[30]. Another study reported that hyperglycemia caused direct glycosylation of proteins and altered the tertiary Structure of complement proteins, and subsequently inhibited immunoglobulin-mediated opsonization of bacteria[31].

Thrombotic microangiopathy (TMA) is a pathological condition that is associated with thrombosis in capillaries and arterioles, which leads to microangiopathic hemolytic anemia, thrombocytopenia, and organ damage, such as neurological, renal and cardiac dysfunction[32]. There are several risk factors that can contribute to the pathogenesis of TMA, including viruses, bacteria, drugs, oxidative stress, complement hyperactivation, and congenital predisposing conditions. All these factors directly or indirectly induce vascular endothelial cell damage, followed by the development of TMA. Studies showed that DM is associated with increased activation of the C3 complement component, which is a central factor of complement cascade[33,34]. Another study also showed that Insulin resistance is linked with elevated circulating complement factor C3 levels[35]. Increased C3 levels in plasma contribute to the hyperactivation of complement cascade that may lead to the development of TMA[36]. Oxidative stress-induced vascular endothelial dysfunction is an important hallmark of DM[37] and may contribute to the development of TMA[38]. Von Willebrand factor (VWF) is a clotting factor that is required for the pathogenesis of thrombotic thrombocytopenic purpura (TTP), a fatal blood disorder[39]. In pathological conditions, a multimeric form of VWF and platelets are prone to form aggregates and subsequently cause TTP[40]. A disintegrin and metalloprotease with thrombospondin type I repeats-13 (ADAMTS13), a zinc-containing metalloprotease that cleaves multimeric form of VWF and mitigates the formation of VWF-platelets aggregates[40]. The deficiency of plasma ADAMTS13 contributes to the progression of TTP[41]. A study in human subjects showed that T2DM-induced oxidative stress modifies the amino acid sequences of VWF and thereby prevents its proteolytic cleavage by ADAMTS13[42]. Another study showed that ADAMTS13 activity is significantly lower in T2DM patients compared with healthy control people[43]. Several virus strains, including SARS-CoV-2, HIV, MCV, EBV, parvovirus, rubella, and measles, have been recognized so far that can cause TTP by modulating the autoimmune process in human and animal species[44,45]. However, the exact molecular mechanism of the novel coronavirus, SARS-CoV-2-induced TTP, is completely unknown. Rapidly emerging data from clinical observations, autopsy-based findings, extrapolations from *in vitro* and *in vivo* studies, and dynamic modeling are not well enough to provide the exact pathophysiology of secondary complications associated with SARS-COV-2 infection[46]. However, a large number of patients with severe COVID-19 demonstrated TMA-like systemic coagulopathy that led to an increased number of deaths[47]. Findings from several studies reported that coagulopathy in COVID-19 patients was confirmed through the presence of elevated D-dimer, elevated lactate dehydrogenase, elevated total bilirubin, and decreased platelets[46,48]. As DM

and SARS-COV-2 both are associated with TMA-like symptoms, the mortality rate should be higher in DM patients when infected with SARS-COV-2. A single-center cross-sectional study that employed 68 patients with COVID-19, including 48 ICU and 20 non-ICU patients, as well as 13 non-hospitalized, asymptomatic controls, showed that the levels of endothelial cell and platelet activation markers, including VWF antigen and soluble P-selectin. This study further demonstrated that the mortality of ICU patients was positively correlated with concentrations of VWF antigen and soluble thrombomodulin[49].

Hemophagocytic lymphohistiocytosis (HLH) is a cytokine storm-induced inflammatory syndrome that is associated with substantial morbidity and mortality due to multiorgan failure[50,51]. Several case reports demonstrated that diabetes insipidus is associated with secondary HLH (sHLH)[52,53]. Accumulating evidence suggests that several patients with severe COVID-19 demonstrated sHLH due to cytokine storm, which is characterized by increased interleukin IL-2, IL-7, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α[51]. Based on the findings stated above, it can be surmised that diabetes patients infected with SARS-COV-2 possess a higher risk of fatality compared with SARS-COV-2 infected non-diabetic subjects.

SARS-CoV-2 infection exacerbates diabetes-induced cardiovascular complications

The prevalence of atrial fibrillation (AF), an important hallmark of arrhythmia, is higher in DM patients. In an observational, age- and sex-matched cohort, a longitudinal study that included 34744 patients with and without diabetes showed that AF was 44% more prevalent and 38% more likely to develop in T2DM[54]. A cohort study with 421855 T2DM patients showed that there is a 35% increased risk of developing AF in T2DM patients compared with age- and sex-matched controls from the general population. This study also showed that the risk of developing AF is exacerbated in T2DM patients with poor glycemic control and renal complications[55]. There are several mechanisms that may lead to the development of AF in DM. Oxidative stress in diabetes is associated with increased formation of reactive oxygen species, carbonyl species, nitrogen species, and AGE, which in turn predisposes to the development of AF through endothelial dysfunction, increased atherogenesis and reduced coronary angiogenesis. T2DM is a leading cause of cardiovascular diseases (CVDs), including atherosclerosis, MI, HF, and cardiomyopathy. There are several mechanisms that result in the pathogenesis of diabetic cardiomyopathy, including impaired insulin signaling, mitochondrial dysfunction, increased oxidative stress, reduced NO levels, elevated AGEs levels, stiffness of extracellular matrix, impaired handling of Ca^{2+} by cardiomyocytes, inflammation, RAAS over activation, cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and several cardiac metabolic abnormalities [56].

Several studies have demonstrated that hospitalization and mortality rate are significantly higher in COVID-19 patients who has preexisting arrhythmia. A study in a cohort of 153760 US veterans who survived in the first 30 d of COVID-19 has experienced different types of CVDs, including dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease[57]. A multicenter study with 696 hospitalized covid-19 patients developed acute HF and multiorgan failure as well as increased mortality which had a history of AF[58]. A retrospective observational study also showed that iCOVID-19 patients with a myocardial injury (determined by increased systemic C-reactive protein levels) are positively correlated with inflammation and coagulopathy and increased hospitalization[59]. Several possible mechanisms may contribute to the pathogenesis of acute myocardial injury in COVID-19 subjects, including microvascular injury, hypoxemia, preexisting CVDs, ventricular/atrial arrhythmias, hypotension, viral myocarditis, cytokine storm, and stress-induced cardiomyopathy[60]. A systematic pathological analysis that included 40 hearts from hospitalized patients dying of COVID-19 showed that the most common pathological cause of cardiomyocyte necrosis in COVID-19 patients was microthrombi. This study further demonstrated that the composition of intramyocardial microthrombi was different between COVID-19-negative and positive subjects[61].

A study using the samples from right atrial appendage biopsies in 57 diabetics and 22 non-diabetic subjects who underwent coronary artery bypass graft surgery showed that ACE2 mRNA expression and protein levels in heart tissue, as well as serum ACE2 levels, were significantly higher in diabetic patients relative to the non-diabetic control subjects. Additionally, ACE2 levels were positively correlated with glycosylated hemoglobin (HbA1c) levels, BMI, and activation of RAAS, and negatively correlated with ejection fraction. This study further demonstrated that the expression of TMPRSS2, metalloprotease *ADAM10*, and *ADAM17* that facilitate viral-*ACE2* complex entry and degradation were increased in diabetic hearts[62]. Diabetes is associated with increased activation of RAAS and subsequent elevation of systemic Ang II levels. However, the direct association of T2DM and SARS-CoV-2 susceptibility to the human heart is still unclear. STZ-induced diabetic mice developed severe cardiovascular complications after influenza virus infection as evaluated with increased circulatory levels of serum cardiac troponin I and creatine-kinase MB, left ventricular structural changes, and right ventricular functional alterations[63]. A prospective cohort study in Germany demonstrated an elevation of myocardial SARS–CoV-2 RNA in 5 out of 12 COVID-19–positive deaths[64]. Another study by Wenzel *et al*[65] showed an increased myocardial SARS-CoV-2 RNA in patients with clinically suspected myocarditis

who were tested negative for COVID-19 in nasopharyngeal swabs. A case study in a 72-years-old male patient who died due to severe COVID-19 reported the presence of SARS-COV-2 RNA as well as SARS-COV-2 antigen in his cardiac tissue and cardiomyocyte, respectively[66]. Another study that employed endomyocardial biopsy samples from four SARS-CoV-2 infected dead patients who were diagnosed with myocarditis showed left ventricular systolic dysfunction due to cardiomyocyte injury and degenerative vacuolization of cardiomyocyte cytoplasm along with myeloid-rich inflammatory cell infiltrate. Additionally, the myocardium of each COVID-19 myocarditis subject also showed an increased expression of SARS-CoV-2 spike and nucleocapsid RNAs as well as nucleocapsid protein levels. This study further demonstrated that SARS-CoV-2 selectively infects hPSC-derived cardiomyocytes through an ACE2 and endosomal cysteine protease-dependent pathway and subsequent production of the infectious virus with peak titers on day three post-inoculation. Infecting engineered heart tissues with SARS-CoV-2 confirmed that cytokine production, myocardial sarcomere disassembly, and cardiomyocyte death were a direct consequence of cardiomyocyte infection[67]. The possible mechanisms of diabetes and SARS-CoV-2-induced cardiovascular dysfunction are stated in Figure 2.

SARS-CoV-2 infection exacerbates diabetes-induced renal complications

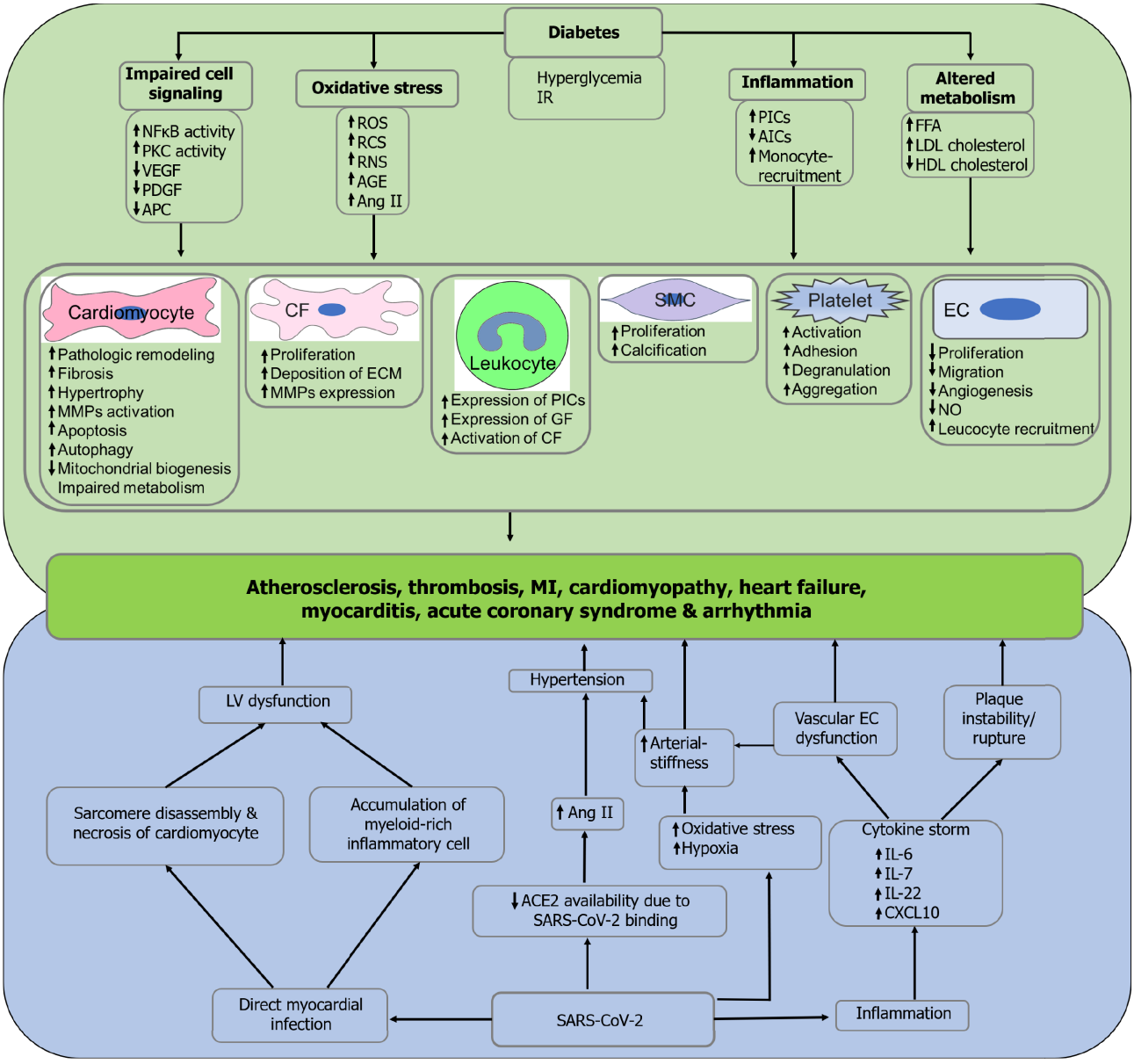
According to the most recent data from the CDC, around 37 million people in the united states are estimated to have chronic kidney disease (CKD)[68], and approximately 1 in 3 adults with diabetes has CKD, which is also known as diabetic kidney disease (DKD) or diabetic nephropathy. Additionally, the increased rate of mortality and associated socioeconomic and medical burden due to CKD-mediated development of end-stage renal disease is receiving more attention as a leading cause of death around the world[69]. DKD is associated with several structural changes in the kidney, including mesangial expansion, thickening of the glomerular and tubular basement membrane, glomerular sclerosis that manifests clinical symptoms including elevated blood pressure, sustained reduction in glomerular filtration rate (GFR), persistent albuminuria, increased cardiovascular events and associated mortality.

There are several possible mechanisms that contribute to the pathogenesis of DKD in diabetes, including impairment in renal hemodynamics, inflammation, abnormal glucose metabolism, oxidative stress, and overactive RAAS. Diabetes is associated with increased dilatation of afferent arteriole in the kidney due to increased generation of important vasoactive peptides, including prostaglandin and NO. A cohort study with 171 subjects showed that plasma prostaglandin E2 levels were increased in 136 T2DM patients compared with 35 non-diabetic controls[70]. Studies in humans and animals showed that poor glycemic control is associated with increased generation of NO and subsequent inhibition of tubuloglomerular feedback–mediated vasoconstriction of afferent arterioles in diabetic kidneys[71,72]. Additionally, T2DM is associated with elevated circulatory Ang II levels due to the overactivation of RAAS, which constricts efferent arteriole and subsequently results in glomerular hypertension and impaired autoregulation. A study in a cohort with COVID-19 patients (n = 89) demonstrated that regardless of their severity, circulatory PEG2 levels increased significantly in SARS-CoV-2 infection compared with age and sex-matched healthy controls. Additionally, this study showed that the entire COVID-19 cohort had an increased rate of diabetes, BMI, as well as elevated circulatory C-reactive protein levels[73], an important prognostic biomarker of COVID-19[74] and CVDs[75].

Similarly, T2DM contributes to the development of renal fibrosis, podocyte injury, and inflammation through an increased generation of renal ET-1, an important vasoconstrictor. Studies showed that pulmonary infection and hypoxia cause an elevation of circulatory ET-1 levels in humans and animals [76]. A study in a cohort showed that plasma levels of the stable precursor protein of endothelin-1, proET-1 were significantly higher in non-survivor COVID-19 patients relative to the survivor COVID-19 patients. This study also showed that plasma proET-1 levels were significantly higher in patients with community-acquired pneumonia compared with both survivors and non-survivors of COVID-19 patients. Additionally, data from this study showed that there is no significant association between proET-1 levels and mortality in a regression model adjusted for age, gender, creatinine level, diastolic blood pressure, as well as cancer and coronary artery disease[77].

Hyperglycemia contributes to the generation of ROS through mitochondrial overload and subsequently leads to podocyte dysfunction and apoptosis. Hyperglycemia and oxidative stress in diabetes mellitus increase intrarenal AGE levels that may cause morphological and functional impairments in the kidney, including modification of basement membranes, glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Studies in humans and animals showed that in most cases, AGE exerts its role through the activation of the receptor for AGE (RAGE) in the kidney[78]. Studies in rodents showed that inhibition of AGE binding with RAGE using RAGE-aptamers attenuates the development and progression of diabetic nephropathy in streptozotocin-induced diabetic rats. This study further showed that continuous administration of RAGE-aptamer significantly suppressed the AGE-induced oxidative stress generation and inflammatory and fibrotic reactions in human cultured mesangial cells[79].

A single-center observational cohort study in Germany showed that serum levels of soluble RAGE (sRAGE) increased significantly with COVID-19 severity, the need for dialysis, and catecholamine support[80].



DOI: 10.5501/wjv.v11.i5.252

Figure 2 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced cardiovascular complications. Hyperglycemia and insulin resistance in diabetes is associated with impaired cell signaling, oxidative stress, inflammation, and altered metabolism and subsequently induce the pathogenesis of cardiovascular diseases, including atherosclerosis, thrombosis, myocardial infarction, cardiomyopathy, heart failure, myocarditis, acute coronary syndrome and arrhythmia due to impaired functioning of cardiomyocytes, cardiac fibroblasts, smooth muscle cells, endothelial cells and endothelial cells, leukocytes, and platelets. On the other hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects the myocardium and subsequently induces left ventricular dysfunction due to sarcomere disassembly, necrosis of cardiomyocytes, and infiltration of myeloid-rich inflammatory cells. Additionally, SARS-CoV-2 infection reduces the availability of angiotensin converting enzyme-2 numbers, which results in elevated angiotensin II levels and subsequent manifestation of hypertension. SARS-CoV-2 infection is also associated with increased oxidative stress and hypoxia that may manifest hypertension due to arterial stiffness. Finally, inflammation in SARS-CoV-2 infection leads to cytokine storm and eventually induces vascular endothelial cell dysfunction and thrombotic plaque instability. Left ventricular dysfunction, hypertension, arterial stiffness, vascular endothelial cell dysfunction, and plaque instability induce the pathophysiology of cardiovascular diseases. IR: Insulin resistance; NFκB: Nuclear factor-κB; PKC: Protein kinase C; VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; APC: Adenomatous polyposis coli; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; RCS: Reactive carbonyl species; AGE: Advanced glycation end products; Ang II: Angiotensin II; PICs: Pro-inflammatory cytokines; AICs: Anti-inflammatory cytokines; FFA: Free fatty acid; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CF: Cardiac fibroblast; ECM: Extracellular matrix; GF: Growth factor; SMC: Smooth muscle cell; EC: Endothelial cell; NO: Nitric oxide; LV: Left ventricle; ACE2: Angiotensin converting enzyme-2; IL-6: Interleukin-6; IL-7: Interleukin-7; IL-22: Interleukin-22; CXCL10: C-X-C motif chemokine ligand 10; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Being a pleiotropic receptor, RAGE also interacts with a wide range of ligands in the S100 family, including S100A8/MRP8, S100A9/MRP14, S100A11, S100A12, S100B, high-mobility group box 1 (HMGB1). A study in Wuhan, China, showed that expression of S100A8, S100A9, S100A11, and S100A12 are significantly elevated in the lung tissue and serum of fatal COVID-19 patients compared to less severe cases of COVID-19[81]. Some other studies also demonstrated a positive association between

COVID-19 severity/fatality and plasma levels of S100A8[82], S100A9[82], HMGB1[82], S100A12[83] and S100B[84]. Additionally, an *in vitro* study revealed that HMGB1 epigenetically upregulates the expression of ACE2 in Vero-E6 cells and subsequently increases the susceptibility to SARS-CoV-1, SARS-CoV-2, and NL63 infection[85].

Prolonged hyperglycemia in diabetes is a renowned risk factor for kidney injury leading to proteinuria in humans[86,87]. A prospective, multicenter study in France showed that 60% of COVID-19 patients developed proteinuria as determined by urinary protein to creatine ratio. Additionally, this study also showed that proteinuria was significantly elevated in severe COVID-19 patients who required ICU admission[88].

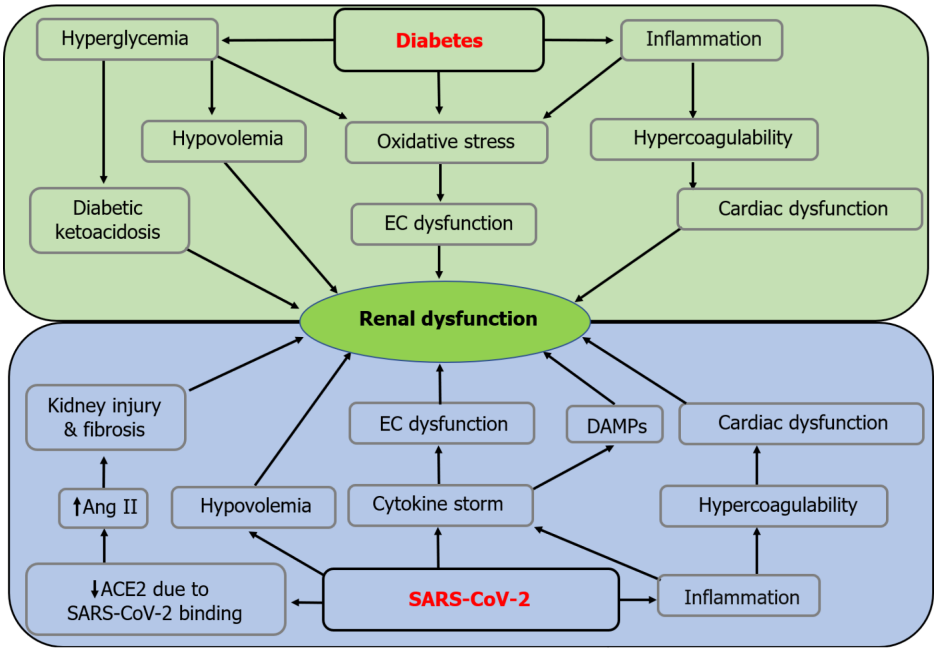
The prevalence of obstructive sleep apnea (OSA) is relatively high in T2DM[89]. A multicenter, observational, cross-sectional study using 214 DKD patients showed that UACR was higher in DKD with severe OSA relative to moderate OSA, mild OSA, or non-OSA subjects. Additionally, this study showed that the estimated GFR (eGFR) decreased in an OSA severity-dependent manner[90]. OSA-induced intermittent hypoxia and increased sympathetic nerve activity are associated with increased vascular complications, including endothelial damage and hypertension that leads to renal dysfunction [91]. A study using 445 COVID-19 patients where 8.5% had OSA showed that OSA is an independent risk factor of severe COVID-19 that requires hospitalization[92]. Findings from the studies above, it can be surmised that T2DM-induced OSA may contribute to the pathogenesis of DKD and subsequent fatality in severe COVID-19 patients.

A retrospective study in 2345 children having both type-1 diabetes and albuminuria demonstrated that the development of acute kidney injury is positively associated with the episodes of DKA[93]. A study that included 658 hospitalized patients with confirmed COVID-19 showed an increase in ketoacidosis in both diabetic and non-diabetic COVID-19 patients regardless of their age and sex[94]. In an observational study with 3993 hospitalized COVID-19 patients without any history of end-stage kidney disease end-stage kidney disease (ESKD) prior to admission, 1835 (46%) patients developed AKI [95]. Another retrospective cohort study that employed 89216 patients who were 30-d survivors of COVID-19 and 1637467 non-infected controls showed that 30-d survivors of COVID-19 exhibited a higher risk of AKI, declined eGFR, ESKD and major adverse kidney events[96].

Hyperglycemic osmotic diuresis in DKA contributes to the progression of dehydration, hypovolemia, and, ultimately, a reduction in the GFR[97]. Sepsis and hypovolemia are two of the major risk factors that contribute to the pathogenesis of AKI[98]. A vast majority of COVID-19 patients experienced several complications, including fever, malaise, nausea, vomiting, and diarrhea for several days before seeking medical care and subsequently developed hypovolemia[99]. A prospective case-control study showed that COVID-19 patients with AKI are associated with reduced renal blood flow compared with healthy controls, which are independent of left/right cardiac dysfunction[100]. Reduced renal blood flow is a common pathophysiological mechanism of subsequent reduction of GFR and culmination of AKI[101]. Hypercoagulability is a common feature of diabetes. A study in humans showed significantly elevated platelet activity as well as more severe blood clots in patients with concomitant diabetes and renal dysfunction compared with healthy controls and patients with renal dysfunction but no diabetes [102]. The possible mechanisms of diabetes and SARS-CoV-2-induced renal dysfunction are stated in Figure 3.

SARS-CoV-2 infection exacerbates diabetes-induced neurological complications

Approximately one-third of COVID-19 patients have been shown to develop neurological symptoms, including headache, disturbed consciousness, paresthesias, brain tissue edema, stroke, neuronal degeneration, and neuronal encephalitis[103]. Plenty of studies determined the association between COVID-19 and brain dysfunction. However, very little is known about the exact pathophysiology of SARS-CoV-2-induced neurological dysfunction. A recent study by Douaud *et al*[104] recruited 785 participants of UK Biobank who went through the magnetic resonance imaging (MRI) twice, including 401 cases which tested positive for SARS-CoV-2 infection on an average of 141 d before the second scan and 384 controls. Contrary to the first scan, data from the second scan of the SARS-CoV-2 positive cases revealed several striking features associated with brain dysfunction, including a reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, significant alteration in the presence of tissue damage markers in regions that are functionally connected to the primary olfactory cortex; and a significant reduction in global brain size in the SARS-CoV-2 cases[104]. A study by Reiken *et al*[103] showed that SARS-CoV-2 infection is associated with Alzheimer's disease-like phenotypes, which are characterized by the upregulation of TGF-β signaling and hyperphosphorylation of tau protein and leaky phenotype of the ryanodine receptor in the brain. STZ-induced diabetic mice exhibited mild hyperphosphorylation of tau protein after 10, 20, and 30 d of STZ injection, and massive hyperphosphorylation of tau protein was observed after 40 d of STZ injection[105]. There are several studies that confirmed the direct involvement/ entry of SARS-CoV-2 in the brain. For instance, a study using the autopsy samples of olfactory nervous tracts and defined CNS regions from 33 individuals with COVID-19 showed the presence of SARS-CoV-2 RNA in olfactory mucosa, its nervous projections, and distinct CNS regions[106].



DOI: 10.5501/wjv.v11.i5.252

Figure 3 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced renal dysfunction. Hyperglycemia in diabetes is associated with increased oxidative stress mediated endothelial cell (EC) dysfunction, hypovolemia, and diabetic ketoacidosis that subsequently induces renal dysfunction. Likewise, inflammation in diabetes is associated with increased oxidative stress mediated EC dysfunction and hypercoagulability mediated cardiac dysfunction that subsequently leads to renal dysfunction. On the other hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection reduces the availability of angiotensin converting enzyme-2 numbers, which results in elevated serum angiotensin II and subsequent kidney injury and fibrosis due to hypertension. Additionally, hypovolemia in SARS-CoV-2 infection induces renal dysfunction. Finally, inflammation in SARS-CoV-2 infection is associated with cytokine storm mediated endothelial cell dysfunction and upregulation of damage-associated molecular patterns, hypercoagulability mediated cardiac dysfunction results in renal dysfunction. EC: Endothelial cell; Ang II: Angiotensin II; ACE2: Angiotensin converting enzyme-2; DAMPs: Damage-associated molecular patterns; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Encephalopathy refers to brain disorders that alter brain function or Structure. Acute encephalopathy is a rare but fatal complication caused by several factors, including metabolic diseases (*e.g.*, diabetes) and pathogen infection. The pathogenesis of encephalopathy caused by diabetes-induced microvascular dysfunction in the brain is called diabetic encephalopathy (DE). DE is a chronic microvascular complication of diabetes mellitus that is characterized by impaired cognitive functions and electrophysiological, neurochemical, and structural abnormalities[107,108]. A case study showed that there is a possible association between T1D and autoimmune neurologic disorders due to elevated systemic levels of glutamic acid decarboxylase antibody, an important biomarker of limbic encephalopathy[109].

One of the most frequent neurological complications in COVID-19 is acute encephalopathy. Several studies have been conducted to understand the neuropathogenesis of COVID-19-induced acute encephalopathy. For instance, a study by Uginet *et al*[110] that recruited 707 COVID-19 hospitalized patients showed that the severity of the pneumonia was not associated with the severity of the COVID-19 encephalopathy. Additionally, increased MRI abnormalities, intracranial vessel gadolinium enhancement, and disruption of BBR disruption were observed in maximum COVID-19 patients who had no history of acute encephalopathy and other neurological disorders. A case study that employed a SARS-CoV-2 positive middle-aged woman who presented to the emergency department of a tertiary care hospital with an episode of generalized tonic-clonic seizures primarily showed neuropsychiatric manifestations, including viral encephalitis rather than the most common COVID-19 symptoms[111]. Another single-center retrospective study that comprised 1683 patients with COVID-19 showed that 23 (1.4%) patients developed cerebrovascular disease. Out of these 23 patients, 17 developed cerebral ischemia, five developed intracerebral hemorrhages, and one developed leukoencephalopathy of posterior reversible encephalopathy type. This study further showed that elevated ferritin levels were observed in hemorrhagic patients at the time of stroke along with subarachnoid hemorrhage, parieto-occipital leukoencephalopathy, microbleeds, and single or multiple focal hematomas, thrombotic microangiopathy, and endothelial injury, with no evidence of vasculitis or necrotizing encephalitis [112]. A study that employed both the human and animal brains showed that the hypothalamus and associated regions express ACE2 and transmembrane proteinase, serine 2, which mediate SARS-CoV-2 cellular entry, along with several genes or pathways involved in physiological functions or viral pathogenesis[113]. A multicenter study employing 25 COVID-19 patients with encephalitis developed acute demyelinating encephalomyelitis and limbic encephalitis along with hyper proteinopathies and/or pleocytosis in the CSF[114]. Another study that recruited 13 encephalitis patients with COVID-

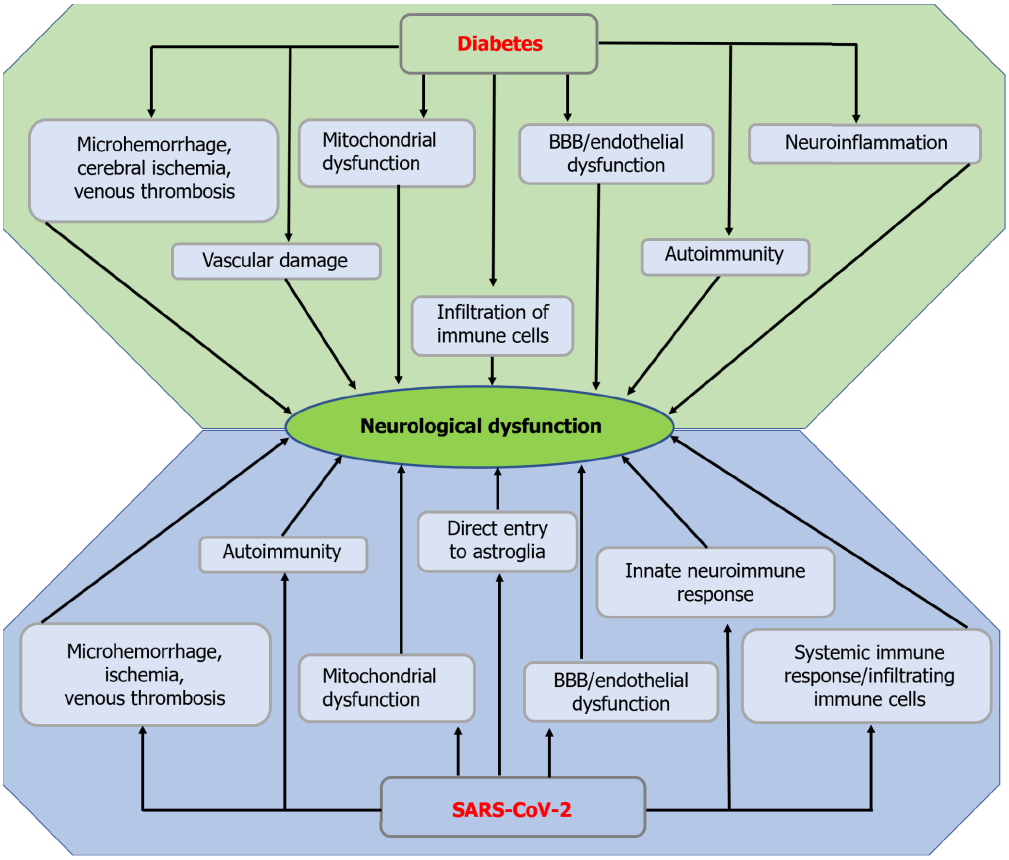
19, 21 encephalitis patients without COVID-19, and 18 healthy controls, showed that CSF from the encephalitis patients with COVID-19 was negative for SARS-CoV-2, whereas the levels of IL-6, IL-8, TNF-α, β2-microglobulin and glial markers including glial fibrillary acidic protein, soluble triggering receptor expressed on myeloid cells 2, and chitinase-3-like protein 1 (YKL-40) were significantly elevated compared with the encephalitis patients without COVID-19[115].

The blood-brain barrier (BBB) is a highly selective semipermeable border that mediates the communication between the periphery and the central nervous system (CNS), composed of endothelial cells, neurons, astrocytic end-feet, pericytes, and a thick basement membrane[116]. This BBB allows the transport of various nutrients, ions, glucose, water, amino acids, and hydrophobic molecules, including O_2, CO_2, and hormones[116], whereas it restricts the entry of pathogens, peripheral inflammatory mediators (*e.g.*, cytokines and antibodies) as well as large or hydrophilic molecules into the CNS[117]. Tight junctions (TJs) form a diffusion barrier between cerebral endothelial cells and prevent blood-borne substances from entering the brain[118].

DM-induced hyperglycemia upregulates the expression and activation of proangiogenic factors, including hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VRGF), and subsequently increases capillary formation at the BBB. Additionally, hyperglycemia downregulates the expression of inter-endothelial tight junction proteins, including occludin, claudin-5, ZO-1, and JAM-1, and subsequently increases tight junction malfunctioning[119]. DM-induced formation of advanced glycation end-products contributes to the loss of BBB integrity through the upregulation of matrix metalloproteinases 2 in BBB ECs. Oxidative stress-induced formation of ROS[120] may disrupt the BBB through increasing systemic inflammation in diabetes[121]. Increased hypoxia associated with severe COVID-19 may increase capillary density in the BBB through the upregulation of HIF-1α and VRGF. Increased capillary formation and malfunctioning/disruption of TJs facilitate the invasion of inflammatory factors, neurotoxins, and pathogens into the CNS[122]. Since the BBB is the only route for the pathogens and systemic proinflammatory cytokines/chemokines to enter inside the brain, pathogens including SARS, MERS, SARS-CoV, and SARS-CoV-2 and proinflammatory cytokines in the systemic circulation generated due to cytokine storm may easily penetrate inside the CNS of a diabetic person through the damaged BBB. Since the human brain tissue is known to express ACE2 receptors[123], SARS-CoV-2 may infect the brain tissue, followed by the expression of several pathophysiological symptoms associated with the CNS infection. For instance, a study that recruited 8 COVID-19 patients exhibited an elevation of anti-SARS-CoV-2 antibodies in the CSF of comatose or encephalopathic patients suggesting intrathecal IgG synthesis or BBB disruption. BBB disruption may facilitate the entry of proinflammatory cytokines and inflammatory mediators into the CNS and subsequent neuroinflammation and neurodegeneration[124]. A study that recruited 15 hospitalized COVID-19 patients with neurological manifestations exhibited lymphocytic pleocytosis, cranial neuropathy with meningopolyradiculitis, brainstem encephalitis, and delirium[125]. The possible mechanisms of diabetes and SARS-CoV-2-induced neurological dysfunction are stated in Figure 4.

SARS-CoV-2 infection exacerbates diabetes-induced eye diseases

Diabetic retinopathy (DR) is prevalent in diabetic patients and is one of the leading causes of blindness worldwide[126]. In 2020, the number of adults worldwide with DR, vision-threatening DR, and clinically significant macular edema was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively, and projection speculated that this number would increase to 160.50 million, 44.82 million, and 28.61 million, respectively in 2045[127]. The manifestation of DR is characterized by microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities, preretinal neovascularization, venous caliber changes, and lipid exudates from the damaged vasculature, capillary nonperfusion with accompanying neuronal infarcts and diabetic macular edema[128]. There are several possible mechanisms that may contribute to the pathogenesis of DR, including hyperglycemia-induced microangiopathy, inflammation, and retinal neurodegeneration[129]. Hyperglycemia has been implicated in the pathogenesis of retinal microvascular dysfunction through the impairment of several metabolic pathways, including the polyol pathway, formation of AGEs, the PKC pathway, and the hexosamine pathway[129]. Hyperglycemia is a well-known factor in pericyte and endothelial dysfunction mediated microaneurysm formation, impairment of blood-retinal barrier (BRB), capillary occlusion, and ischemia in DR[126]. Additionally, ischemia in diabetic eyes upregulates the expression of VEGF through the activation of HIF1[130] and phospholipase A2[131] and subsequently induces the pathogenesis of proliferative DR and diabetic macular edema by increasing vascular permeability. An *in vitro* cell culture study showed that VEGF-A mediates the early glucose-induced damage in human retinal endothelial cells through the activation of the ERK1/2/PLA2 signaling pathway[132]. A retrospective cohort study comprising 241196 DM patients showed that the prevalence of retinal artery occlusion is 2.30-times higher in DM patients compared to their age and sex-match healthy controls[133]. Leucocyte plays an important role in the pathogenesis of DR through the leukostasis-mediated retinal occlusion. A study in humans showed that subjects with central retinal vein occlusion were characterized by elevated levels of monocyte chemotactic protein-1, macrophage inflammatory protein-1alpha (MIP-1α), and MIP-1β that regulate the activation and binding of leukocytes[134]. STZ-induced diabetic mice showed retinal inflammation, which was characterized by leukostasis, increased expression of ICAM-1 on the luminal surface of the vascular endothelium, elevated retinal IL-6, CXCL1 expression, and superoxide



DOI: 10.5501/wjv.v11.i5.252

Figure 4 Possible mechanism of diabetes and severe acute respiratory syndrome coronavirus 2-induced neurological dysfunction. Microhemorrhage, cerebral ischemia, venous thrombosis, mitochondrial dysfunction, endothelial or blood-brain barrier dysfunction, vascular damage, autoimmunity, infiltration of immune cells, and neuroinflammation in diabetes result in neurological dysfunction. On the other hand, microhemorrhage, ischemia, venous thrombosis, autoimmunity, mitochondrial dysfunction, endothelial or blood-brain barrier dysfunction, innate neuroimmune response, systemic immune response or infiltration of immune cells, and direct entry to astroglia lead to neurological dysfunction. BBB: Blood-brain barrier; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

generation[135]. Another preclinical study in STZ-induced diabetic rats showed that leukocytes lead to the pathogenesis of DME through Fas-FasL-dependent retinal endothelial cell apoptosis and subsequent dysfunction of BRB[136]. A prospective study that employed 22 DR patients and 28 non-diabetic subjects showed that inflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-1β were significantly upregulated in the vitreous samples from DR patients and their levels were proportional to the severity of DR[137]. Some other studies demonstrated that retinal Müller glial cells and microglia as the initiators of retinal inflammation and subsequent pathogenesis of DR. For instance, a study by Portillo *et al*[138] showed that STZ-induced diabetic mice with overexpressed CD40 in Müller cells upregulated retinal expression of TNF-α, IL-1β, ICAM-1, and nitric oxide synthase (NOS2), developed leukostasis and capillary degeneration. This study further showed that overexpression of CD40 did not cause TNF-α or IL-1β secretion in Müller cells. Rather, TNF-α was upregulated in macrophages/microglia in the retina. The CD40 overexpressing Müller cells induced PLC–dependent ATP release and subsequent $P2X_7$-dependent production of TNF-α and IL-1β by macrophages. Findings from this study suggest that CD40 in Müller cells is sufficient to upregulate retinal inflammatory markers and appears to promote experimental DR through the activation of the CD40-ATP-$P2X_7$ pathway[138]. Hyperglycemia in diabetes is also implicated in mitochondrial dysfunction mediated apoptosis of retinal neurons and subsequent pathogenesis of DR. An *in vitro* cell culture study showed that rat retinal Müller cells grown in a high-glucose medium developed mitochondrial dysfunction that may contribute to retinal Müller cell loss and subsequent pathogenesis of DR[139]. Retinal neurodegeneration is a hallmark of the pathogenesis of early DR. Recent studies have reported that vascular changes are preceded by the damage and loss of retinal neurons due to apoptosis or autophagy. According to Silva *et al*[140] STZ-induced diabetic rats started to show DR symptoms after one month of STZ injection.

STZ-induced diabetic mice showed loss of rod cells, reduced thickness of the outer and inner synaptic layers along with the upregulation of autophagic proteins, including Beclin-1 and Atg5. Findings from this study suggest that the pathogenic pathways leading to cell death develop with the initial dysregulation of autophagy and subsequent vascular damage[141]. For instance, STZ-induced diabetic mice increased ERK activation and subsequent reduction of synaptophysin and depletion of a brain-derived neurotrophic factor in the diabetic retina after one month of STZ injection[142].

Although the respiratory tract is considered the predominant route of SARS-CoV-2 infection, several studies hypothesized that the conjunctiva could be contaminated by SARS-CoV-2 droplets and dirty hands, thereby initiating the viral entry into the body[143]. A study using 14 retinal biopsies (RB) samples and 13 optic nerve biopsy (ONB) samples collected from COVID-19 deaths showed that 7 out of 14 RB samples and 10 out of 13 ONB samples contained the SARS-CoV-2 RNA[144]. Similarly, a study in 91 hospitalized COVID-19 patients showed the presence of SARS-CoV-2 RNA on the ocular surfaces of 52 patients (57.1%). This study further showed that the virus was detected on the ocular surface in 10 out of 17 patients whose nasopharyngeal swab was negative[145]. However, the mechanism of direct eye infection by SARS-CoV-2 is still unknown. A study using human post-mortem eyes and surgical specimens showed the expression of both ACE2 and TMPRSS2 in conjunctiva, limbus, and cornea[146]. A study by Menuchin-Lasowski *et al*[147] showed that SARS-CoV-2 infected human stem cell-derived retinal organoids increased the production of several inflammatory genes associated with acute COVID-19 and retinal degeneration, including IL-33, CXCL2, and CXCL10. This study further showed that the inhibition of ACE2 activity with antibody significantly reduced SARS-CoV-2 infection of retinal organoids, indicating that SARS-CoV-2 infects retinal cells in an ACE2-dependent manner[147].

Conjunctivitis is the most common ophthalmic manifestation documented in COVID-19 patients [148]. A retrospective cross-sectional, single-center study using 127 COVID-19 patients with mild symptoms showed that 11 out of 127 (8.66%) patients had conjunctivitis[149]. Another study that recruited 535 COVID-19 patients showed that 27 patients (5.0%) presented with conjunctival congestion, which may result from direct hand contact with the eyes[150]. However, the mechanism of SARS-CoV-2-induced conjunctivitis is poorly understood. A case study in a 53-year-old man showed viral conjunctivitis along with the presence of SARS-CoV-2 RNA in the left eye after ten days of COVID-19 onset. The symptoms of the left eye conjunctivitis were completely cured in 5 d with proper medications. However, the patients experienced viral keratoconjunctivitis with progressive spot staining observed at the periphery of the corneal epithelium in both eyes; after five days, the symptoms in the left eye were completely cured. At this stage, the patient also showed an elevation of IL-6 levels in both eyes as well as in the circulation[151]. Findings from this study suggest that SARS-CoV-2-induced cytokine storm may contribute to the pathogenesis of conjunctivitis and keratoconjunctivitis. A population-based case-control study in 16 193 adults showed that diabetes is a risk factor for acute infectious conjunctivitis[152].

SARS-CoV-2 infection exacerbates diabetes-induced bone loss

DM is an important risk factor for osteoporosis. A single-center cross-sectional study that enrolled 388 Japanese patients with a history of T1D showed that long-term hypoglycemia is significantly associated with a higher risk of bone fracture[153]. A prospective and retrospective cohort study demonstrated that DM patients had a greater risk of total hip, upper arm, and ankle fractures, and this risk was pronounced in T1DM patients than T2DM patients[154]. Several mechanisms may contribute to the pathogenesis of DM-induced osteoporosis. Hyperglycemia and/or IR in DM are associated with increased production of proinflammatory cytokines, including IL-1, IL-6, and TNF-α, and vasoactive peptides, including Ang II. In contrast, it decreases the levels of vitamin D, which may downregulate osteoblast number/activity and upregulate osteoclast number/activity. Decrease in osteoblast/osteoclast ratio results in increased bone resorption and subsequent osteoporosis[155].

COVID-19 has been recognized to induce osteo-metabolic complications that are characterized by hypocalcemia, chronic hypovitaminosis D, and a high prevalence of bone fragility[156,157]. The presence of SARS-CoV-2 in bone cells has not been identified so far; however, the expression of ACE2 in the bone cells has been identified as a positive regulator of bone health. For instance, cell culture and human gingival bone samples have been shown to express ACE2 in osteoblast and osteoclast. Using both *in vitro* and *in vivo* models, this study further demonstrated that pharmacological activation of ACE2 with diminazene aceturate, an essential activator of ACE 2, significantly decreased alveolar bone loss through the improvement of osteoblast/osteoclast ratio[158]. Since SARS-CoV-2 bindings with the ACE2 receptors result in a decrease in ACE2 numbers, SARS-CoV-2 infection may increase bone loss. A study by Awosanya *et al*[159] has shown that human ACE2 expressing mice (TG) developed severe health problems and a significant reduction in trabecular bone volume due to an increase in the number and surface area of osteoclasts after 14 d of SARS-CoV-2 infection. However, more studies are required to confirm this finding. Cytokine storm upon SARS-CoV-2 infection is associated with increased circulatory levels of CXCL-10, TNF-α, IL-1β, and IL-6[160], whereas decreased reduced vitamin D levels are associated with increased infection and severity of COVID-19[161]. Many COVID-19 patients have experienced conjunctivitis in their eyes[148]. Therefore, it can be surmised that the possibility of fall-mediated bone fracture in COVID-19 patients who has conjunctivitis should be higher than the healthy people.

SARS-CoV-2 infection exacerbates diabetes-induced gastrointestinal complications

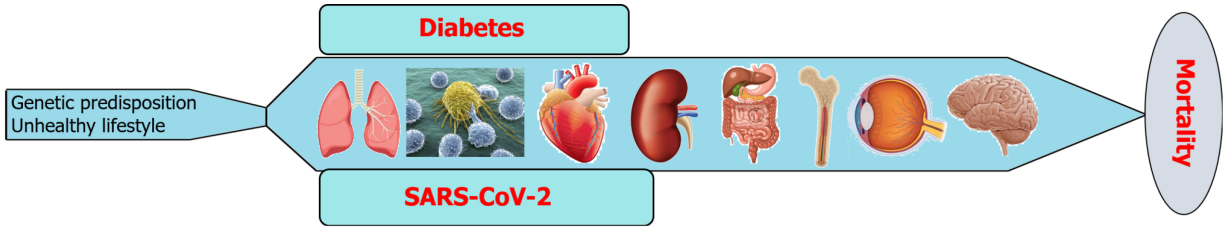
A study in a cohort including 59 patients with COVID-19 showed that 15 patients had GI dysfunction, and nine patients had stool containing SARS-CoV-2 RNA. This study also conducted a meta-analysis comprising 4243 COVID-19 patients showed that the prevalence of GI symptoms in COVID-19 patients was 17.6%, and 48.1% of COVID-19 patients exhibited the presence of SARS-CoV-2 RNA in their stool

samples, although 70.3% of those samples were collected after the loss of virus from respiratory specimens tested positive for the virus[162]. The expression of ACE2 in the human GI tract has been confirmed through several studies[163,164]. Several studies demonstrated the direct infection of SARS-CoV-2 in the GI tract. For instance, an *in vitro* study using gastric organoids from fetal, pediatric, and adult biopsies showed that pediatric and late fetal gastric organoids are susceptible to SARS-CoV-2 infection, while viral replication is significantly lower in undifferentiated organoids of early fetal and adult origin. Through transcriptomic analysis, they further showed that SARS-CoV-2 infected stomach sample elicits a moderate innate antiviral response and a lack of differentially expressed genes belonging to the interferon family. Findings from this study suggest that SARS-CoV-2 can efficiently infect the gastric epithelium, suggesting that the stomach might have an active role in fecal-oral SARS-CoV-2 transmission[165]. A retrospective, single-center study comprising 95 cases with SARS-CoV-2 infection demonstrated that GI symptoms, including diarrhea, anorexia, and nausea, were observed in 58 cases[166]. Findings from another retrospective cohort study comprising 104 patients with COVID-19 demonstrated that GI infection with SARS-CoV-2 prolongs the duration of SARS-CoV-2 shedding and hospitalization in the patients with COVID-19[167].

Diabetic patients are implicated in developing several GI complications, including gastroparesis, intestinal enteropathy, non-alcoholic fatty liver disease (NAFLD), pancreatitis, and peptic ulcer disease. There are clinical and preclinical studies that confirmed the association of diabetes with GI abnormalities. For instance, a study that recruited 50 DM patients and 20 non-DM healthy controls showed that patients with long-term DM exhibited lower maximal squeeze pressure, a higher mean threshold of minimal rectal sensation, and enhanced features of dyssynergic defection compared with the control group. Findings from this study suggest that DM patients demonstrated an impaired function of the external anal sphincter, enhanced features of dyssynergic defecation as well as impaired visceral sensation[168]. A case study that comprised ten patients with maternally inherited diabetes and deafness syndrome (MIDD) showed that GI symptoms, including constipation and diarrhea along with the mucosal accumulation of normal mitochondria and lipid droplets, are frequent in MIDD[169]. A study using the GI mucosal biopsy samples from subjects with and without type 2 diabetes exhibited that taste signaling molecules that modulate the upper GI function and energy intake are decreased in diabetic subjects with elevated blood glucose concentration and decreased by luminal glucose in mice [170]. A cohort study that recruited 5699 T2DM patients and 11226 age and sex-matched non-diabetic controls showed that in a 7-year follow-up period, T2DM patients had a significantly higher cumulative hazard of peptic ulcer bleeding than the controls with adjusted age, sex, and comorbidities[171]. Another study that recruited healthy subjects and peptic ulcer patients with or without T2DM showed that the number of circulating EPCs and their colony-forming ability, essential prerequisites for vascular repair and angiogenesis, was significantly reduced in peptic ulcer patients with T2DM[172]. There are findings from many preclinical and clinical studies that confirm diabetes as a significant risk factor for NAFLD[173-175]. A 14-years follow-up study by Han *et al*[176] that recruited 3047 subjects without underlying DM showed that NAFLD could be used as a biomarker better than BMI in predicting incident DM.

DISCUSSION AND FUTURE DIRECTIONS

Diabetes is a chronic metabolic disease that differentially induces the pathogenesis of several complications associated with different organs, including the brain, eyes, bone, GI tract, kidneys, heart, immune system, and lungs (Figure 5). On the other hand, SARS-CoV-2 infection has both acute and chronic effects on the manifestation of all diseases (Figure 5). In addition to their independent mechanisms for the pathogenesis of any disease, the coexistence of diabetes and SARS-CoV-2 infection exacerbates the disease severity and subsequent fatality (Figure 5). There are several approaches, including medications, diet and exercise that can reduce the blood glucose levels in both type 1 and type 2 DM patients. Insulin therapy and amylinomimetic drugs are used to reduce bold glucose levels in type 1 DM patients. Similarly, biguanides (*e.g.*, metformin), dopamine agonist (*e.g.*, bromocriptine), dipeptidyl peptidase-4 inhibitors (*e.g.*, alogliptin), glucagon-like peptide-1 receptor agonists (*e.g.*, albiglutide), meglitinides (*e.g.*, nateglinide), sodium-glucose transporter 2 inhibitors (*e.g.*, dapagliflozin), sulfonylureas (*e.g.*, glimepiride), and thiazolidinediones (*e.g.*, rosiglitazone) are well known type 2 DM medications[177]. However, there is no effective treatment that can completely cure diabetes or diabetic complications. On the other hand, there are several approaches that can prevent the transmission as well as the severity of SARS-CoV-2 infection, including mRNA vaccines (*e.g.*, Pfizer-BioNTech covid-19 vaccine), and antiviral drugs (*e.g.*, remdesivir) and monoclonal antibodies (*e.g.*, bebtelovimab)[178]. However, there is no effective therapy yet that can completely prevent the transmission of SARS-CoV-2 and cure COVID-19 without any side effects. Since SARS-CoV-2 is still circulating among the community, new variants like delta and omicron are evolving that can be even more transmissible and lethal than the existing variants. Because of these new mutant variants, COVID-19 is out of control despite widespread vaccination in the United States as well as other countries. There are some drugs that can prevent viral entry into the host cells as well as decrease blood glucose levels. For instance, Camostat mesylate, a



DOI: 10.5501/wjv.v11.i5.252

Figure 5 Role of diabetes and severe acute respiratory syndrome coronavirus 2 co-existence in multi-system organ failure. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

serine protease inhibitor used primarily for treating postoperative reflux esophagitis and chronic pancreatitis. However, studies showed that blocking TMPRSS2 with Camostat mesylate and its metabolite 4-(4-guanidinobenzoyloxy) phenylacetic acid can prevent upper respiratory tract infection by SARS-CoV-2[179]. Chloroquine and hydroxychloroquine are glucose-lowering drugs and have been used extensively to treat COVID-19 due to their antiviral properties. However, these drugs have adverse health effects. Therefore, patients with DM and/or other underlying health conditions should be aware that SARS-CoV-2 infection can elevate blood glucose levels, and, as such, they should follow clinical guidelines for the management of DM more strictly.

CONCLUSION

People with diabetes possess a higher risk of SARS-CoV-2 infection and subsequent severe COVID-19 manifestation. On the other hand, the prevalence of SARS-CoV-2 infection-mediated manifestation of diabetes is also increasing. It is more likely to develop severe consequences due to the global increase in diabetic patients and the co-existence of diabetes and SARS-CoV-2. Still, we need to wait longer, and more research should be conducted to see the long-term effects of post-COVID-19 manifestation. To prevent or cure the long-term coexistence of diabetes and COVID-19 in the human body, we should more adhere to standardized prevention and control, cutting the transmission chain of the virus and blocking it to a minimum. Maintaining a healthy lifestyle with a healthy diet, regular exercise, and proper hygiene can reduce the risk of developing diabetes as well as the number of SARS-CoV-2 infection.

FOOTNOTES

Author contributions: Roy B conceived the review design and wrote the draft; Runa SA revised the manuscript; all authors gave final approval of the version to be published.

Supported by a Predoctoral Fellowship Grant from the American Heart Association, No. 835262 (to Roy B).

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: United States

ORCID number: Bipradas Roy 0000-0001-6472-951X.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

REFERENCES

1 **Beckman JA**, Creager MA. Vascular Complications of Diabetes. *Circ Res* 2016; **118**: 1771-1785 [PMID: 27230641 DOI: 10.1161/CIRCRESAHA.115.306884]

2 **Centers for Disease Control and Prevention**. National Diabetes Statistics Report. [cited January 18, 2022] Available from: https://www.cdc.gov/diabetes/data/statistics-report/index.html

3 **Xie Y**, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol* 2022; **10**: 311-321 [PMID: 35325624 DOI: 10.1016/S2213-8587(22)00044-4]

4 **Wander PL**, Lowy E, Beste LA, Tulloch-Palomino L, Korpak A, Peterson AC, Kahn SE, Boyko EJ. The Incidence of Diabetes Among 2,777,768 Veterans With and Without Recent SARS-CoV-2 Infection. *Diabetes Care* 2022; **45**: 782-788 [PMID: 35085391 DOI: 10.2337/dc21-1686]

5 **Ehrlich SF**, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 2010; **33**: 55-60 [PMID: 19808918 DOI: 10.2337/dc09-0880]

6 **Forno E**. Asthma and diabetes: Does treatment with metformin improve asthma? *Respirology* 2016; **21**: 1144-1145 [PMID: 27533627 DOI: 10.1111/resp.12869]

7 **Mao X**, Liang C, Niu H, Dong F, Huang K, Chen Y, Zhan Q, Zhang Y, Huang Y, Yang T, Wang C. Outcomes associated with comorbid diabetes among patients with COPD exacerbation: findings from the ACURE registry. *Respir Res* 2021; **22**: 7 [PMID: 33407433 DOI: 10.1186/s12931-020-01607-6]

8 **Tai H**, Jiang XL, Yao SC, Liu Y, Wei H, Li LB, Jiao ZJ, Wang TQ, Kuang JS, Jia LQ. Vascular Endothelial Function as a Valid Predictor of Variations in Pulmonary Function in T2DM Patients Without Related Complications. *Front Endocrinol (Lausanne)* 2021; **12**: 622768 [PMID: 33776922 DOI: 10.3389/fendo.2021.622768]

9 **Gallo de Moraes A**, Surani S. Effects of diabetic ketoacidosis in the respiratory system. *World J Diabetes* 2019; **10**: 16-22 [PMID: 30697367 DOI: 10.4239/wjd.v10.i1.16]

10 **Wijnant SRA**, Jacobs M, Van Eeckhoutte HP, Lapauw B, Joos GF, Bracke KR, Brusselle GG. Expression of ACE2, the SARS-CoV-2 Receptor, in Lung Tissue of Patients With Type 2 Diabetes. *Diabetes* 2020; **69**: 2691-2699 [PMID: 33024003 DOI: 10.2337/db20-0669]

11 **Kornum JB**, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care* 2008; **31**: 1541-1545 [PMID: 18487479 DOI: 10.2337/dc08-0138]

12 **Eren G**, Cukurova Z, Hergunsel O, Demir G, Kucur M, Uslu E, Dalo E, Uhri M, Tugcu V. Protective effect of the nuclear factor kappa B inhibitor pyrrolidine dithiocarbamate in lung injury in rats with streptozotocin-induced diabetes. *Respiration* 2010; **79**: 402-410 [PMID: 19996572 DOI: 10.1159/000264920]

13 **Alkan M**, Çelik A, Bilge M, Kiraz HA, Kip G, Özer A, Şıvgın V, Erdem Ö, Arslan M, Kavutçu M. The effect of levosimendan on lung damage after myocardial ischemia reperfusion in rats in which experimental diabetes was induced. *J Surg Res* 2015; **193**: 920-925 [PMID: 25288204 DOI: 10.1016/j.jss.2014.08.038]

14 **Hu JF**, Zhang GJ, Wang L, Kang PF, Li J, Wang HJ, Gao Q, Chen YQ. Ethanol at low concentration attenuates diabetes induced lung injury in rats model. *J Diabetes Res* 2014; **2014**: 107152 [PMID: 25019090 DOI: 10.1155/2014/107152]

15 **Yang J**, Tan Y, Zhao F, Ma Z, Wang Y, Zheng S, Epstein PN, Yu J, Yin X, Zheng Y, Li X, Miao L, Cai L. Angiotensin II plays a critical role in diabetic pulmonary fibrosis most likely *via* activation of NADPH oxidase-mediated nitrosative damage. *Am J Physiol Endocrinol Metab* 2011; **301**: E132-E144 [PMID: 21487074 DOI: 10.1152/ajpendo.00629.2010]

16 **Zheng H**, Wu J, Jin Z, Yan LJ. Potential Biochemical Mechanisms of Lung Injury in Diabetes. *Aging Dis* 2017; **8**: 7-16 [PMID: 28203478 DOI: 10.14336/AD.2016.0627]

17 **Rao S**, Lau A, So HC. Exploring Diseases/Traits and Blood Proteins Causally Related to Expression of ACE2, the Putative Receptor of SARS-CoV-2: A Mendelian Randomization Analysis Highlights Tentative Relevance of Diabetes-Related Traits. *Diabetes Care* 2020; **43**: 1416-1426 [PMID: 32430459 DOI: 10.2337/dc20-0643]

18 **Saheb Sharif-Askari N**, Saheb Sharif-Askari F, Alabed M, Temsah MH, Al Heialy S, Hamid Q, Halwani R. Airways Expression of SARS-CoV-2 Receptor, ACE2, and TMPRSS2 Is Lower in Children Than Adults and Increases with Smoking and COPD. *Mol Ther Methods Clin Dev* 2020; **18**: 1-6 [PMID: 32537478 DOI: 10.1016/j.omtm.2020.05.013]

19 **Gheware A**, Ray A, Rana D, Bajpai P, Nambirajan A, Arulselvi S, Mathur P, Trikha A, Arava S, Das P, Mridha AR, Singh G, Soneja M, Nischal N, Lalwani S, Wig N, Sarkar C, Jain D. ACE2 protein expression in lung tissues of severe COVID-19 infection. *Sci Rep* 2022; **12**: 4058 [PMID: 35260724 DOI: 10.1038/s41598-022-07918-6]

20 **Wark PAB**, Pathinayake PS, Kaiko G, Nichol K, Ali A, Chen L, Sutanto EN, Garratt LW, Sohal SS, Lu W, Eapen MS, Oldmeadow C, Bartlett N, Reid A, Veerati P, Hsu AC, Looi K, Iosifidis T, Stick SM, Hansbro PM, Kicic A. ACE2 expression is elevated in airway epithelial cells from older and male healthy individuals but reduced in asthma. *Respirology* 2021; **26**: 442-451 [PMID: 33455043 DOI: 10.1111/resp.14003]

21 **Ackermann M**, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; **383**: 120-128 [PMID: 32437596 DOI: 10.1056/NEJMoa2015432]

22 **Valdebenito S**, Bessis S, Annane D, Lorin de la Grandmaison G, Cramer-Bordé E, Prideaux B, Eugenin EA, Bomsel M. COVID-19 Lung Pathogenesis in SARS-CoV-2 Autopsy Cases. *Front Immunol* 2021; **12**: 735922 [PMID: 34671353 DOI: 10.3389/fimmu.2021.735922]

23 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

24 **Duarte-Neto AN**, Monteiro RAA, da Silva LFF, Malheiros DMAC, de Oliveira EP, Theodoro-Filho J, Pinho JRR, Gomes-Gouvêa MS, Salles APM, de Oliveira IRS, Mauad T, Saldiva PHN, Dolhnikoff M. Pulmonary and systemic involvement in COVID-19 patients assessed with ultrasound-guided minimally invasive autopsy. *Histopathology* 2020;

77: 186-197 [PMID: 32443177 DOI: 10.1111/his.14160]
25 **Zhang H**, Zhou P, Wei Y, Yue H, Wang Y, Hu M, Zhang S, Cao T, Yang C, Li M, Guo G, Chen X, Chen Y, Lei M, Liu H, Zhao J, Peng P, Wang CY, Du R. Histopathologic Changes and SARS-CoV-2 Immunostaining in the Lung of a Patient With COVID-19. *Ann Intern Med* 2020; **172**: 629-632 [PMID: 32163542 DOI: 10.7326/M20-0533]
26 **Kerget B**, Kerget F, Koçak AO, Kızıltunç A, Araz Ö, Uçar EY, Akgün M. Are Serum Interleukin 6 and Surfactant Protein D Levels Associated with the Clinical Course of COVID-19? *Lung* 2020; **198**: 777-784 [PMID: 32918573 DOI: 10.1007/s00408-020-00393-8]
27 **Bellisai F**, Morozzi G, Scaccia F, Chellini F, Simpatico A, Pecetti G, Galeazzi M. Evaluation of the effect of Bosentan treatment on proinflammatory cytokine serum levels in patients affected by Systemic Sclerosis. *Int J Immunopathol Pharmacol* 2011; **24**: 261-264 [PMID: 21496413 DOI: 10.1177/039463201102400134]
28 **Merle NS**, Church SE, Fremeaux-Bacchi V, Roumenina LT. Complement System Part I - Molecular Mechanisms of Activation and Regulation. *Front Immunol* 2015; **6**: 262 [PMID: 26082779 DOI: 10.3389/fimmu.2015.00262]
29 **Casqueiro J**, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian J Endocrinol Metab* 2012; **16** Suppl 1: S27-S36 [PMID: 22701840 DOI: 10.4103/2230-8210.94253]
30 **Mauriello CT**, Hair PS, Rohn RD, Rister NS, Krishna NK, Cunnion KM. Hyperglycemia inhibits complement-mediated immunological control of S. aureus in a rat model of peritonitis. *J Diabetes Res* 2014; **2014**: 762051 [PMID: 25610878 DOI: 10.1155/2014/762051]
31 **Jafar N**, Edriss H, Nugent K. The Effect of Short-Term Hyperglycemia on the Innate Immune System. *Am J Med Sci* 2016; **351**: 201-211 [PMID: 26897277 DOI: 10.1016/j.amjms.2015.11.011]
32 **Gavriilaki E**, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. *Br J Haematol* 2020; **189**: e227-e230 [PMID: 32369610 DOI: 10.1111/bjh.16783]
33 **McMillan DE**. Elevation of complement components in diabetes mellitus. *Diabete Metab* 1980; **6**: 265-270 [PMID: 6907148]
34 **Engström G**, Hedblad B, Eriksson KF, Janzon L, Lindgärde F. Complement C3 is a risk factor for the development of diabetes: a population-based cohort study. *Diabetes* 2005; **54**: 570-575 [PMID: 15677517 DOI: 10.2337/diabetes.54.2.570]
35 **Wlazlo N**, van Greevenbroek MM, Ferreira I, Feskens EJ, van der Kallen CJ, Schalkwijk CG, Bravenboer B, Stehouwer CD. Complement factor 3 is associated with insulin resistance and with incident type 2 diabetes over a 7-year follow-up period: the CODAM Study. *Diabetes Care* 2014; **37**: 1900-1909 [PMID: 24760264 DOI: 10.2337/dc13-2804]
36 **Park MH**, Caselman N, Ulmer S, Weitz IC. Complement-mediated thrombotic microangiopathy associated with lupus nephritis. *Blood Adv* 2018; **2**: 2090-2094 [PMID: 30131343 DOI: 10.1182/bloodadvances.2018019596]
37 **Shi Y**, Vanhoutte PM. Macro- and microvascular endothelial dysfunction in diabetes. *J Diabetes* 2017; **9**: 434-449 [PMID: 28044409 DOI: 10.1111/1753-0407.12521]
38 **Goldberg RJ**, Nakagawa T, Johnson RJ, Thurman JM. The role of endothelial cell injury in thrombotic microangiopathy. *Am J Kidney Dis* 2010; **56**: 1168-1174 [PMID: 20843591 DOI: 10.1053/j.ajkd.2010.06.006]
39 **Zheng XL**. ADAMTS13 and von Willebrand factor in thrombotic thrombocytopenic purpura. *Annu Rev Med* 2015; **66**: 211-225 [PMID: 25587650 DOI: 10.1146/annurev-med-061813-013241]
40 **Tsai HM**. Pathophysiology of thrombotic thrombocytopenic purpura. *Int J Hematol* 2010; **91**: 1-19 [PMID: 20058209 DOI: 10.1007/s12185-009-0476-1]
41 **Zander CB**, Cao W, Zheng XL. ADAMTS13 and von Willebrand factor interactions. *Curr Opin Hematol* 2015; **22**: 452-459 [PMID: 26186678 DOI: 10.1097/MOH.0000000000000169]
42 **Oggianu L**, Lancellotti S, Pitocco D, Zaccardi F, Rizzo P, Martini F, Ghirlanda G, De Cristofaro R. The oxidative modification of von Willebrand factor is associated with thrombotic angiopathies in diabetes mellitus. *PLoS One* 2013; **8**: e55396 [PMID: 23383177 DOI: 10.1371/journal.pone.0055396]
43 **Skeppholm M**, Kallner A, Kalani M, Jörneskog G, Blombäck M, Wallén HN. ADAMTS13 and von Willebrand factor concentrations in patients with diabetes mellitus. *Blood Coagul Fibrinolysis* 2009; **20**: 619-626 [PMID: 19809308 DOI: 10.1097/MBC.0b013e32832da183]
44 **Han H**, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020; **58**: 1116-1120 [PMID: 32172226 DOI: 10.1515/cclm-2020-0188]
45 **Magdi M**, Rahil A. Severe Immune Thrombocytopenia Complicated by Intracerebral Haemorrhage Associated with Coronavirus Infection: A Case Report and Literature Review. *Eur J Case Rep Intern Med* 2019; **6**: 001155 [PMID: 31410357 DOI: 10.12890/2019_001155]
46 **Becker RC**. COVID-19 update: Covid-19-associated coagulopathy. *J Thromb Thrombolysis* 2020; **50**: 54-67 [PMID: 32415579 DOI: 10.1007/s11239-020-02134-3]
47 **Levi M**, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020; **7**: e438-e440 [PMID: 32407672 DOI: 10.1016/S2352-3026(20)30145-9]
48 **Campbell CM**, Kahwash R. Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? *Circulation* 2020; **141**: 1739-1741 [PMID: 32271624 DOI: 10.1161/CIRCULATIONAHA.120.047419]
49 **Goshua G**, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ, Dela Cruz CS, Dumont A, Halene S, Hwa J, Koff J, Menninger H, Neparidze N, Price C, Siner JM, Tormey C, Rinder HM, Chun HJ, Lee AI. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol* 2020; **7**: e575-e582 [PMID: 32619411 DOI: 10.1016/S2352-3026(20)30216-7]
50 **Ahmed A**, Merrill SA, Alsawah F, Bockenstedt P, Campagnaro E, Devata S, Gitlin SD, Kaminski M, Cusick A, Phillips T, Sood S, Talpaz M, Quiery A, Boonstra PS, Wilcox RA. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol* 2019; **6**: e630-e637 [PMID: 31537486 DOI: 10.1016/S2352-3026(19)30156-5]
51 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

52 **Pajvani U**, Lipton ML, Grajower MM. Diabetes insipidus associated with hemophagocytic lymphohistiocytosis: first case report. *Endocr Pract* 2011; **17**: e118-e122 [PMID: 21742615 DOI: 10.4158/EP10409.CR]

53 **Machaczka M**. Hemophagocytic lymphohistiocytosis in adults. *Ups J Med Sci* 2013; **118**: 201-203 [PMID: 23682633 DOI: 10.3109/03009734.2013.795634]

54 **Nichols GA**, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. *Diabetes Care* 2009; **32**: 1851-1856 [PMID: 19794003 DOI: 10.2337/dc09-0939]

55 **Seyed Ahmadi S**, Svensson AM, Pivodic A, Rosengren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol* 2020; **19**: 9 [PMID: 31954408 DOI: 10.1186/s12933-019-0983-1]

56 **Jia G**, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. *Circ Res* 2018; **122**: 624-638 [PMID: 29449364 DOI: 10.1161/CIRCRESAHA.117.311586]

57 **Xie Y**, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; **28**: 583-590 [PMID: 35132265 DOI: 10.1038/s41591-022-01689-3]

58 **Paris S**, Inciardi RM, Lombardi CM, Tomasoni D, Ameri P, Carubelli V, Agostoni P, Canale C, Carugo S, Danzi G, Di Pasquale M, Sarullo F, La Rovere MT, Mortara A, Piepoli M, Porto I, Sinagra G, Volterrani M, Gnecchi M, Leonardi S, Merlo M, Iorio A, Giovinazzo S, Bellasi A, Zaccone G, Camporotondo R, Catagnano F, Dalla Vecchia L, Maccagni G, Mapelli M, Margonato D, Monzo L, Nuzzi V, Pozzi A, Provenzale G, Specchia C, Tedino C, Guazzi M, Senni M, Metra M. Implications of atrial fibrillation on the clinical course and outcomes of hospitalized COVID-19 patients: results of the Cardio-COVID-Italy multicentre study. *Europace* 2021; **23**: 1603-1611 [PMID: 34297833 DOI: 10.1093/europace/euab146]

59 **Arévalos V**, Ortega-Paz L, Rodríguez-Arias JJ, Calvo M, Castrillo L, Salazar A, Roque M, Dantas AP, Sabaté M, Brugaletta S. Myocardial Injury in COVID-19 Patients: Association with Inflammation, Coagulopathy and In-Hospital Prognosis. *J Clin Med* 2021; **10** [PMID: 34068127 DOI: 10.3390/jcm10102096]

60 **Hendren NS**, Drazner MH, Bozkurt B, Cooper LT Jr. Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome. *Circulation* 2020; **141**: 1903-1914 [PMID: 32297796 DOI: 10.1161/CIRCULATIONAHA.120.047349]

61 **Pellegrini D**, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, Nasr A, Kutys R, Guo L, Cornelissen A, Faggi L, Mori M, Sato Y, Pescetelli I, Brivio M, Romero M, Virmani R, Finn AV. Microthrombi as a Major Cause of Cardiac Injury in COVID-19: A Pathologic Study. *Circulation* 2021; **143**: 1031-1042 [PMID: 33480806 DOI: 10.1161/CIRCULATIONAHA.120.051828]

62 **Herman-Edelstein M**, Guetta T, Barnea A, Waldman M, Ben-Dor N, Barac YD, Kornowski R, Arad M, Hochhauser E, Aravot D. Expression of the SARS-CoV-2 receptorACE2 in human heart is associated with uncontrolled diabetes, obesity, and activation of the renin angiotensin system. *Cardiovasc Diabetol* 2021; **20**: 90 [PMID: 33906662 DOI: 10.1186/s12933-021-01275-w]

63 **Sinclair JE**, Bloxham CJ, Chiu H, Chew KY, Russell J, Yoshikawa Y, Bielefeldt-Ohmann H, Steele LE, Hulme KD, Verzele NA, Noye EC, Wu M, Reichelt ME, Thomas WG, Gallo LA, Redd MA, Short KR. Type I Diabetes Mellitus Increases the Cardiovascular Complications of Influenza Virus Infection. *Front Cell Infect Microbiol* 2021; **11**: 714440 [PMID: 34595130 DOI: 10.3389/fcimb.2021.714440]

64 **Wichmann D**, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med* 2020; **173**: 268-277 [PMID: 32374815 DOI: 10.7326/M20-2003]

65 **Wenzel P**, Kopp S, Göbel S, Jansen T, Geyer M, Hahn F, Kreitner KF, Escher F, Schultheiss HP, Münzel T. Evidence of SARS-CoV-2 mRNA in endomyocardial biopsies of patients with clinically suspected myocarditis tested negative for COVID-19 in nasopharyngeal swab. *Cardiovasc Res* 2020; **116**: 1661-1663 [PMID: 32562489 DOI: 10.1093/cvr/cvaa160]

66 **Nakamura Y**, Katano H, Nakajima N, Sato Y, Suzuki T, Sekizuka T, Kuroda M, Izutani Y, Morimoto S, Maruyama J, Koie M, Kitamura T, Ishikura H. SARS-CoV-2 is localized in cardiomyocytes: a postmortem biopsy case. *Int J Infect Dis* 2021; **111**: 43-46 [PMID: 34384897 DOI: 10.1016/j.ijid.2021.08.015]

67 **Bailey AL**, Dmytrenko O, Greenberg L, Bredemeyer AL, Ma P, Liu J, Penna V, Winkler ES, Sviben S, Brooks E, Nair AP, Heck KA, Rali AS, Simpson L, Saririan M, Hobohm D, Stump WT, Fitzpatrick JA, Xie X, Zhang X, Shi PY, Hinson JT, Gi WT, Schmidt C, Leuschner F, Lin CY, Diamond MS, Greenberg MJ, Lavine KJ. SARS-CoV-2 Infects Human Engineered Heart Tissues and Models COVID-19 Myocarditis. *JACC Basic Transl Sci* 2021; **6**: 331-345 [PMID: 33681537 DOI: 10.1016/j.jacbts.2021.01.002]

68 **Centers for Disease Control and Prevention**. Chronic Kidney Disease in the United States, 2019. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention

69 **Li S**, Wang F, Sun D. The renal microcirculation in chronic kidney disease: novel diagnostic methods and therapeutic perspectives. *Cell Biosci* 2021; **11**: 90 [PMID: 34001267 DOI: 10.1186/s13578-021-00606-4]

70 **Fenske R**, Weeks A, Brill A, Nall R, Pabitch S, Punt M, Daniels M, Blaha S, Davis DB, Kimple M. Prostaglandin E2 (PGE2) Levels As a Predictor of Type 2 Diabetes Control in Human Subjects: A cross-sectional view of initial cohort study data. *FASEB J* 2018; **31**: 675.6 [DOI: 10.1096/fasebj.31.1_supplement.675.6]

71 **Ito S**, Ren Y. Evidence for the role of nitric oxide in macula densa control of glomerular hemodynamics. *J Clin Invest* 1993; **92**: 1093-1098 [PMID: 8349792 DOI: 10.1172/JCI116615]

72 **Schneider MP**, Ott C, Schmidt S, Kistner I, Friedrich S, Schmieder RE. Poor glycemic control is related to increased nitric oxide activity within the renal circulation of patients with type 2 diabetes. *Diabetes Care* 2013; **36**: 4071-4075 [PMID: 24130344 DOI: 10.2337/dc13-0806]

73 **Ricke-Hoch M**, Stelling E, Lasswitz L, Gunesch A, Kasten M, Zapatero-Belinchón F, Brogden G, Gerold G, Battmer K, Pietschmann T, Montiel V, Balligand J, Facciotti F, Hirsch E, Elbahesh H, Rimmelzwaan G, Hoefer A, Kühnel M, Jonigk

D, Eigendorf J, Tegtbur U, Mink L, Scherr M, Illig T, Schambach A, Pfeffer T, Andrée B, Hilfiker A, Haverich A, Hilfiker-Kleiner D. SARS-CoV-2-induced impaired immune response by Prostaglandin E2 is accelerated by age, male sex and air pollution. *Research Square* 2021 [DOI: 10.21203/rs.3.rs-129664/v1]

74 **Ali N**. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *J Med Virol* 2020; **92**: 2409-2411 [PMID: 32516845 DOI: 10.1002/jmv.26097]

75 **Emerging Risk Factors Collaboration**, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, Walker M, Thompson A, Sarwar N, Caslake M, Butterworth AS, Amouyel P, Assmann G, Bakker SJ, Barr EL, Barrett-Connor E, Benjamin EJ, Björkelund C, Brenner H, Brunner E, Clarke R, Cooper JA, Cremer P, Cushman M, Dagenais GR, D'Agostino RB Sr, Dankner R, Davey-Smith G, Deeg D, Dekker JM, Engström G, Folsom AR, Fowkes FG, Gallacher J, Gaziano JM, Giampaoli S, Gillum RF, Hofman A, Howard BV, Ingelsson E, Iso H, Jørgensen T, Kiechl S, Kitamura A, Kiyohara Y, Koenig W, Kromhout D, Kuller LH, Lawlor DA, Meade TW, Nissinen A, Nordestgaard BG, Onat A, Panagiotakos DB, Psaty BM, Rodriguez B, Rosengren A, Salomaa V, Kauhanen J, Salonen JT, Shaffer JA, Shea S, Ford I, Stehouwer CD, Strandberg TE, Tipping RW, Tosetto A, Wassertheil-Smoller S, Wennberg P, Westendorp RG, Whincup PH, Wilhelmsen L, Woodward M, Lowe GD, Wareham NJ, Khaw KT, Sattar N, Packard CJ, Gudnason V, Ridker PM, Pepys MB, Thompson SG, Danesh J. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 2012; **367**: 1310-1320 [PMID: 23034020 DOI: 10.1056/NEJMoa1107477]

76 **Carpenter TC**, Schomberg S, Stenmark KR. Endothelin-mediated increases in lung VEGF content promote vascular leak in young rats exposed to viral infection and hypoxia. *Am J Physiol Lung Cell Mol Physiol* 2005; **289**: L1075-L1082 [PMID: 16040626 DOI: 10.1152/ajplung.00251.2005]

77 **Gregoriano C**, Damm D, Kutz A, Koch D, Wolfisberg S, Haubitz S, Conen A, Bernasconi L, Hammerer-Lercher A, Fux CA, Mueller B, Schuetz P. Association of endothelial activation assessed through endothelin-I precursor peptide measurement with mortality in COVID-19 patients: an observational analysis. *Respir Res* 2021; **22**: 148 [PMID: 33985491 DOI: 10.1186/s12931-021-01742-8]

78 **Tanji N**, Markowitz GS, Fu C, Kislinger T, Taguchi A, Pischetsrieder M, Stern D, Schmidt AM, D'Agati VD. Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. *J Am Soc Nephrol* 2000; **11**: 1656-1666 [PMID: 10966490 DOI: 10.1681/ASN.V1191656]

79 **Matsui T**, Higashimoto Y, Nishino Y, Nakamura N, Fukami K, Yamagishi SI. RAGE-Aptamer Blocks the Development and Progression of Experimental Diabetic Nephropathy. *Diabetes* 2017; **66**: 1683-1695 [PMID: 28385802 DOI: 10.2337/db16-1281]

80 **Lim A**, Radujkovic A, Weigand MA, Merle U. Soluble receptor for advanced glycation end products (sRAGE) as a biomarker of COVID-19 disease severity and indicator of the need for mechanical ventilation, ARDS and mortality. *Ann Intensive Care* 2021; **11**: 50 [PMID: 33751264 DOI: 10.1186/s13613-021-00836-2]

81 **Wu M**, Chen Y, Xia H, Wang C, Tan CY, Cai X, Liu Y, Ji F, Xiong P, Liu R, Guan Y, Duan Y, Kuang D, Xu S, Cai H, Xia Q, Yang D, Wang MW, Chiu IM, Cheng C, Ahern PP, Liu L, Wang G, Surana NK, Xia T, Kasper DL. Transcriptional and proteomic insights into the host response in fatal COVID-19 cases. *Proc Natl Acad Sci U S A* 2020; **117**: 28336-28343 [PMID: 33082228 DOI: 10.1073/pnas.2018030117]

82 **Chen L**, Long X, Xu Q, Tan J, Wang G, Cao Y, Wei J, Luo H, Zhu H, Huang L, Meng F, Wang N, Zhou X, Zhao L, Chen X, Mao Z, Chen C, Li Z, Sun Z, Zhao J, Wang D, Huang G, Wang W, Zhou J. Elevated serum levels of S100A8/A9 and HMGB1 at hospital admission are correlated with inferior clinical outcomes in COVID-19 patients. *Cell Mol Immunol* 2020; **17**: 992-994 [PMID: 32620787 DOI: 10.1038/s41423-020-0492-x]

83 **Arunachalam PS**, Wimmers F, Mok CKP, Perera RAPM, Scott M, Hagan T, Sigal N, Feng Y, Bristow L, Tak-Yin Tsang O, Wagh D, Coller J, Pellegrini KL, Kazmin D, Alaaeddine G, Leung WS, Chan JMC, Chik TSH, Choi CYC, Huerta C, Paine McCullough M, Lv H, Anderson E, Edupuganti S, Upadhyay AA, Bosinger SE, Maecker HT, Khatri P, Rouphael N, Peiris M, Pulendran B. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science* 2020; **369**: 1210-1220 [PMID: 32788292 DOI: 10.1126/science.abc6261]

84 **Aceti A**, Margarucci LM, Scaramucci E, Orsini M, Salerno G, Di Sante G, Gianfranceschi G, Di Liddo R, Valeriani F, Ria F, Simmaco M, Parnigotto PP, Vitali M, Romano Spica V, Michetti F. Serum S100B protein as a marker of severity in Covid-19 patients. *Sci Rep* 2020; **10**: 18665 [PMID: 33122776 DOI: 10.1038/s41598-020-75618-0]

85 **Wei J**, Alfajaro MM, DeWeirdt PC, Hanna RE, Lu-Culligan WJ, Cai WL, Strine MS, Zhang SM, Graziano VR, Schmitz CO, Chen JS, Mankowski MC, Filler RB, Ravindra NG, Gasque V, de Miguel FJ, Patil A, Chen H, Oguntuyo KY, Abriola L, Surovtseva YV, Orchard RC, Lee B, Lindenbach BD, Politi K, van Dijk D, Kadoch C, Simon MD, Yan Q, Doench JG, Wilen CB. Genome-wide CRISPR Screens Reveal Host Factors Critical for SARS-CoV-2 Infection. *Cell* 2021; **184**: 76-91.e13 [PMID: 33147444 DOI: 10.1016/j.cell.2020.10.028]

86 **Gross JL**, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care* 2005; **28**: 164-176 [PMID: 15616252 DOI: 10.2337/diacare.28.1.164]

87 **Liang H**, Kennedy C, Manne S, Lin JH, Dolin P. Monitoring for proteinuria in patients with type 2 diabetes mellitus. *BMJ Open Diabetes Res Care* 2015; **3**: e000071 [PMID: 25893098 DOI: 10.1136/bmjdrc-2014-000071]

88 **Ouahmi H**, Courjon J, Morand L, François J, Bruckert V, Lombardi R, Esnault V, Seitz-Polski B, Demonchy E, Dellamonica J, Boyer-Suavet S. Proteinuria as a Biomarker for COVID-19 Severity. *Front Physiol* 2021; **12**: 611772 [PMID: 33767630 DOI: 10.3389/fphys.2021.611772]

89 **Trinh MD**, Plihalova A, Gojda J, Westlake K, Spicka J, Lattova Z, Pretl M, Polak J. Obstructive sleep apnoea increases lipolysis and deteriorates glucose homeostasis in patients with type 2 diabetes mellitus. *Sci Rep* 2021; **11**: 3567 [PMID: 33574418 DOI: 10.1038/s41598-021-83018-1]

90 **Zamarrón E**, Jaureguizar A, García-Sánchez A, Díaz-Cambriles T, Alonso-Fernández A, Lores V, Mediano O, Rodríguez-Rodríguez P, Cabello-Pelegrín S, Morales-Ruíz E, Ramírez-Prieto MT, Valiente-Díaz MI, Gómez-García T, García-Río F; Spanish Sleep Network. Obstructive sleep apnea is associated with impaired renal function in patients with diabetic kidney disease. *Sci Rep* 2021; **11**: 5675 [PMID: 33707611 DOI: 10.1038/s41598-021-85023-w]

91 **Lin CH**, Perger E, Lyons OD. Obstructive sleep apnea and chronic kidney disease. *Curr Opin Pulm Med* 2018; **24**: 549-554 [PMID: 30239379 DOI: 10.1097/MCP.0000000000000525]

92 **Strausz S**, Kiiskinen T, Broberg M, Ruotsalainen S, Koskela J, Bachour A; FinnGen, Palotie A, Palotie T, Ripatti S, Ollila HM. Sleep apnoea is a risk factor for severe COVID-19. *BMJ Open Respir Res* 2021; **8** [PMID: 33436406 DOI: 10.1136/bmjresp-2020-000845]

93 **Huang JX**, Casper TC, Pitts C, Myers S, Loomba L, Ramesh J, Kuppermann N, Glaser N. Association of Acute Kidney Injury During Diabetic Ketoacidosis With Risk of Microalbuminuria in Children With Type 1 Diabetes. *JAMA Pediatr* 2022; **176**: 169-175 [PMID: 34842908 DOI: 10.1001/jamapediatrics.2021.5038]

94 **Li J**, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab* 2020; **22**: 1935-1941 [PMID: 32314455 DOI: 10.1111/dom.14057]

95 **Chan L**, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I, Somani S, Richter F, Miotto R, Lala A, Kia A, Timsina P, Li L, Freeman R, Chen R, Narula J, Just AC, Horowitz C, Fayad Z, Cordon-Cardo C, Schadt E, Levin MA, Reich DL, Fuster V, Murphy B, He JC, Charney AW, Böttinger EP, Glicksberg BS, Coca SG, Nadkarni GN; Mount Sinai COVID Informatics Center (MSCIC). AKI in Hospitalized Patients with COVID-19. *J Am Soc Nephrol* 2021; **32**: 151-160 [PMID: 32883700 DOI: 10.1681/ASN.2020050615]

96 **Bowe B**, Xie Y, Xu E, Al-Aly Z. Kidney Outcomes in Long COVID. *J Am Soc Nephrol* 2021; **32**: 2851-2862 [PMID: 34470828 DOI: 10.1681/ASN.2021060734]

97 **Liamis G**, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. *World J Clin Cases* 2014; **2**: 488-496 [PMID: 25325058 DOI: 10.12998/wjcc.v2.i10.488]

98 **Montomoli J**, Donati A, Ince C. Acute Kidney Injury and Fluid Resuscitation in Septic Patients: Are We Protecting the Kidney? *Nephron* 2019; **143**: 170-173 [PMID: 31394531 DOI: 10.1159/000501748]

99 **Kazory A**, Ronco C, McCullough PA. SARS-CoV-2 (COVID-19) and intravascular volume management strategies in the critically ill. *Proc (Bayl Univ Med Cent)* 2020; **0**: 1-6 [PMID: 32336959 DOI: 10.1080/08998280.2020.1754700]

100 **Watchorn J**, Huang DY, Joslin J, Bramham K, Hutchings SD. Critically Ill COVID-19 Patients With Acute Kidney Injury Have Reduced Renal Blood Flow and Perfusion Despite Preserved Cardiac Function: A Case-Control Study Using Contrast-Enhanced Ultrasound. *Shock* 2021; **55**: 479-487 [PMID: 32890313 DOI: 10.1097/SHK.0000000000001659]

101 **Matejovic M**, Ince C, Chawla LS, Blantz R, Molitoris BA, Rosner MH, Okusa MD, Kellum JA, Ronco C; ADQI XIII Work Group. Renal Hemodynamics in AKI: In Search of New Treatment Targets. *J Am Soc Nephrol* 2016; **27**: 49-58 [PMID: 26510884 DOI: 10.1681/ASN.2015030234]

102 **Brophy DF**, Martin RJ, Gehr TW, Carr ME Jr. A hypothesis-generating study to evaluate platelet activity in diabetics with chronic kidney disease. *Thromb J* 2005; **3**: 3 [PMID: 15796773 DOI: 10.1186/1477-9560-3-3]

103 **Reiken S**, Sittenfeld L, Dridi H, Liu Y, Liu X, Marks AR. Alzheimer's-like signaling in brains of COVID-19 patients. *Alzheimers Dement* 2022; **18**: 955-965 [PMID: 35112786 DOI: 10.1002/alz.12558]

104 **Douaud G**, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, Lange F, Andersson JLR, Griffanti L, Duff E, Jbabdi S, Taschler B, Keating P, Winkler AM, Collins R, Matthews PM, Allen N, Miller KL, Nichols TE, Smith SM. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 2022; **604**: 697-707 [PMID: 35255491 DOI: 10.1038/s41586-022-04569-5]

105 **Planel E**, Tatebayashi Y, Miyasaka T, Liu L, Wang L, Herman M, Yu WH, Luchsinger JA, Wadzinski B, Duff KE, Takashima A. Insulin dysfunction induces in vivo tau hyperphosphorylation through distinct mechanisms. *J Neurosci* 2007; **27**: 13635-13648 [PMID: 18077675 DOI: 10.1523/JNEUROSCI.3949-07.2007]

106 **Meinhardt J**, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, Laue M, Schneider J, Brünink S, Greuel S, Lehmann M, Hassan O, Aschman T, Schumann E, Chua RL, Conrad C, Eils R, Stenzel W, Windgassen M, Rößler L, Goebel HH, Gelderblom HR, Martin H, Nitsche A, Schulz-Schaeffer WJ, Hakroush S, Winkler MS, Tampe B, Scheibe F, Körtvélyessy P, Reinhold D, Siegmund B, Kühl AA, Elezkurtaj S, Horst D, Oesterhelweg L, Tsokos M, Ingold-Heppner B, Stadelmann C, Drosten C, Corman VM, Radbruch H, Heppner FL. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci* 2021; **24**: 168-175 [PMID: 33257876 DOI: 10.1038/s41593-020-00758-5]

107 **Díaz-Gerevini GT**, Daín A, Pasqualini ME, López CB, Eynard AR, Repossi G. Diabetic encephalopathy: beneficial effects of supplementation with fatty acids ω3 and nordihydroguaiaretic acid in a spontaneous diabetes rat model. *Lipids Health Dis* 2019; **18**: 43 [PMID: 30736810 DOI: 10.1186/s12944-018-0938-7]

108 **Cai XJ**, Xu HQ, Lu Y. C-peptide and diabetic encephalopathy. *Chin Med Sci J* 2011; **26**: 119-125 [PMID: 21703121 DOI: 10.1016/s1001-9294(11)60031-x]

109 **Akın O**, Kılınç Uğurlu A, Akbaş ED, Döğer E, Akbaş Y, Bideci A, Yüce Ö, Gücüyener K, Çamurdan MO, Karabacak N, Cinaz P. Autoimmune Limbic Encephalitis Associated with Type 1 Diabetes Mellitus. *J Clin Res Pediatr Endocrinol* 2017; **9**: 387-388 [PMID: 28720552 DOI: 10.4274/jcrpe.3818]

110 **Uginet M**, Breville G, Assal F, Lövblad KO, Vargas MI, Pugin J, Serratrice J, Herrmann FR, Lalive PH, Allali G. COVID-19 encephalopathy: Clinical and neurobiological features. *J Med Virol* 2021; **93**: 4374-4381 [PMID: 33782993 DOI: 10.1002/jmv.26973]

111 **Siddiqui AF**, Saadia S, Ejaz T, Mushtaq Z. COVID-19 encephalopathy: an unusual presentation with new-onset seizure causing convulsive status epilepticus. *BMJ Case Rep* 2022; **15** [PMID: 35260396 DOI: 10.1136/bcr-2021-245387]

112 **Hernández-Fernández F**, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, Molina-Nuevo JD, García-García J, Lozano-Setién E, Alcahut-Rodriguez C, Martínez-Martín Á, Sánchez-López A, Segura T. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. *Brain* 2020; **143**: 3089-3103 [PMID: 32645151 DOI: 10.1093/brain/awaa239]

113 **Nampoothiri S**, Sauve F, Ternier G, Fernandois D, Coelho C, Imbernon M, Deligia E, Perbet R, Florent V, Baroncini M, Pasquier F, Trottein F, Maurage CA, Mattot V, Giacobini P, Rasika S, Prevot V. The hypothalamus as a hub for SARS-CoV-2 brain infection and pathogenesis. *bioRxiv* 2020 [DOI: 10.1101/2020.06.08.139329]

114 **Pilotto A**, Masciocchi S, Volonghi I, Crabbio M, Magni E, De Giuli V, Caprioli F, Rifino N, Sessa M, Gennuso M, Cotelli MS, Turla M, Balducci U, Mariotto S, Ferrari S, Ciccone A, Fiacco F, Imarisio A, Risi B, Benussi A, Premi E, Focà E, Caccuri F, Leonardi M, Gasparotti R, Castelli F, Zanusso G, Pezzini A, Padovani A; SARS-CoV-2 related encephalopaties (ENCOVID) Study Group. Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome

Coronavirus 2-Related Encephalitis: The ENCOVID Multicenter Study. *J Infect Dis* 2021; **223**: 28-37 [PMID: 32986824 DOI: 10.1093/infdis/jiaa609]

115 **Pilotto A**, Masciocchi S, Volonghi I, De Giuli V, Caprioli F, Mariotto S, Ferrari S, Bozzetti S, Imarisio A, Risi B, Premi E, Benussi A, Focà E, Castelli F, Zanusso G, Monaco S, Stefanelli P, Gasparotti R, Zekeridou A, McKeon A, Ashton NJ, BlennoW K, Zetterberg H, Padovani A. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Encephalitis Is a Cytokine Release Syndrome: Evidences From Cerebrospinal Fluid Analyses. *Clin Infect Dis* 2021; **73**: e3019-e3026 [PMID: 33395482 DOI: 10.1093/cid/ciaa1933]

116 **Rhea EM**, Banks WA. Role of the Blood-Brain Barrier in Central Nervous System Insulin Resistance. *Front Neurosci* 2019; **13**: 521 [PMID: 31213970 DOI: 10.3389/fnins.2019.00521]

117 **Małkiewicz MA**, Szarmach A, Sabisz A, Cubała WJ, Szurowska E, Winklewski PJ. Blood-brain barrier permeability and physical exercise. *J Neuroinflammation* 2019; **16**: 15 [PMID: 30678702 DOI: 10.1186/s12974-019-1403-x]

118 **Abbott NJ**, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis* 2010; **37**: 13-25 [PMID: 19664713 DOI: 10.1016/j.nbd.2009.07.030]

119 **Prasad S**, Sajja RK, Naik P, Cucullo L. Diabetes Mellitus and Blood-Brain Barrier Dysfunction: An Overview. *J Pharmacovigil* 2014; **2**: 125 [PMID: 25632404 DOI: 10.4172/2329-6887.1000125]

120 **Hussain T**, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? *Oxid Med Cell Longev* 2016; **2016**: 7432797 [PMID: 27738491 DOI: 10.1155/2016/7432797]

121 **Dénes A**, Ferenczi S, Kovács KJ. Systemic inflammatory challenges compromise survival after experimental stroke *via* augmenting brain inflammation, blood- brain barrier damage and brain oedema independently of infarct size. *J Neuroinflammation* 2011; **8**: 164 [PMID: 22114895 DOI: 10.1186/1742-2094-8-164]

122 **Sandoval KE**, Witt KA. Blood-brain barrier tight junction permeability and ischemic stroke. *Neurobiol Dis* 2008; **32**: 200-219 [PMID: 18790057 DOI: 10.1016/j.nbd.2008.08.005]

123 **Li MY**, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020; **9**: 45 [PMID: 32345362 DOI: 10.1186/s40249-020-00662-x]

124 **Alexopoulos H**, Magira E, Bitzogli K, Kafasi N, Vlachoyiannopoulos P, Tzioufas A, Kotanidou A, Dalakas MC. Anti-SARS-CoV-2 antibodies in the CSF, blood-brain barrier dysfunction, and neurological outcome: Studies in 8 stuporous and comatose patients. *Neurol Neuroimmunol Neuroinflamm* 2020; **7** [PMID: 32978291 DOI: 10.1212/NXI.0000000000000893]

125 **Guilmot A**, Maldonado Slootjes S, Sellimi A, Bronchain M, Hanseeuw B, Belkhir L, Yombi JC, De Greef J, Pothen L, Yildiz H, Duprez T, Fillée C, Anantharajah A, Capes A, Hantson P, Jacquerye P, Raymackers JM, London F, El Sankari S, Ivanoiu A, Maggi P, van Pesch V. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. *J Neurol* 2021; **268**: 751-757 [PMID: 32734353 DOI: 10.1007/s00415-020-10108-x]

126 **Eshaq RS**, Aldalati AMZ, Alexander JS, Harris NR. Diabetic retinopathy: Breaking the barrier. *Pathophysiology* 2017; **24**: 229-241 [PMID: 28732591 DOI: 10.1016/j.pathophys.2017.07.001]

127 **Teo ZL**, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, Bikbov MM, Wang YX, Tang Y, Lu Y, Wong IY, Ting DSW, Tan GSW, Jonas JB, Sabanayagam C, Wong TY, Cheng CY. Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045: Systematic Review and Meta-analysis. *Ophthalmology* 2021; **128**: 1580-1591 [PMID: 33940045 DOI: 10.1016/j.ophtha.2021.04.027]

128 **Duh EJ**, Sun JK, Stitt AW. Diabetic retinopathy: current understanding, mechanisms, and treatment strategies. *JCI Insight* 2017; **2** [PMID: 28724805 DOI: 10.1172/jci.insight.93751]

129 **Wang W**, Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. *Int J Mol Sci* 2018; **19** [PMID: 29925789 DOI: 10.3390/ijms19061816]

130 **Huang H**, He J, Johnson D, Wei Y, Liu Y, Wang S, Lutty GA, Duh EJ, Semba RD. Deletion of placental growth factor prevents diabetic retinopathy and is associated with Akt activation and HIF1α-VEGF pathway inhibition. *Diabetes* 2015; **64**: 200-212 [PMID: 25187372 DOI: 10.2337/db14-0016]

131 **Lupo G**, Motta C, Giurdanella G, Anfuso CD, Alberghina M, Drago F, Salomone S, Bucolo C. Role of phospholipases A2 in diabetic retinopathy: in vitro and in vivo studies. *Biochem Pharmacol* 2013; **86**: 1603-1613 [PMID: 24076420 DOI: 10.1016/j.bcp.2013.09.008]

132 **Giurdanella G**, Lupo G, Gennuso F, Conti F, Furno DL, Mannino G, Anfuso CD, Drago F, Salomone S, Bucolo C. Activation of the VEGF-A/ERK/PLA2 Axis Mediates Early Retinal Endothelial Cell Damage Induced by High Glucose: New Insight from an In Vitro Model of Diabetic Retinopathy. *Int J Mol Sci* 2020; **21** [PMID: 33065984 DOI: 10.3390/ijms21207528]

133 **Chang YS**, Ho CH, Chu CC, Wang JJ, Tseng SH, Jan RL. Risk of retinal artery occlusion in patients with diabetes mellitus: A retrospective large-scale cohort study. *PLoS One* 2018; **13**: e0201627 [PMID: 30091989 DOI: 10.1371/journal.pone.0201627]

134 **Suzuki Y**, Nakazawa M, Suzuki K, Yamazaki H, Miyagawa Y. Expression profiles of cytokines and chemokines in vitreous fluid in diabetic retinopathy and central retinal vein occlusion. *Jpn J Ophthalmol* 2011; **55**: 256-263 [PMID: 21538000 DOI: 10.1007/s10384-011-0004-8]

135 **Tang J**, Allen Lee C, Du Y, Sun Y, Pearlman E, Sheibani N, Kern TS. MyD88-dependent pathways in leukocytes affect the retina in diabetes. *PLoS One* 2013; **8**: e68871 [PMID: 23874797 DOI: 10.1371/journal.pone.0068871]

136 **Joussen AM**, Poulaki V, Mitsiades N, Cai WY, Suzuma I, Pak J, Ju ST, Rook SL, Esser P, Mitsiades CS, Kirchhof B, Adamis AP, Aiello LP. Suppression of Fas-FasL-induced endothelial cell apoptosis prevents diabetic blood-retinal barrier breakdown in a model of streptozotocin-induced diabetes. *FASEB J* 2003; **17**: 76-78 [PMID: 12475915 DOI: 10.1096/fj.02-0157fje]

137 **Boss JD**, Singh PK, Pandya HK, Tosi J, Kim C, Tewari A, Juzych MS, Abrams GW, Kumar A. Assessment of Neurotrophins and Inflammatory Mediators in Vitreous of Patients With Diabetic Retinopathy. *Invest Ophthalmol Vis Sci* 2017; **58**: 5594-5603 [PMID: 29084332 DOI: 10.1167/iovs.17-21973]

138 **Portillo JC**, Lopez Corcino Y, Miao Y, Tang J, Sheibani N, Kern TS, Dubyak GR, Subauste CS. CD40 in Retinal Müller Cells Induces P2X7-Dependent Cytokine Expression in Macrophages/Microglia in Diabetic Mice and Development of

Early Experimental Diabetic Retinopathy. *Diabetes* 2017; **66**: 483-493 [PMID: 27474370 DOI: 10.2337/db16-0051]
139 **Tien T**, Zhang J, Muto T, Kim D, Sarthy VP, Roy S. High Glucose Induces Mitochondrial Dysfunction in Retinal Müller Cells: Implications for Diabetic Retinopathy. *Invest Ophthalmol Vis Sci* 2017; **58**: 2915-2921 [PMID: 28586916 DOI: 10.1167/iovs.16-21355]
140 **Silva VAO**, André ND, Sousa TAE, Alves VM, Kettelhut IDC, De Lucca FL. Nuclear PKR in retinal neurons in the early stage of diabetic retinopathy in streptozotocininduced diabetic rats. *Mol Med Rep* 2021; **24** [PMID: 34184090 DOI: 10.3892/mmr.2021.12253]
141 **Piano I**, Novelli E, Della Santina L, Strettoi E, Cervetto L, Gargini C. Involvement of Autophagic Pathway in the Progression of Retinal Degeneration in a Mouse Model of Diabetes. *Front Cell Neurosci* 2016; **10**: 42 [PMID: 26924963 DOI: 10.3389/fncel.2016.00042]
142 **Sasaki M**, Ozawa Y, Kurihara T, Kubota S, Yuki K, Noda K, Kobayashi S, Ishida S, Tsubota K. Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. *Diabetologia* 2010; **53**: 971-979 [PMID: 20162412 DOI: 10.1007/s00125-009-1655-6]
143 **Loffredo L**, Pacella F, Pacella E, Tiscione G, Oliva A, Violi F. Conjunctivitis and COVID-19: A meta-analysis. *J Med Virol* 2020; **92**: 1413-1414 [PMID: 32330304 DOI: 10.1002/jmv.25938]
144 **Casagrande M**, Fitzek A, Spitzer M, Püschel K, Glatzel M, Krasemann S, Aepfelbacher M, Nörz D, Lütgehetmann M, Pfefferle S, Schultheiss M. Detection of SARS-CoV-2 genomic and subgenomic RNA in retina and optic nerve of patients with COVID-19. *Br J Ophthalmol* 2021 [PMID: 33836988 DOI: 10.1136/bjophthalmol-2020-318618]
145 **Azzolini C**, Donati S, Premi E, Baj A, Siracusa C, Genoni A, Grossi PA, Azzi L, Sessa F, Dentali F, Severgnini P, Minoja G, Cabrini L, Chiaravalli M, Veronesi G, Carcano G, Maffioli LS, Tagliabue A. SARS-CoV-2 on Ocular Surfaces in a Cohort of Patients With COVID-19 From the Lombardy Region, Italy. *JAMA Ophthalmol* 2021; **139**: 956-963 [PMID: 33662099 DOI: 10.1001/jamaophthalmol.2020.5464]
146 **Zhou L**, Xu Z, Castiglione GM, Soiberman US, Eberhart CG, Duh EJ. ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection. *Ocul Surf* 2020; **18**: 537-544 [PMID: 32544566 DOI: 10.1016/j.jtos.2020.06.007]
147 **Menuchin-Lasowski Y**, Schreiber A, Lecanda A, Mecate-Zambrano A, Brunotte L, Psathaki OE, Ludwig S, Rauen T, Schöler HR. SARS-CoV-2 infects and replicates in photoreceptor and retinal ganglion cells of human retinal organoids. *Stem Cell Reports* 2022; **17**: 789-803 [PMID: 35334213 DOI: 10.1016/j.stemcr.2022.02.015]
148 **Sen M**, Honavar SG, Sharma N, Sachdev MS. COVID-19 and Eye: A Review of Ophthalmic Manifestations of COVID-19. *Indian J Ophthalmol* 2021; **69**: 488-509 [PMID: 33595463 DOI: 10.4103/ijo.IJO_297_21]
149 **Sindhuja K**, Lomi N, Asif MI, Tandon R. Clinical profile and prevalence of conjunctivitis in mild COVID-19 patients in a tertiary care COVID-19 hospital: A retrospective cross-sectional study. *Indian J Ophthalmol* 2020; **68**: 1546-1550 [PMID: 32709772 DOI: 10.4103/ijo.IJO_1319_20]
150 **Chen L**, Deng C, Chen X, Zhang X, Chen B, Yu H, Qin Y, Xiao K, Zhang H, Sun X. Ocular manifestations and clinical characteristics of 535 cases of COVID-19 in Wuhan, China: a cross-sectional study. *Acta Ophthalmol* 2020; **98**: e951-e959 [DOI: 10.1111/aos.14472]
151 **Guo D**, Xia J, Wang Y, Zhang X, Shen Y, Tong JP. Relapsing viral keratoconjunctivitis in COVID-19: a case report. *Virol J* 2020; **17**: 97 [PMID: 32641169 DOI: 10.1186/s12985-020-01370-6]
152 **Kruse A**, Thomsen RW, Hundborg HH, Knudsen LL, Sørensen HT, Schønheyder HC. Diabetes and risk of acute infectious conjunctivitis--a population-based case-control study. *Diabet Med* 2006; **23**: 393-397 [PMID: 16620267 DOI: 10.1111/j.1464-5491.2006.01812.x]
153 **Komorita Y**, Minami M, Maeda Y, Yoshioka R, Ohkuma T, Kitazono T. Prevalence of bone fracture and its association with severe hypoglycemia in Japanese patients with type 1 diabetes. *BMJ Open Diabetes Res Care* 2021; **9** [PMID: 33888545 DOI: 10.1136/bmjdrc-2020-002099]
154 **Wang H**, Ba Y, Xing Q, Du JL. Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis. *BMJ Open* 2019; **9**: e024067 [PMID: 30610024 DOI: 10.1136/bmjopen-2018-024067]
155 **Roy B**. Biomolecular basis of the role of diabetes mellitus in osteoporosis and bone fractures. *World J Diabetes* 2013; **4**: 101-113 [PMID: 23961320 DOI: 10.4239/wjd.v4.i4.101]
156 **Lauwers M**, Au M, Yuan S, Wen C. COVID-19 in Joint Ageing and Osteoarthritis: Current Status and Perspectives. *Int J Mol Sci* 2022; **23** [PMID: 35054906 DOI: 10.3390/ijms23020720]
157 **di Filippo L**, Frara S, Giustina A. The emerging osteo-metabolic phenotype of COVID-19: clinical and pathophysiological aspects. *Nat Rev Endocrinol* 2021; **17**: 445-446 [PMID: 34079100 DOI: 10.1038/s41574-021-00516-y]
158 **Queiroz-Junior CM**, Santos ACPM, Galvão I, Souto GR, Mesquita RA, Sá MA, Ferreira AJ. The angiotensin converting enzyme 2/angiotensin-(1-7)/Mas Receptor axis as a key player in alveolar bone remodeling. *Bone* 2019; **128**: 115041 [PMID: 31442676 DOI: 10.1016/j.bone.2019.115041]
159 **Awosanya OD**, Dalloul CE, Blosser RJ, Dadwal UC, Carozza M, Boschen K, Klemsz MJ, Johnston NA, Bruzzaniti A, Robinson CM, Srour EF, Kacena MA. Osteoclast-mediated bone loss observed in a COVID-19 mouse model. *Bone* 2022; **154**: 116227 [PMID: 34607050 DOI: 10.1016/j.bone.2021.116227]
160 **Tripathy AS**, Vishwakarma S, Trimbake D, Gurav YK, Potdar VA, Mokashi ND, Patsute SD, Kaushal H, Choudhary ML, Tilekar BN, Sarje P, Dange VS, Abraham P. Pro-inflammatory CXCL-10, TNF-α, IL-1β, and IL-6: biomarkers of SARS-CoV-2 infection. *Arch Virol* 2021; **166**: 3301-3310 [PMID: 34554303 DOI: 10.1007/s00705-021-05247-z]
161 **Demir M**, Demir F, Aygun H. Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease. *J Med Virol* 2021; **93**: 2992-2999 [PMID: 33512007 DOI: 10.1002/jmv.26832]
162 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]
163 **Harmer D**, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of

angiotensin converting enzyme. *FEBS Lett* 2002; **532**: 107-110 [PMID: 12459472 DOI: 10.1016/s0014-5793(02)03640-2]

164 **Yan R**, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 2020; **367**: 1444-1448 [PMID: 32132184 DOI: 10.1126/science.abb2762]

165 **Giobbe GG**, Bonfante F, Jones BC, Gagliano O, Luni C, Zambaiti E, Perin S, Laterza C, Busslinger G, Stuart H, Pagliari M, Bortolami A, Mazzetto E, Manfredi A, Colantuono C, Di Filippo L, Pellegata AF, Panzarin V, Thapar N, Li VSW, Eaton S, Cacchiarelli D, Clevers H, Elvassore N, De Coppi P. SARS-CoV-2 infection and replication in human gastric organoids. *Nat Commun* 2021; **12**: 6610 [PMID: 34785679 DOI: 10.1038/s41467-021-26762-2]

166 **Lin L**, Jiang X, Zhang Z, Huang S, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020; **69**: 997-1001 [PMID: 32241899 DOI: 10.1136/gutjnl-2020-321013]

167 **Xu Z**, Tang M, Chen P, Cai H, Xiao F. SARS-CoV-2 Gastrointestinal Infection Prolongs the Time to Recover From COVID-19. *Front Med (Lausanne)* 2021; **8**: 683551 [PMID: 34150815 DOI: 10.3389/fmed.2021.683551]

168 **Reszczyńska M**, Kempiński R. The Prevalence of Enteropathy Symptoms from the Lower Gastrointestinal Tract and the Evaluation of Anorectal Function in Diabetes Mellitus Patients. *J Clin Med* 2021; **10** [PMID: 33499216 DOI: 10.3390/jcm10030415]

169 **Narbonne H**, Paquis-Fluckinger V, Valero R, Heyries L, Pellissier JF, Vialettes B. Gastrointestinal tract symptoms in Maternally Inherited Diabetes and Deafness (MIDD). *Diabetes Metab* 2004; **30**: 61-66 [PMID: 15029099 DOI: 10.1016/S1262-3636(07)70090-3]

170 **Young RL**, Sutherland K, Pezos N, Brierley SM, Horowitz M, Rayner CK, Blackshaw LA. Expression of taste molecules in the upper gastrointestinal tract in humans with and without type 2 diabetes. *Gut* 2009; **58**: 337-346 [PMID: 19039089 DOI: 10.1136/gut.2008.148932]

171 **Peng YL**, Leu HB, Luo JC, Huang CC, Hou MC, Lin HC, Lee FY. Diabetes is an independent risk factor for peptic ulcer bleeding: a nationwide population-based cohort study. *J Gastroenterol Hepatol* 2013; **28**: 1295-1299 [PMID: 23488965 DOI: 10.1111/jgh.12190]

172 **Nie Z**, Xu L, Li C, Tian T, Xie P, Chen X, Li B. Association of endothelial progenitor cells and peptic ulcer treatment in patients with type 2 diabetes mellitus. *Exp Ther Med* 2016; **11**: 1581-1586 [PMID: 27168776 DOI: 10.3892/etm.2016.3114]

173 **Williams KH**, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic Fatty liver disease: a pathogenic duo. *Endocr Rev* 2013; **34**: 84-129 [PMID: 23238855 DOI: 10.1210/er.2012-1009]

174 **Dharmalingam M**, Yamasandhi PG. Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus. *Indian J Endocrinol Metab* 2018; **22**: 421-428 [PMID: 30090738 DOI: 10.4103/ijem.IJEM_585_17]

175 **Tomah S**, Alkhouri N, Hamdy O. Nonalcoholic fatty liver disease and type 2 diabetes: where do Diabetologists stand? *Clin Diabetes Endocrinol* 2020; **6**: 9 [PMID: 32518675 DOI: 10.1186/s40842-020-00097-1]

176 **Han JE**, Shin HB, Ahn YH, Cho HJ, Cheong JY, Park B, Kim SS. Relationship between the dynamics of non-alcoholic fatty liver disease and incident diabetes mellitus. *Sci Rep* 2022; **12**: 2538 [PMID: 35169195 DOI: 10.1038/s41598-022-06205-8]

177 **Kuzulugil D**, Papeix G, Luu J, Kerridge RK. Recent advances in diabetes treatments and their perioperative implications. *Curr Opin Anaesthesiol* 2019; **32**: 398-404 [PMID: 30958402 DOI: 10.1097/ACO.0000000000000735]

178 **Dixit SB**, Zirpe KG, Kulkarni AP, Chaudhry D, Govil D, Mehta Y, Jog SA, Khatib KI, Pandit RA, Samavedam S, Rangappa P, Bandopadhyay S, Shrivastav O, Mhatre U. Current Approaches to COVID-19: Therapy and Prevention. *Indian J Crit Care Med* 2020; **24**: 838-846 [PMID: 33132570 DOI: 10.5005/jp-journals-10071-23470]

179 **Hoffmann M**, Hofmann-Winkler H, Smith JC, Krüger N, Arora P, Sørensen LK, Søgaard OS, Hasselstrøm JB, Winkler M, Hempel T, Raich L, Olsson S, Danov O, Jonigk D, Yamazoe T, Yamatsuta K, Mizuno H, Ludwig S, Noé F, Kjolby M, Braun A, Sheltzer JM, Pöhlmann S. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. *EBioMedicine* 2021; **65**: 103255 [PMID: 33676899 DOI: 10.1016/j.ebiom.2021.103255]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 275-282

DOI: 10.5501/wjv.v11.i5.275

ISSN 2220-3249 (online)

MINIREVIEWS

Hepatitis B virus infection reactivation in patients under immunosuppressive therapies: Pathogenesis, screening, prevention and treatment

Anna Maria Spera

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cheng H, China; Zhu C, China

Received: March 18, 2022
Peer-review started: March 18, 2022
First decision: May 12, 2022
Revised: May 20, 2022
Accepted: July 26, 2022
Article in press: July 26, 2022
Published online: September 25, 2022

Anna Maria Spera, Infectious Disease Unit, Universitary Hospital OORR San Giovanni di Dio e Ruggi d'Aragona, Salerno 84131, Italy

Corresponding author: Anna Maria Spera, Doctor, PhD, Doctor, Postdoctoral Fellow, Infectious Disease Unit, Universitary Hospital OORR San Giovanni di Dio e Ruggi d'Aragona, Largo Ippocrate, Salerno 84131, Italy. annamariaspera@hotmail.it

Abstract

With a 5.3% of the global population involved, hepatitis B virus (HBV) is a major public health challenge requiring an urgent response. After a possible acute phase, the natural history of HBV infection can progress in chronicity. Patients with overt or occult HBV infection can undergo HBV reactivation (HBVr) in course of immunosuppressive treatments that, apart from oncological and hematological diseases, are also used in rheumatologic, gastrointestinal, neurological and dermatological settings, as well as to treat severe acute respiratory syndrome coronavirus 2 infection. The risk of HBV reactivation is related to the immune status of the patient and the baseline HBV infection condition. The aim of the present paper is to investigate the risk of HBVr in those not oncological settings in order to suggest strategies for preventing and treating this occurrence. The main studies about HBVr for patients with occult hepatitis B infection and chronic HBV infection affected by non-oncologic diseases eligible for immunosuppressive treatment have been analyzed. The occurrence of this challenging event can be reduced screening the population eligible for immunosuppressant to assess the best strategies according to any virological status. Further prospective studies are needed to increase data on the risk of HBVr related to newer immunomodulant agents employed in non-oncological setting.

Key Words: Hepatitis B Virus infection; Reactivation; Occult B infection; Chronic B infection; Immunosuppression; Disease-modifying antirheumatic drugs

Core Tip: Hepatitis B Virus (HBV) is a major public health challenge requiring an urgent response. Patients with overt or occult HBV infection can undergo HBV reactivation (HBVr) in course of immunosuppressive treatments, also used in rheumatologic, gastrointestinal, neurological and dermatological settings and to treat Sars severe acute respiratory syndrome coronavirus 2 infection. The aim of the present paper is to investigate the risk of HBVr in those not oncological settings in order to suggest strategies for preventing and treating this occurrence. The occurrence of this challenging event can be reduced screening the population eligible for immunosuppressant to assess the best strategies according to any virological status.

Citation: Spera AM. Hepatitis B virus infection reactivation in patients under immunosuppressive therapies: Pathogenesis, screening, prevention and treatment. *World J Virol* 2022; 11(5): 275-282
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/275.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.275

INTRODUCTION

Hepatitis B Virus (HBV) is a major public health challenge requiring an urgent response. According to the Global Hepatitis Report endorsed by World Health Organization (WHO) in 2017, the proportion of children 5 years old become chronically infected felt to 1.3% in 2015, compared with 4.7% of the pre-vaccine era, ranging 1980s to 2000s worldwide[1]. The spread of HBV vaccination during the childhood reduced the incidence of new HBV infections and the related possible chronicity[1]. However, it is estimated that about 3.5% of the global population (257 million people) in 2015 are affected by chronic HBV infection, most of them born before the availability of HBV vaccination: 68% of them are localized in Africa and in Western Pacific Region[1]. About 2.7 million of persons are co-infected with HBV, HDV and HIV and, among those with hepatitis, the estimated cumulative 5 years incidence of progression is estimated around 8%-20%[2] and 5%-15% of cirrhotic patients develop hepatocellular cancer (HCC) during the lifetime[2].

HBV belongs to the Hepadnaviridae family. It is a double stranded DNA virus with a lipoprotein envelope and a high hepatic tropism. Its transmission happens through the vertical route or intra-family contacts among infants and by sexual or parenteral contact. The first case is typical in regions with the highest prevalence determining the high endemicity described in these areas and the associated high rate of chronicization. The second case is common in regions with low prevalence among adults; nevertheless, high Hepatitis B surface antigen (HBsAg) prevalence there, can be encountered among immigrants from high HBV endemic area, People Who Inject Drugs (PWID), Men who have Sex with Men and People Living With HIV[3]. After a possible acute phase, the natural history of HBV infection can progress in chronicity, which consists of 5 phases, based on the HBeAg serostatus, the viral load, the transaminases levels and the grading/staging of the liver disease[4-6]. During the first one, once known as "immunotollerant phase" and currently named "HBeAg positive chronic infection", the immune response against the virus is limited or absent: Thus, there is a high viral replication with HBeAg positivity, unchanged transaminases and liver parenchyma. The second phase, called "HBeAg positive chronic hepatitis" is characterized by the production of active immune response of the host against viral antigens, with a reduction of viral load and an increase of transaminase levels along with liver inflammation. In case of immune response's control of the infection, the infection moves to the third phase, known as "HBeAg negative chronic infection" with HBeAg sero-clearance, low viral replication (HBV-DNA < 2000 IU/mL), normalization of transaminase levels and mild liver inflammation. However, severe liver inflammation and rapid progression of disease can still occurs, despite the presence of HBeAb, in case of mutation of the pre-core or basal core promoter regions. The fourth phase is the "HBeAg negative chronic hepatitis" one, with detectable anti HBe, moderate levels of serum HBV-DNA and ALT with hepatic necroinflammation. The last phase is HBsAg negative phase, with serum negative HBsAg and positive anti HBc with or without anti HBs. This phase is also called "occult hepatitis B virus infection" (OBI) defined as the replication of competent HBV DNA in the liver and blood in the absence of detectable HBsAg that contributes to the advancement of liver fibrosis and development of HCC. Patients with overt or occult hepatitis B virus infection can undergo HBV reactivation (HBVr) in course of immunosuppressive treatments. Apart from oncological and hematological diseases, immunosuppressants are also used in rheumatologic, gastrointestinal, neurological and dermatological settings, as well as to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The aim of the present paper is to investigate the risk of HBVr in those not oncological settings in order to suggest strategies for preventing and treating this occurrence. HBVr can be defined as the novo detection of HBV DNA or a ≥ 10 fold increase in HBV DNA level compared to its baseline value in HBsAg positive subject and seroreversion to HBsAg positive status in previously negative patients[7]. The viral genome can be detected as cccDNA in hepatocites. The HBVr following immunosuppressive

treatments is commensurate to patient's characteristics and the kind of immunosuppressive agent employed. As regards as host characteristics, apart from the male gender[8], the old age[9] and any underlying lymphoproliferative diseases[10], the serostatus during immunosuppression is crucial. In fact, patients affected by chronic HBV infection have a greater risk of reactivation compared to those with OBI. Moreover, the presence of anti HBs among HBsAg negative subjects, is related to a lower risk of reactivation even in hematologic setting, according to Seto *et al*[11]. Regarding immunosuppressant, the risk of related HBVr can be classified as high, with frequency of reactivation > 10% without prophylaxis[7]; medium, with frequency of reactivation 1%-10%[12] or low, with frequency of reactivation < 1%[13]. A high risk of reactivation is described with the administration of B cell depleting agents[14], anthracycline derivatives[15] and corticosteroids at high dose, for treatments of more than 4 wk[7], along with inhibitors of cytokine, integrin[16], tyrosine kinases[17] and JAK kinases inhibitors[18].

The risk of HBVr is related to the immune status of the patient and the baseline HBV infection condition. The risk of developing HBVr is quite low for HBsAg positive or negative patients under csDMARDs and short low dose cortisone based therapy. The same risk is however higher for patients under anti-TNFs and tyrosine kinase inhibitors: when in combination, the risk is the highest.

Here reported are the main studies about HBVr for patients with OBI and chronic HBV infection affected by non-oncologic diseases eligible for immunosuppressive treatment.

RISK OF HBVR IN PATIENTS AFFECTED BY CORONAVIRUS DISEASE 2019

The ongoing SARS-CoV-2 pandemic, responsible for more than 50 million cases from 2020, still represents a challenge for the scientific community, not only regarding its pathogenesis but mostly its treatment. In fact, despite there is no available curative option yet, several immunosuppressive and immunomodulating agents have been proposed for the treatment of coronavirus disease 2019 (COVID-19) pneumonia in those last two years. Corticosteroids are currently recommended by the WHO for severe COVID-19; other employed immunosuppressive agents are interleukin 6 inhibitors (such as tocilizumab), JAK inhibitors (such as baricitinib, tofacitinib and ruxolitinib) associated with risk of HBVr in other settings[19]. Apart from a couple of retrospective studies reporting HBVr among patients receiving methylprednisolone[20] and tocilizumab[21], no data are already available in literature about the risk of HBVr among patients with COVID-19 treated with immunosuppressants. The short duration of immunosuppressive treatment in this specific setting probably limits the risk of HBVr. However, all the patients with COVID-19 pneumonia eligible for corticosteroid or immunosuppressants are routinely screened for HBV infection according to national and international guidelines to evaluate the risk of HBVr prior to prescribe those above mentioned drugs and start antiviral prophylaxis when needed.

HBVR IN RHEUMATOLOGIC SETTING

The spread of rheumatic diseases in Western Countries resulted in a greater interest of the scientific community engaged in research of efficacious therapeutic options. Giving that recognize an autoimmune pathogenesis, therapeutic committed strategies are based on immunosuppression and include Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), analgesic drugs and disease-modifying antirheumatic drugs (DMARDs) which can be divided into conventional synthetics (csDMARDs) and biological drugs (bDMARDs). The csDMARDs include leflunomide, azathioprine, sulfasalazine, hydroxychloroquine; gold salts, methotrexate and minocycline[22]. The bDMARDs can be instead divided into IL-1 inhibitors (canakinumab and anakinra), TNF inhibitors (infliximab, adalimumab, etanercept, certolizumab and golimumab), inhibitors of IL-17 (ixekizumab and secukinumab), IL-6 and IL-6R inhibitors (respectively, tocilizumab and sarilumab), IL-23 inhibitors (guselkumab and ustekinumab), and JAK kinase inhibitors (peficitinib, tofacitinib, filgotinib, upadacitinib and baricitinib) based on their mechanism of action[23,24].

HBVr is quite common among unvaccinated people with rheumatic diseases (RD); Canzoni *et al*[25] reports that 2% of this study population (292 patients) affected by RD had a prevalence of HBsAg positivity and any kind of HBV infection markers retrieved in 24% of cases (70 patients): At least, 30% of those tested positive patients were unaware of their condition[25]. Despite European Association for the Study of Liver (EASL)[4] and AASLD[23] indication about HBV routine screening schedule before starting immunosuppressive therapies, the coverage still appears inadequate as in 2015 Lin *et al*[27] demonstrated in a retrospective cross national comparison of hepatic testing in rheumatic arthritis (RA) patients eligible to DMARD between the US and Taiwan[26]. The authors found that only 20.3% of patients in the US and 24.5% of patients in Taiwan were tested for HBV infection[27]. Similar results were found in Japan[28] where laboratory test for HBsAg, anti HBs and anti HBc were performed only in 28.33%, 12.52% and 14.63% of patients with RA, at baseline[28]. The deleterious role of HBV infection in recovery of patients with RA has been investigated by Chen *et al*[29]: Their case control study evaluated 32 patients with RA and chronic HBV infection, eligible to glucocorticosteroids, DMARDs and biologics. The study records, in a year, a worsening of hepatopathy of patients with chronic HBV

infection under immunosuppressant with no antiviral intervention; moreover patients failed in achieving the therapeutic target in 6 mo. HBVr was reported in 34% of patients at one year follow up. Among those 32 studied patients, 14 were treated with prophylaxis with lamivudine, adefovir or entecavir: 4 of them developed HBVr and 2 of them also a hepatitis flare. The remaining 18 patients enrolled did not received antiviral prophylaxis and 7 of them experienced HBVr.

HBVR IN DERMATOLOGIC SETTING

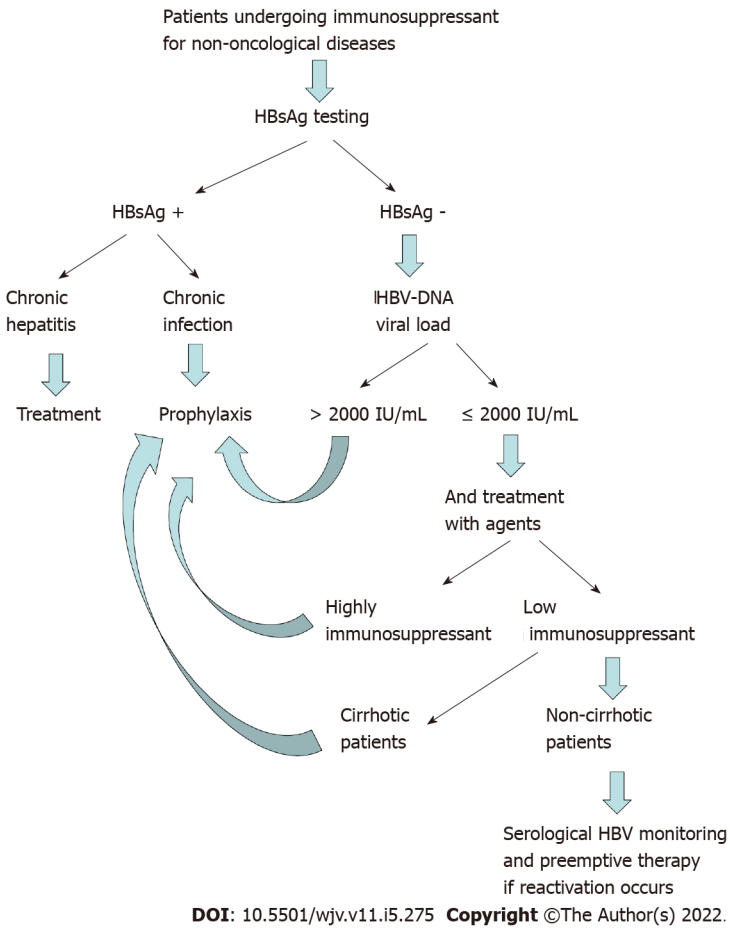
cDMARDs such as acitretin, methotrexate and cyclosporin A along with bDMARDs including etanercept, infliximab, golimumab, certolizumab, adalimumab and secukinumab are currently used in several different dermatologic diseases, like psoriasis. The safety of those immunosuppressive drugs is not properly investigated, since trials conceived to explore new efficient drugs barely involve HBV patients. However, the reactivation risk of HBV in 14 (11 HBsAg positive, 3 HBsAg negative/HBcAb positive) patients with psoriasis eligible for ustekinumab based therapy has been evaluated by Chiu *et al* [30]. No reactivation was observed among all the HBsAg negative HBcAb positive patients, while HBVr was registered among two of the HBsAg positive patients under ustekinumab not receiving prophylaxis [30]. The incidence rate of annual HBVr was calculated by Ting *et al*[31] in a retrospective cohort study including 54 inactive HBV carrier patients without prophylaxis and occult hepatitis B virus infection: only 1.5% of OBI patients developed HBVr, while 17.4% of inactive HBV carriers experienced it, under ustekinumab. According to the available evidence, HBsAg positive patients under immunosuppressive drugs at moderate risk of HBVr should be prevented with antiviral based prophylaxis, while HBsAg negative/HBcAb positive patients eligible for immunosuppressant should be close monitored in order to prescribe pre-emptive therapy, when needed.

RISK OF HBVR IN GASTROENTEROLOGICAL SETTING

The use of immunosuppressants is often required for patients affected by autoimmune, inflammatory gastroenterological disorders like Crohn disease and ulcerative colitis. The drug selected depends on the disease severity and the relapsing or remitting cause of the inflammatory bowel disease (IBD). Corticosteroids, immunomodulatory agents (methotrexate, azathioprine, mercaptopurine), anti IL12/23 p40 antibodies, JAK inhibitors, anti-adhesion therapies and biological therapies such as TNF inhibitors are widely used. Studies performed to evaluate the risk of HBVr in HBsAg positive patients with gastroenteric diseases under immunosuppressive agents clearly demonstrated that the use of more than two immunosuppressive agents is an independent predictor of HBVr[32]. A lower rate of reactivation has been registered for patients treated with antiviral prophylaxis[33]. Few cases of HBVr have been reported among HBsAg negative/HBcAb positive patients with IBD under immunosuppressants[34-37]. Thus, a complete serology for HBV is required in IBD patients to determine the active/inactive carrier status of IBD patients eligible for immunosuppressants in order to determine whether to treat, prescribe prophylaxis or monitor them, according to their HBV profile. HBsAg positive patients with IBD should undergo prophylaxis with nucleotide or nucleoside analogues before starting moderate or high doses steroids for more than 4 wk, anti TNF drugs, azathioprine or ustekinumab. This prophylaxis should last for at least one year after discontinuing immunomodulants. No standardized approach exists for HBsAg negative/HBcAb positive patients with IBD. In fact, while the American Gastroenterology Association recommends antiviral prophylaxis for this population under anti TNF or corticosteroids at moderate/high doses[38], the EASL and The European Crohn and Colitis Organization both recommend close monitoring of this population and the use of antiviral agents only after detection of HBV DNA viremia or seroreversion to HBsAg positivity[4,39].

HBVR RISK IN NEUROLOGICAL SETTING

Among neurodegenerative diseases requiring disease modifying drugs to be treated, multiple sclerosis (MS) is one of the most frequent. MS causes chronic inflammation of the central nervous system, demyelination and disability. Apart from glucocorticoids, widely used in the acute phase of MS, DMD such as anti CD52 antibodies (alemtuzumab), anti CD20, a4b1 integrin inhibitor, sphingosine 1 phosphate inhibitors and its modulators (namely, fingolimod and siponimod), anti CD20 monoclonal antibodies[40] are employed to treat MS. Since limited data concerning the risk of HBVr in neurological setting are available from literature, there is no clear, definitive consensus on the best strategies to prevent HBVr in subjects with neurologic diseases requiring immunosuppressive drugs[41]. However, HBVr in a patient with a story of HBV infection and no proper prohylaxis, under ocrelizumab treatment for MS, has been reported by Ciardi *et al*[42], highlighting the need for antiviral prophylaxis in this setting.



DOI: 10.5501/wjv.v11.i5.275

Figure 1 Algorithm of hepatitis B virus reactivation diagnosis and management in patients eligible for immunosuppressant in non-oncological setting. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen.

PREVENTION AND TREATMENT OF HBVR

The risk of HBVr following immunosuppressive treatments depends mostly on type, duration and intensity of the iatrogenic immunosuppression. It is necessary to modulate any kind of therapeutic strategies to avoid HBVr, according to the risk profile of reactivation itself. Close monitoring of liver function test and qualitative/quantitative HBV DNA viral load is necessary at baseline, during and after the discontinuation of immunosuppressive therapy, taking into account that HBVr can still occur after the interruption of immunosuppressants. The management of HBVr in patients under immunosuppressant for non-oncological diseases depends, firstly, on HBsAg laboratory tests. In fact, in case of HBsAg positive value, patients with chronic hepatitis must undergo treatments of HBV with high genetic barrier nucleo(t)side analogues (entecavir, tenofovir, tenofovir alafenamide)[4,38,43-45], while those with chronic infection must be considered for prophylaxis with lamivudine in case of undetectable HBV DNA or in case of expected duration of prophylaxis less than 6 mo[38]. Otherwise, because of emergence of resistance to lamivudine in patients requiring therapy for more than 6 mo long duration, the above mentioned newer nucleoside agents can represent an effective option for antiviral prophylaxis in this setting. In case of HBsAg negative and HBcAb positive laboratory test results, the HBV DNA viral load can guide physicians in determining if the patient requires prophylaxis or clinical and laboratory's close monitoring, followed, where appropriate, by preemptive therapy[4,38]. In fact, in case of HBV DNA positivity or in case of HBV DNA negativity occurred in patients under agents at moderate or high risk of immunosuppression, or affected by liver cirrhosis, a trimestral monitoring of HBsAg/HBsAb and HBV DNA is enough, and a preemptive therapy can be considered in case of reactivation[4,38]. The prophylaxis must be started before the immunosuppressive regimen and continued up to 12-18 mo after the end of the immunosuppressive treatment[38,46-48]. In Figure 1 briefly is summarized the algorithm of HBVr diagnosis and management in patients eligible for immunosuppressant in non-oncological setting.

CONCLUSION

The widespread use of immunosuppressive and immunomodulant therapies in non-oncological setting highlighted the risk of HBVr in patients with overt or occult hepatitis B virus infection. The occurrence of this challenging event can be reduced screening the population eligible for immunosuppressant to assess the best strategies according to any virological status. Further prospective studies are needed to increase data on the risk of HBVr related to newer immunomodulant agents employed in non-oncological setting, in order to better prevent and treat HBVr recurrence.

ACKNOWLEDGEMENTS

Dr Spera sincerely thanks Prof Grazia Tosone, MD for having taught her almost everything she knows about hepatitis B and for having passed on to her the love and passion for the study of infectious diseases.

FOOTNOTES

Author contributions: Spera AM study conception and design; data collection; analysis and interpretation of results; draft manuscript preparation; Spera AM finally reviewed the results and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Country/Territory of origin: Italy

ORCID number: Anna Maria Spera 0000-0003-1292-3040.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **WHO|Guidelines for the Prevention**, Care and Treatment of Persons with Chronic Hepatitis B Infection. (accessed on 16 March 2022). Available from: http://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/
2 **Raimondo G**, Locarnini S, Pollicino T, Levrero M, Zoulim F, Lok AS; Taormina Workshop on Occult HBV Infection Faculty Members. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. *J Hepatol* 2019; **71**: 397-408 [PMID: 31004683 DOI: 10.1016/j.jhep.2019.03.034]
3 **van Houdt R**, Bruisten SM, Speksnijder AG, Prins M. Unexpectedly high proportion of drug users and men having sex with men who develop chronic hepatitis B infection. *J Hepatol* 2012; **57**: 529-533 [PMID: 22612997 DOI: 10.1016/j.jhep.2012.04.030]
4 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
5 **Ditto MC**, Parisi S, Varisco V, Talotta R, Batticciotto A, Antivalle M, Gerardi MC, Agosti M, Borrelli R, Fusaro E, Sarzi-Puttini P. Prevalence of hepatitis B virus infection and risk of reactivation in rheumatic population undergoing biological therapy. *Clin Exp Rheumatol* 2021; **39**: 546-554 [PMID: 32940216 DOI: 10.55563/clinexprheumatol/c25fja]
6 **Mok CC**. Hepatitis B and C infection in patients undergoing biologic and targeted therapies for rheumatic diseases. *Best Pract Res Clin Rheumatol* 2018; **32**: 767-780 [PMID: 31427054 DOI: 10.1016/j.berh.2019.03.008]
7 **Perrillo RP**, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 221-244.e3 [PMID: 25447852 DOI: 10.1053/j.gastro.2014.10.038]
8 **Yeo W**, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; **62**: 299-307 [PMID: 11055239 DOI: 10.1002/1096-9071(200011)62:3<299::aid-jmv1>3.0.co;2-0]
9 **Yeo W**, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, Lam KC, Johnson PJ. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer*

2004; **90**: 1306-1311 [PMID: 15054446 DOI: 10.1038/sj.bjc.6601699]
10 **Wang B**, Mufti G, Agarwal K. Reactivation of hepatitis B virus infection in patients with hematologic disorders. *Haematologica* 2019; **104**: 435-443 [PMID: 30733266 DOI: 10.3324/haematol.2018.210252]
11 **Seto WK**, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lie AK, Lai CL, Kwong YL, Yuen MF. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014; **32**: 3736-3743 [PMID: 25287829 DOI: 10.1200/JCO.2014.56.7081]
12 **Pisaturo M**, Di Caprio G, Calò F, Portunato F, Martini S, Coppola N. Management of HBV reactivation in non-oncological patients. *Expert Rev Anti Infect Ther* 2018; **16**: 611-624 [PMID: 30058401 DOI: 10.1080/14787210.2018.1505501]
13 **Smalls DJ**, Kiger RE, Norris LB, Bennett CL, Love BL. Hepatitis B Virus Reactivation: Risk Factors and Current Management Strategies. *Pharmacotherapy* 2019; **39**: 1190-1203 [PMID: 31596963 DOI: 10.1002/phar.2340]
14 **Mozessohn L**, Chan KK, Feld JJ, Hicks LK. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for lymphoma: a meta-analysis. *J Viral Hepat* 2015; **22**: 842-849 [PMID: 25765930 DOI: 10.1111/jvh.12402]
15 **Paul S**, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Hepatitis B Virus Reactivation and Prophylaxis During Solid Tumor Chemotherapy: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016; **164**: 30-40 [PMID: 26595058 DOI: 10.7326/M15-1121]
16 **Navarro R**, Vilarrasa E, Herranz P, Puig L, Bordas X, Carrascosa JM, Taberner R, Ferrán M, García-Bustinduy M, Romero-Maté A, Pedragosa R, García-Diez A, Daudén E. Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. *Br J Dermatol* 2013; **168**: 609-616 [PMID: 22985451 DOI: 10.1111/bjd.12045]
17 **Orlandi EM**, Elena C, Bono E. Risk of hepatitis B reactivation under treatment with tyrosine-kinase inhibitors for chronic myeloid leukemia. *Leuk Lymphoma* 2017; **58**: 1764-1766 [PMID: 27892750 DOI: 10.1080/10428194.2016.1260127]
18 **Chen YM**, Huang WN, Wu YD, Lin CT, Chen YH, Chen DY, Hsieh TY. Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib: a real-world study. *Ann Rheum Dis* 2018; **77**: 780-782 [PMID: 28663308 DOI: 10.1136/annrheumdis-2017-211322]
19 **Harigai M**, Winthrop K, Takeuchi T, Hsieh TY, Chen YM, Smolen JS, Burmester G, Walls C, Wu WS, Dickson C, Liao R, Genovese MC. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open* 2020; **6** [PMID: 32098857 DOI: 10.1136/rmdopen-2019-001095]
20 **Liu J**, Wang T, Cai Q, Sun L, Huang D, Zhou G, He Q, Wang FS, Liu L, Chen J. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res* 2020; **50**: 1211-1221 [PMID: 32761993 DOI: 10.1111/hepr.13553]
21 **Rodríguez-Tajes S**, Miralpeix A, Costa J, López-Suñé E, Laguno M, Pocurull A, Lens S, Mariño Z, Forns X. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. *J Viral Hepat* 2021; **28**: 89-94 [PMID: 32969557 DOI: 10.1111/jvh.13410]
22 **Singh JA**, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T; American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2016; **68**: 1-25 [PMID: 26545825 DOI: 10.1002/acr.22783]
23 **Ramiro S**, Smolen JS, Landewé R, van der Heijde D, Dougados M, Emery P, de Wit M, Cutolo M, Oliver S, Gossec L. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2016; **75**: 490-498 [PMID: 26660203 DOI: 10.1136/annrheumdis-2015-208466]
24 **Ho Lee Y**, Gyu Song G. Comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib as monotherapy for active rheumatoid arthritis. *J Clin Pharm Ther* 2020; **45**: 674-681 [PMID: 32495356 DOI: 10.1111/jcpt.13142]
25 **Canzoni M**, Marignani M, Sorgi ML, Begini P, Biondo MI, Caporuscio S, Colonna V, Casa FD, Conigliaro P, Marrese C, Celletti E, Modesto I, Peragallo MS, Laganà B, Picchianti-Diamanti A, Rosa RD, Ferlito C, Salemi S, D'Amelio R, Stroffolini T. Prevalence of Hepatitis B Virus Markers in Patients with Autoimmune Inflammatory Rheumatic Diseases in Italy. *Microorganisms* 2020; **8** [PMID: 33207663 DOI: 10.3390/microorganisms8111792]
26 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]
27 **Lin TC**, Hashemi N, Kim SC, Yang YK, Yoshida K, Tedeschi S, Desai R, Solomon DH. Practice Pattern of Hepatitis B Testing in Rheumatoid Arthritis Patients: A Cross-National Comparison Between the US and Taiwan. *Arthritis Care Res (Hoboken)* 2018; **70**: 30-38 [PMID: 28320050 DOI: 10.1002/acr.23241]
28 **Fujita M**, Sugiyama M, Sato Y, Nagashima K, Takahashi S, Mizokami M, Hata A. Hepatitis B virus reactivation in patients with rheumatoid arthritis: Analysis of the National Database of Japan. *J Viral Hepat* 2018; **25**: 1312-1320 [PMID: 29770539 DOI: 10.1111/jvh.12933]
29 **Chen YL**, Lin JZ, Mo YQ, Ma JD, Li QH, Wang XY, Yang ZH, Yan T, Zheng DH, Dai L. Deleterious role of hepatitis B virus infection in therapeutic response among patients with rheumatoid arthritis in a clinical practice setting: a case-control study. *Arthritis Res Ther* 2018; **20**: 81 [PMID: 29720221 DOI: 10.1186/s13075-018-1548-5]
30 **Chiu HY**, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. *Br J Dermatol* 2013; **169**: 1295-1303 [PMID: 23746170 DOI: 10.1111/bjd.12461]
31 **Ting SW**, Chen YC, Huang YH. Risk of Hepatitis B Reactivation in Patients with Psoriasis on Ustekinumab. *Clin Drug Investig* 2018; **38**: 873-880 [PMID: 29968197 DOI: 10.1007/s40261-018-0671-z]
32 **Loras C**, Gisbert JP, Mínguez M, Merino O, Bujanda L, Saro C, Domenech E, Barrio J, Andreu M, Ordás I, Vida L,

Bastida G, González-Huix F, Piqueras M, Ginard D, Calvet X, Gutiérrez A, Abad A, Torres M, Panés J, Chaparro M, Pascual I, Rodriguez-Carballeira M, Fernández-Bañares F, Viver JM, Esteve M; REPENTINA study; GETECCU (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa) Group. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010; **59**: 1340-1346 [PMID: 20577000 DOI: 10.1136/gut.2010.208413]

33 **Pérez-Alvarez R**, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, Retamozo S, Bové A, Bosch X, Sanchez-Tapias JM, Forns X, Ramos-Casals M; BIOGEAS Study Group. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine (Baltimore)* 2011; **90**: 359-371 [PMID: 22033451 DOI: 10.1097/MD.0b013e3182380a76]

34 **Clarke WT**, Amin SS, Papamichael K, Feuerstein JD, Cheifetz AS. Patients with core antibody positive and surface antigen negative Hepatitis B (anti-HBc+, HBsAg-) on anti-TNF therapy have a low rate of reactivation. *Clin Immunol* 2018; **191**: 59-62 [PMID: 29601854 DOI: 10.1016/j.clim.2018.03.013]

35 **Solay AH**, Acar A, Eser F, Kuşcu F, Tütüncü EE, Kul G, Şentürk GÇ, Gürbüz Y. Reactivation rates in patients using biological agents, with resolved HBV infection or isolated anti-HBc IgG positivity. *Turk J Gastroenterol* 2018; **29**: 561-565 [PMID: 30260778 DOI: 10.5152/tjg.2018.18032]

36 **Pauly MP**, Tucker LY, Szpakowski JL, Ready JB, Baer D, Hwang J, Lok AS. Incidence of Hepatitis B Virus Reactivation and Hepatotoxicity in Patients Receiving Long-term Treatment With Tumor Necrosis Factor Antagonists. *Clin Gastroenterol Hepatol* 2018; **16**: 1964-1973.e1 [PMID: 29702293 DOI: 10.1016/j.cgh.2018.04.033]

37 **Papa A**, Felice C, Marzo M, Andrisani G, Armuzzi A, Covino M, Mocci G, Pugliese D, De Vitis I, Gasbarrini A, Rapaccini GL, Guidi L. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-α agents. *J Crohns Colitis* 2013; **7**: 113-119 [PMID: 22464811 DOI: 10.1016/j.crohns.2012.03.001]

38 **Reddy KR**, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 215-9; quiz e16 [PMID: 25447850 DOI: 10.1053/j.gastro.2014.10.039]

39 **Rahier JF**, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]

40 **McGinley MP**, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA* 2021; **325**: 765-779 [PMID: 33620411 DOI: 10.1001/jama.2020.26858]

41 **Epstein DJ**, Dunn J, Deresinski S. Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management. *Open Forum Infect Dis* 2018; **5**: ofy174 [PMID: 30094293 DOI: 10.1093/ofid/ofy174]

42 **Ciardi MR**, Iannetta M, Zingaropoli MA, Salpini R, Aragri M, Annecca R, Pontecorvo S, Altieri M, Russo G, Svicher V, Mastroianni CM, Vullo V. Reactivation of Hepatitis B Virus With Immune-Escape Mutations After Ocrelizumab Treatment for Multiple Sclerosis. *Open Forum Infect Dis* 2019; **6**: ofy356 [PMID: 30697576 DOI: 10.1093/ofid/ofy356]

43 **Brost S**, Schnitzler P, Stremmel W, Eisenbach C. Entecavir as treatment for reactivation of hepatitis B in immunosuppressed patients. *World J Gastroenterol* 2010; **16**: 5447-5451 [PMID: 21086562 DOI: 10.3748/wjg.v16.i43.5447]

44 **Chen FW**, Coyle L, Jones BE, Pattullo V. Entecavir versus lamivudine for hepatitis B prophylaxis in patients with haematological disease. *Liver Int* 2013; **33**: 1203-1210 [PMID: 23522150 DOI: 10.1111/liv.12154]

45 **Koskinas JS**, Deutsch M, Adamidi S, Skondra M, Tampaki M, Alexopoulou A, Manolakopoulos S, Pectasides D. The role of tenofovir in preventing and treating hepatitis B virus (HBV) reactivation in immunosuppressed patients. A real life experience from a tertiary center. *Eur J Intern Med* 2014; **25**: 768-771 [PMID: 25037900 DOI: 10.1016/j.ejim.2014.06.028]

46 **Marrone A**, Capoluongo N, D'Amore C, Pisaturo M, Esposito M, Guastafierro S, Siniscalchi I, Macera M, Boemio A, Onorato L, Rinaldi L, Minichini C, Adinolfi LE, Sagnelli E, Mastrullo L, Coppola N. Eighteen-month lamivudine prophylaxis on preventing occult hepatitis B virus infection reactivation in patients with haematological malignancies receiving immunosuppression therapy. *J Viral Hepat* 2018; **25**: 198-204 [PMID: 29029365 DOI: 10.1111/jvh.12802]

47 **Chew E**, Thursky K, Seymour JF. Very late onset hepatitis-B virus reactivation following rituximab despite lamivudine prophylaxis: the need for continued vigilance. *Leuk Lymphoma* 2014; **55**: 938-939 [PMID: 23772645 DOI: 10.3109/10428194.2013.813502]

48 **Dai MS**, Chao TY, Kao WY, Shyu RY, Liu TM. Delayed hepatitis B virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. *Ann Hematol* 2004; **83**: 769-774 [PMID: 15338194 DOI: 10.1007/s00277-004-0899-y]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 283-292

DOI: 10.5501/wjv.v11.i5.283

ISSN 2220-3249 (online)

MINIREVIEWS

Acute kidney injury and electrolyte disorders in COVID-19

Gabriel Martins Nogueira, Noel Lucas Oliveira Rodrigues Silva, Ana Flávia Moura, Marcelo Augusto Duarte Silveira, José A Moura-Neto

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Naswhan AJ, Qatar; Singh N, United States

Received: March 31, 2022
Peer-review started: March 31, 2022
First decision: June 16, 2022
Revised: June 30, 2022
Accepted: August 22, 2022
Article in press: August 22, 2022
Published online: September 25, 2022

Gabriel Martins Nogueira, Noel Lucas Oliveira Rodrigues Silva, Ana Flávia Moura, José A Moura-Neto, Department of Medicine, Bahiana School of Medicine and Public Health, Salvador 40290-000, Bahia, Brazil

Marcelo Augusto Duarte Silveira, Department of Nephrology, D'Or Institute for Research and Education, Hospital São Rafael, Salvador 41253900, Bahia, Brazil

Corresponding author: José A Moura-Neto, MD, FASN Professor, Department of Medicine, Bahiana School of Medicine and Public Health, Av. Dom Joao VI, Salvador 40290-000, Bahia, Brazil. jamouraneto@hotmail.com

Abstract

Acute kidney injury (AKI) and electrolyte disorders are important complications of hospitalized coronavirus disease 2019 (COVID-19) patients. AKI is thought to occur due to multiple pathophysiological mechanisms, such as multiple organ dysfunction (mainly cardiac and respiratory), direct viral entry in the renal tubules, and cytokine release syndrome. AKI is present in approximately one in every ten hospitalized COVID-19 patients. The incidence rates of AKI increase in patients who are admitted to the intensive care unit (ICU), with levels higher than 50%. Additionally, renal replacement therapy (RRT) is used in 7% of all AKI cases, but in nearly 20% of patients admitted to an ICU. COVID-19 patients with AKI are considered moderate-to-severe cases and are managed with multiple interdisciplinary conducts. AKI acts as a risk factor for mortality in severe acute respiratory syndrome coronavirus 2 infection, especially when RRT is needed. Electrolyte disorders are also common manifestations in hospitalized COVID-19 patients, mainly hyponatremia, hypokalemia, and hypocalcemia. Hyponatremia occurs due to a combination of syndrome of inappropriate secretion of antidiuretic hormone and gastrointestinal fluid loss from vomiting and diarrhea. When it comes to hypokalemia, its mechanism is not fully understood but may derive from hyperaldosteronism due to renin angiotensin aldosterone system overstimulation and gastrointestinal fluid loss as well. The clinical features of hypokalemia in COVID-19 are similar to those in other conditions. Hypocalcemia is the most common electrolyte disorder in COVID-19 and seems to occur because of vitamin D deficiency and parathyroid imbalance. It is also highly associated with longer hospital and ICU stay.

Key Words: COVID-19; SARS-CoV-2; Acute kidney injury; Electrolyte disorders; Renal dialysis

Core Tip: Acute kidney injury and electrolyte disorders are frequent clinical complications in hospitalized patients with coronavirus disease 2019, being directly related to the severity of the disease and increasing the mortality.

Citation: Nogueira GM, Silva NLOR, Moura AF, Duarte Silveira MA, Moura-Neto JA. Acute kidney injury and electrolyte disorders in COVID-19. *World J Virol* 2022; 11(5): 283-292
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/283.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.283

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak initiated in the first months of 2020. It corresponds to an illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although frequently asymptomatic, the malady is known for its wide variety of clinical signs and symptoms. These can range from pulmonary manifestations, such as dyspnea and cough, to extrapulmonary ones, which include fever, anosmia, ageusia, diarrhea, and myalgia[1-3]. This heterogeneity of clinical features is an indicative of the systemic character of COVID-19.

COVID-19 had an outstanding impact in the nephrology community. With over 4 million chronic kidney disease patients on maintenance dialysis at risk, the pandemic caused profound changes to the sector[4,5]. The kidney was also a commonly affected organ by COVID-19; one in every four patients presented abnormal renal function at hospital admission[6]. According to the classification proposed by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, acute kidney injury is defined as any of the following situations: Increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 h; or increase in SCr ≥ 1.5 times baseline from 7 d prior; or urinary volume < 0.5 mL/kg/h for a period of 6 h. The KDIGO guidelines also propose a stratification of AKI in three stages, numbered from 1 to 3 in crescent order of injury severity[7].

In primary analyses of patients with COVID-19, it was also noticed that, among the various systemic complications caused by the SARS-CoV-2, changes in electrolyte concentrations are not only present, but also independently associated with a poor outcome[8,9].

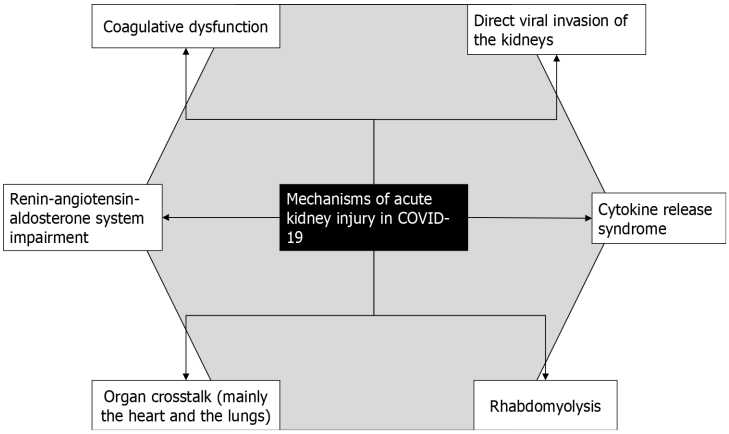
In this review, we discuss the pathophysiology, epidemiology, clinical history, risk factors, management, and prognosis of COVID-19 associated acute kidney injury (AKI) and the most reported electrolyte disorders in COVID-19, which are hyponatremia, hypokalemia, and hypocalcemia.

ACUTE KIDNEY INJURY

The mechanism of AKI in COVID-19 is most likely multifactorial. Some of the proposed alterations induced by the viral disease that could damage the kidneys can be seen in Figure 1[10].

Coronaviruses have high affinity for the angiotensin-converting enzyme 2 (ACE2), a metallopeptidase often bound to cell membranes that is responsible for catalyzing the conversion of angiotensin 2 to angiotensin 1-7[11-13]. The transmembrane protease serine 2 contributes to the entry of SARS-CoV-2 in the cell by cleaving and activating the spike (S) protein[14]. After entry, followed by endocytosis, coronavirus infection causes upregulation of PAK1, a kinase that mediates inflammation and is associated with risk factors for mortality. Increased PAK1 levels also suppress the adaptive immune response, facilitating viral replication[15]. It was previously shown that SARS-CoV could bind to ACE2 *via* the virus' S protein[16]. Being structurally similar to SARS-CoV, SARS-CoV-2 also uses ACE2 in order to enter the host cell and replicate in its cytoplasm[17]. This enzyme is distributed across multiple tissues, such as the vascular endothelium, alveolar epithelium, proximal tubular cells of the kidney, and glomerular epithelium[18].

The fact that kidney cells express ACE2 explains how they also act as host cells of the novel coronavirus, a piece of information that was shown in autopsy studies. Histopathological examination found out varying degrees of tubular injury, such as diffuse proximal tubule injury with loss of the brush border, vacuolar degeneration, necrosis, hemosiderin granules, and pigment casts[19-21]. RNA *in situ* hybridization and electron microscopy also found evidence that SARS-CoV-2 directly infects the renal tubules[20,21]. A small number of patients with AKI may present virus in urine samples, which also supports a direct viral cytopathic effect hypothesis. These patients may have a greater predilection for proteinuria[22].



DOI: 10.5501/wjv.v11.i5.283

Figure 1 Pathophysiological mechanisms of acute kidney injury in coronavirus disease 2019.

Due to the binding of SARS-CoV-2 to ACE2, the expression of this molecule is downregulated, which leads to increased activity of angiotensin 2 that is unopposed by angiotensin 1-7[23,24]. In normal conditions, angiotensin 1-7 has anti-thrombotic, anti-inflammatory, and vasodilator effects that counter the actions of angiotensin 2 through activation of Mas receptors[25-27]. It is suggested that the overactivation of angiotensin type 1 receptors may contribute to AKI onset mostly due to hemodynamic alterations, such as hypoxia, hypertension-induced proteinuria, and oxidative stress[27,28].

Furthermore, a hypercoagulative state induced by the lack of anti-thrombotic effects of angiotensin 1-7 could cause renal microangiopathy capable of causing AKI[29]. Rhabdomyolysis is also a frequent cause of COVID-19 associated AKI, being responsible for around 7% of the cases[30]. The occurrence of skeletal muscle injury is present in up to one in every five COVID-19 patients, which explains the occurrence of rhabdomyolysis nephropathy in this disease[29].

Cytokine release syndrome consists of an extreme rise of inflammatory cytokines, frequently called a "cytokine storm", caused by a systemic response that can be triggered by a wide variety of conditions [31,32]. It has been implied that cytokine storm is a significant component of the disease course of severe cases of COVID-19[33]. The binding of SARS-CoV-2 to ACE2 promotes an inflammatory response with a prominent release of inflammatory cytokines, such as IL-6, IL-8, IL-22, and TNF-α, and chemokines, like CCL2, CCL3, and CCL5[29,34,35]. Lymphopenia, a common feature of SARS-CoV-2 infection, also contributes to the rise of inflammatory cytokines[36].

The crosstalk between the kidneys, lungs, and cardiovascular system seems to be significant for the development of AKI. Cases of acute respiratory distress syndrome (ARDS) are knowingly associated with a greater risk of AKI onset, including those related to SARS-CoV-2 infection[37-39]. This is likely a result of renal damage triggered by inflammatory mediators that cause tubular injury, which by itself culminates in IL-6 upregulation that harms the lungs[39,40].

The cardiovascular system is another important topic regarding AKI in COVID-19. Acute viral myocarditis and cytokine cardiomyopathy can induce a reduction of the estimated glomerular filtration rate (eGFR) through hemodynamic changes. Type 1 cardiorenal syndrome (CRS) can occur due to a cytokine storm or myocarditis and type 3 CRS can occur after the onset of AKI. Furthermore, upon the onset of sepsis, type 5 CRS can occur[41,42]. Right ventricular failure caused by pneumonia induced by SARS-CoV-2 and reduction of cardiac output due to left ventricle failure are also possible mechanisms of eGFR diminishment and AKI[43,44].

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Data available refers to hospitalized patients, since AKI is a complication typical of moderate and severe cases of COVID-19 that require inpatient healthcare[45-50]. The incidence of AKI in COVID-19 is highly variable depending on the study analyzed. Our review found results between 5% and 75%, and the article with the largest sample size indicated a frequency of approximately 36%, whilst a systematic review of observational studies found an incidence of AKI of 11%[30,45-49,51-53].

A multicenter study showed that about 45% of the patients had no significant kidney injury caused by the viral illness; that 34% developed AKI without need for renal replacement therapy (RRT); and that 26% developed COVID-19 AKI with need of RRT (AKI-RRT)[44]. In contrast, a systematic review found that RRT was used in only 7% of COVID-19 cases with renal manifestations[51]. The modality of first choice is usually continuous renal replacement therapy, mostly because it is a suitable modality for hemodynamically unstable patients[54].

In a Chinese cohort study, three quarters of the patients had developed renal symptomatology, including proteinuria and/or hematuria, but only one in every ten patients had an AKI onset[55]. Out of all renal clinical findings, the most common ones were proteinuria, hematuria, elevated SCr and blood urea nitrogen, reduction of eGFR, and AKI[46,47,55-57]. One study found that three in every four patients that were at least moderately ill had renal involvement to some extent. These levels were as low as 62% in moderately (3.5% being AKI) ill patients and as high as 91% in critically ill patients (43% being AKI). It is suspected that most cases of AKI in COVID-19 occur due to intrinsic rather than prerenal mechanisms[55].

A multicenter American study found that patients who developed AKI because of SARS-CoV-2 infection were older and predominantly male individuals with higher levels of comorbidities associated with more severe cases of COVID-19, such as systemic arterial hypertension, diabetes mellitus, and heart failure. Additionally, the same article shows that patients who developed AKI were usually admitted to an intensive care unit (ICU) and were more likely to be on use of vasopressors (52.6% *vs* 3.4%) as well as mechanical ventilation (89.7% *vs* 21.7% in nonventilated patients), indicating that patients who developed AKI were critically ill. In that sample of AKI patients, about one third of patients died[46]. Independent risk factors for the development of COVID-19 associated AKI include pre-existing renal impairment (such as chronic kidney disease), hypertension, and inpatient diuretic use [45,51,52,57].

It is also known that there is an association between ARDS and AKI in general and it also applies to COVID-19 due to the release of inflammatory cytokines, especially IL-6[37-40]. This is clinically notable as well, since patients on mechanical ventilators are more likely to develop AKI with or without need of RRT[45-47]. Additionally, abnormal serum urea and serum creatinine values were associated in a bivariate Cox regression model with either ARDS development or progression from ARDS to death[58].

Laboratory examinations show that most AKI patients are admitted with abnormal kidney function, represented by high levels of SCr and low eGFR. Patients who do not develop AKI are admitted with higher levels of SCr and lower eGFR than at discharge, while AKI patients are discharged with worsened kidney function[45-47]. Patients who develop stage 3 AKI are usually discharged with a median SCr of 4.0 mg/dL and median eGFR of 14.0 mL/min/1.73 m², as opposed to a median SCr of 1.19 mg/dL and median eGFR of 62 mL/min/1.73m² at admission[46].

MANAGEMENT AND PROGNOSIS

The management of COVID-19 associated AKI is a largely discussed theme among intensive care professionals. The 25th Acute Disease Quality Initiative Workgroup defined a few strategies for dealing with COVID-19 associated AKI[54]. The standard measures that have an evidence level of 1B or above include:

Measurement of kidney function through serum creatinine and urine output[56].

Use of dynamic assessment of cardiovascular status to mitigate the risk of AKI and ARDS, avoiding hemodynamic imbalance[56].

Volume expansion with balanced crystalloids to decrease the chances of developing AKI, unless there are indications for the use of other kinds of fluids[56].

Limit the patients' exposure to nephrotoxins whenever possible and monitor their kidney functionality when the use of nephrotoxins is necessary[56].

When contrast media are required, optimize intravascular volume as a means to prevent AKI[56].

The prognosis of COVID-19 associated AKI and AKI-RRT is arguably poor. AKI was associated with a longer median hospital stay, which was approximately twice as long when compared to non-AKI patients[59]. One study found that mortality is about ten times higher in patients with moderate-to-severe COVID-19 who developed AKI in comparison to those who did not[55]. Another observational study concluded that AKI is almost 2.5 times more frequent in non-survivors than in survivors of critical COVID-19 cases[60]. It is also stated that AKI is an independent risk factor for 30 d mortality among COVID-19 patients[52].

Although remission from proteinuria and hematuria is a common outcome for patients with renal COVID-19 manifestations, less than half of AKI patients recover their kidney function[55]. Mortality rates were as high as 35% of AKI patients and use of RRT increases the lethality of the disease to levels over 60%. Furthermore, approximately one in every three RRT patients that were discharged remained RRT-dependent[46,47].

ELECTROLYTE DISORDERS

Patients with COVID-19 may experience diverse electrolyte disturbances with clinical impact. The main disorders are hyponatremia, hypokalemia, and hypocalcemia. The pathophysiological mechanisms are diverse and imply changes in the renin angiotensin aldosterone system as well as immuno-inflammatory phenomena underlying the coronavirus, which are generally associated with kidney and/or

gastrointestinal damage[61]. Table 1 gives a general overview of the pathophysiology of the most frequent electrolyte disorders associated with COVID-19.

HYPONATREMIA

Hyponatremia is the most frequent electrolyte disorder in clinical practice, with a prevalence of 20% to 30% in hospitalized patients, and is defined by serum sodium levels below 135 mEq/L[62]. The association between pneumonia and hyponatremia was firstly described in 1962, mainly related to community-acquired pneumonia, which was later reported in other respiratory infections[63]. Thus, with the emergence of the COVID-19 pandemic, preliminary studies indicated that hyponatremia was one of the possible complications caused by the viral disease[64]. In general, COVID-19 patients with hyponatremia have more severe forms of the disease, with higher levels of hospitalization, when compared to normonatremic patients, both in infirmary and ICU beds. Most of these patients also have other markers of severity, such as higher levels of C-reactive protein (CRP), ferritin, and IL-6; consolidation lesions more present on chest CT; and greater need for oxygen support[65].

The pathophysiology of hyponatremia in patients with COVID-19 is considered multifactorial, but the main cause is the syndrome of inappropriate antidiuresis (SIAD). SIAD is characterized by hyponatremia (serum sodium less than 135 mEq/L) and elevated urinary osmolarity (> 100 mOsm/kg) compared to plasma osmolarity (< 280 mOsm/kg) in euvolemic patients that have normal renal, thyroid, hepatic, cardiac, and adrenal functions and are not on use of diuretics[66]. Despite its mechanism not being fully understood, SIAD in patients with COVID-19 is apparently related to elevated levels of IL-6, which induce the non-osmotic release of antidiuretic hormone. In addition, these cytokines can damage lung tissue and alveolar cells, generating hypoxic pulmonary vasoconstriction, which may induce SIAD[67]. Evidence demonstrates a directly proportional relationship between the serum sodium level and the PaO_2/FiO_2 ratio and an inversely proportional relationship between the serum sodium level and the IL-6 level[68]. Furthermore, some other factors may contribute to the secretion of this hormone, such as patients who experience fluid loss from vomiting and diarrhea (reported symptoms of COVID-19)[69].

HYPOKALEMIA

Hypokalemia corresponds to the most frequent potassium disorder and is characterized by a serum concentration of potassium below 3.5 mEq/L. The presence of hypokalemia can be variable and data in the literature point to an incidence between 10% and 41% of patients who were hospitalized for COVID-19[70,71]. Furthermore, in another study carried out in Italy, hypokalemia was associated with a longer hospital stay[71].

There are many factors that can generate hypokalemia, so a precise mechanism for this complication in patients with COVID-19 has not yet been determined. However, some hypotheses can be taken into consideration, such as: (1) Viral interaction with its input receptor (ACE2), altering the classic renin-angiotensin-aldosterone pathway and stimulating the release of aldosterone, thus increasing potassium secretion in the urine; (2) Volume loss due to gastrointestinal symptoms caused by the viral infection, mainly diarrhea; and (3) Being secondary to the use of medications, such as diuretics and glucocorticoids[9,71].

The clinical manifestations of symptomatic hypokalemia include muscle weakness and fatigue. However, in more severe cases, low levels of potassium can cause cardiac arrhythmias with alterations on the electrocardiogram tracing, and respiratory muscular weakness[72]. Therefore, it is correct to say that hypokalemia can increase respiratory stress and the risk of cardiac injury[61]. Regarding coronaviruses, hypokalemia was reported upon the onset of SARS-CoV-1 infection, back in 2003, and was also described in some preliminary studies during the beginning of the COVID-19 pandemic[71].

HYPOCALCEMIA

Calcium plays an important role in the mechanism of entering a host cell and viral replication, something that was already reported in the pathophysiology of Ebola and SARS-CoV-1 viruses[73,74]. In addition, hypocalcemia represents an independent factor for increased mortality among critically ill patients with long hospital stay[75].

In a study carried out in China, the incidence of hypocalcemia in COVID-19 patients was 62.6%. Other laboratory findings included lymphocytosis and higher levels of CRP, D-dimer, and IL-6 when compared to the normocalcemic group. In addition, in that same study, the hypocalcemia group was more likely to have a poor outcome in comparison to the normocalcemic group (47.8% *vs* 25%, respectively)[76]. In another study carried out in Italy, the incidence of hypocalcemia in patients with

Table 1 Pathophsyiology of the most common electrolyte disorders in coronavirus disease 2019

Electrolyte disorder	Pathophysiological mechanisms
Hyponatremia	Syndrome of inappropriate secretion of antidiuretic hormone
Hypokalemia	Excessive aldosterone liberation, volume loss, and use of diuretics and glucocorticoids
Hypocalcemia	Vitamin D deficiency and parathyroid imbalance

COVID-19 was 78.6%, and this electrolyte imbalance also had a strong association with ICU admissions and death when compared to patients with normal calcium levels[77].

Parathyroid hormone and vitamin D play a key role in calcium metabolism. Patients with chronic hypovitaminosis D and who are affected by COVID-19 are more predisposed to hypocalcemia, as this vitamin alters calcium metabolism by reducing the intestinal absorption of calcium and phosphorus. These patients may have a compensatory tendency to secondary hyperparathyroidism, but this is not always sufficient to prevent hypocalcemia[78].

COVID-19 hypocalcemia has been associated with higher mortality rates when compared to other patients with respiratory conditions that have similar clinical manifestations. Hypocalcemia is also more incident and quantitatively significant in COVID-19 than in other infections. The main factors responsible for hypocalcemia in hospitalized patients include low dietary intake, hypoparathyroidism, hypoproteinemia, vitamin D deficiency, and drug interaction. However, when it comes to COVID-19, vitamin D deficiency and parathyroid imbalance are identified as the main causes of said electrolyte disorder[75]. Parathyroid gland function can be impaired during critical systemic illness and inflammatory response with increased circulating cytokines[78].

CONCLUSION

Besides the respiratory complications caused by the SARS-CoV-2 virus, infected patients are also subject to manifestations regarding other systems, such as the renal system. AKI is a multifactorial and fairly common complication in moderate-to-severe COVID-19. Patients that develop AKI due to COVID-19 are usually older males with other comorbidities and are usually admitted to ICUs. Clinical management involves measurement of kidney function, cardiovascular status assessment, volume expansion, and nephrotoxin exposure limitation, as well as standard AKI care measures. AKI also acts as a risk factor for death in SARS-CoV-2 infected patients, specially concerning those on RRT.

Hyponatremia, hypokalemia, and hypocalcemia are the most relevant electrolyte disorders in hospitalized patients with COVID-19. The cause of these laboratory alterations is multifactorial and may be secondary to renal and gastrointestinal lesions caused by inflammatory response, or even by pathophysiological alterations caused by the entry mechanism of the virus. In patients with COVID-19, electrolyte disorders are associated with worse outcomes, with increased hospitalization length and mortality.

FOOTNOTES

Author contributions: Nogueira GM and Silva NLOR collected and read the literature; Nogueira GM wrote the section on acute kidney injury; Silva NLOR wrote the section on electrolyte disorders; Moura AF, Silveira MAD, and Moura-Neto JA reviewed the article.

Conflict-of-interest statement: All authors declare no conflicts of interest for this article.

Country/Territory of origin: Brazil

ORCID number: Gabriel Martins Nogueira 0000-0002-8819-6874; Ana Flávia Moura 0000-0001-7368-4704; José A Moura-Neto 0000-0003-1339-3731.

Corresponding Author's Membership in Professional Societies: Brazilian Society of Nephrology; International Society for Hemodialysis; International Society of Nephrology; National Academy of Medicine (Brazil); American Society of Nephrology.

S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

REFERENCES

1 **Li LQ**, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020; **92**: 577-583 [PMID: 32162702 DOI: 10.1002/jmv.25757]
2 **Lechien JR**, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-Laryngology* 2020 [DOI: 10.1007/s00405-020-05965-1]
3 **Agyeman AA**, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. *Mayo Clin Proc* 2020; **95**: 1621-1631 [PMID: 32753137 DOI: 10.1016/j.mayocp.2020.05.030]
4 **Moura-Neto JA**, Divino-Filho JC, Ronco C. Nephrology Worldwide: the Vision, the Project, and the Mission. In: Moura-Neto JA, Divino-Filho JC, Ronco C, editors. Nephrology Worldwide. Basel: Springer Nature Switzerland AG, 2021 [DOI: 10.1007/978-3-030-56890-0_1]
5 **Nogueira GM**, Oliveira MS, Moura AF, Cruz CMS, Moura-Neto JA. COVID-19 in dialysis units: A comprehensive review. *World J Virol* 2021; **10**: 264-274 [PMID: 34631476 DOI: 10.5501/wjv.v10.i5.264]
6 **Zhu J**, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *J Med Virol* 2020; **92**: 1902-1914 [PMID: 32293716 DOI: 10.1002/jmv.25884]
7 **Kellum JA**, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1-138 [DOI: 10.1186/cc11455]
8 **Lippi G**, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Ann Clin Biochem* 2020; **57**: 262-265 [PMID: 32266828 DOI: 10.1177/0004563220922255]
9 **Lim JH**, Jung HY, Choi JY, Park SH, Kim CD, Kim YL, Cho JH. Hypertension and Electrolyte Disorders in Patients with COVID-19. *Electrolyte Blood Press* 2020; **18**: 23-30 [PMID: 33408744 DOI: 10.5049/EBP.2020.18.2.23]
10 **Faour WH**, Choaib A, Issa E, Choueiry FE, Shbaklo K, Alhajj M, Sawaya RT, Harhous Z, Alefishat E, Nader M. Mechanisms of COVID-19-induced kidney injury and current pharmacotherapies. *Inflamm Res* 2022; **71**: 39-56 [PMID: 34802072 DOI: 10.1007/s00011-021-01520-8]
11 **Tipnis SR**, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem* 2000; **275**: 33238-33243 [PMID: 10924499 DOI: 10.1074/jbc.M002615200]
12 **Donoghue M**, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 2000; **87**: E1-E9 [PMID: 10969042 DOI: 10.1161/01.res.87.5.e1]
13 **Patel VB**, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/Angiotensin 1-7 Axis of the Renin-Angiotensin System in Heart Failure. *Circ Res* 2016; **118**: 1313-1326 [PMID: 27081112 DOI: 10.1161/CIRCRESAHA.116.307708]
14 **Pan XW**, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. *Intensive Care Med* 2020; **46**: 1114-1116 [PMID: 32236644 DOI: 10.1007/s00134-020-06026-1]
15 **Maruta H**, He H. PAK1-blockers: Potential Therapeutics against COVID-19. *Med Drug Discov* 2020; **6**: 100039 [PMID: 32313880 DOI: 10.1016/j.medidd.2020.100039]
16 **Li W**, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454 [PMID: 14647384 DOI: 10.1038/nature02145]
17 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]
18 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]
19 **Puelles VG**, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfefferle S, Schröder AS, Edler C, Gross O, Glatzel M, Wichmann D, Wiech T, Kluge S, Pueschel K, Aepfelbacher M, Huber TB. Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med* 2020; **383**: 590-592 [PMID: 32402155 DOI: 10.1056/NEJMc2011400]
20 **Su H**, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X, Zhang C. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; **98**: 219-227 [PMID: 32327202 DOI: 10.1016/j.kint.2020.04.003]
21 **Diao B**, Wang C, Wang R, Feng Z, Zhang J, Yang H, Tan Y, Wang H, Liu L, Liu Y, Wang G, Yuan Z, Hou X, Ren L, Wu Y, Chen Y. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. *Nat Commun* 2021; **12**: 2506 [PMID: 33947851 DOI: 10.1038/s41467-021-22781-1]

22 **de Souza SP**, Silveira MAD, Souza BSF, Cabral JB, de Melo EBDSG, Nonaka CKV, Coelho FO, da Hora Passos R. Evaluation of urine SARS-COV-2 RT-PCR as a predictor of acute kidney injury and disease severity in patients with critical COVID-19. *J Int Med Res* 2021; **49**: 3000605211015555 [PMID: 33990155 DOI: 10.1101/2021.01.13.21249576]

23 **Wiese OJ**, Allwood BW, Zemlin AE. COVID-19 and the renin-angiotensin system (RAS): A spark that sets the forest alight? *Med Hypotheses* 2020; **144**: 110231 [PMID: 33254538 DOI: 10.1016/j.mehy.2020.110231]

24 **Verdecchia P**, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020; **76**: 14-20 [PMID: 32336612 DOI: 10.1016/j.ejim.2020.04.037]

25 **Fraga-Silva RA**, Pinheiro SV, Gonçalves AC, Alenina N, Bader M, Santos RA. The antithrombotic effect of angiotensin-(1-7) involves mas-mediated NO release from platelets. *Mol Med* 2008; **14**: 28-35 [PMID: 18026570 DOI: 10.2119/2007-00073.fraga-silva]

26 **Fraga-Silva RA**, Costa-Fraga FP, De Sousa FB, Alenina N, Bader M, Sinisterra RD, Santos RA. An orally active formulation of angiotensin-(1-7) produces an antithrombotic effect. *Clinics (Sao Paulo)* 2011; **66**: 837-841 [PMID: 21789389 DOI: 10.1590/s1807-59322011000500021]

27 **Forrester SJ**, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, Scalia R, Eguchi S. Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. *Physiol Rev* 2018; **98**: 1627-1738 [PMID: 29873596 DOI: 10.1152/ajpcell.00287.2006]

28 **Long DA**, Price KL, Herrera-Acosta J, Johnson RJ. How does angiotensin II cause renal injury? *Hypertension* 2004; **43**: 722-723 [PMID: 14967828 DOI: 10.1161/01.hyp.0000120964.22281.3e]

29 **Ahmadian E**, Hosseiniyan Khatibi SM, Razi Soofiyani S, Abediazar S, Shoja MM, Ardalan M, Zununi Vahed S. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. *Rev Med Virol* 2021; **31**: e2176 [PMID: 33022818 DOI: 10.1002/rmv.2176]

30 **Mohamed MMB**, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, Alqudsi M, LeDoux JR, Velez JCQ. Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. *Kidney360* 2020; **1**: 614-622 [PMID: 35372932 DOI: 10.34067/KID.0002652020]

31 **Shimabukuro-Vornhagen A**, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. Cytokine release syndrome. *J Immunother Cancer* 2018; **6**: 56 [PMID: 29907163 DOI: 10.1186/s40425-018-0343-9]

32 **Chatenoud L**, Ferran C, Reuter A, Legendre C, Gevaert Y, Kreis H, Franchimont P, Bach JF. Systemic reaction to the anti-T-cell monoclonal antibody OKT3 in relation to serum levels of tumor necrosis factor and interferon-gamma [corrected]. *N Engl J Med* 1989; **320**: 1420-1421 [PMID: 2785642 DOI: 10.1056/NEJM198905253202117]

33 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

34 **Law HK**, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, Nicholls JM, Peiris JS, Lau YL. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. *Blood* 2005; **106**: 2366-2374 [PMID: 15860669 DOI: 10.1182/blood-2004-10-4166]

35 **Li X**, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal* 2020; **10**: 102-108 [PMID: 32282863 DOI: 10.1016/j.jpha.2020.03.001]

36 **Chen G**, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: 32217835 DOI: 10.1172/JCI137244]

37 **Panitchote A**, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, Mireles-Cabodevila E, Krishnan S, Duggal A. Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann Intensive Care* 2019; **9**: 74 [PMID: 31264042 DOI: 10.1186/s13613-019-0552-5]

38 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/s2213-2600(20)30079-5]

39 **Joannidis M**, Forni LG, Klein SJ, Honore PM, Kashani K, Ostermann M, Prowle J, Bagshaw SM, Cantaluppi V, Darmon M, Ding X, Fuhrmann V, Hoste E, Husain-Syed F, Lubnow M, Maggiorini M, Meersch M, Murray PT, Ricci Z, Singbartl K, Staudinger T, Welte T, Ronco C, Kellum JA. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. *Intensive Care Med* 2020; **46**: 654-672 [PMID: 31820034 DOI: 10.1007/s00134-019-05869-7]

40 **Husain-Syed F**, Slutsky AS, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. *Am J Respir Crit Care Med* 2016; **194**: 402-414 [PMID: 27337068 DOI: 10.1164/rccm.201602-0420cp]

41 **Rangaswami J**, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, Lerma EV, Mezue K, Molitch M, Mullens W, Ronco C, Tang WHW, McCullough PA; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation* 2019; **139**: e840-e878 [PMID: 30852913 DOI: 10.1161/CIR.0000000000000664]

42 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal Syndrome [Internet]. *J Am Coll Cardiol* 2008; **52** [DOI: 10.1016/j.jacc.2008.07.051]

43 **Ronco C**, Bellomo R, Kellum JA. Acute kidney injury. *Lancet* 2019; **394**: 1949-1964 [PMID: 31777389 DOI: 10.1016/s0140-6736(19)32563-2]

44 **Ronco C**, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med* 2020; **8**: 738-742 [PMID: 32416769 DOI: 10.1016/s2213-2600(20)30229-0]

45 **Cheng Y**, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; **97**: 829-838 [PMID: 32247631 DOI:

10.1016/j.kint.2020.03.005]
46 **Hirsch JS**, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; **98**: 209-218 [PMID: 32416116 DOI: 10.1016/j.kint.2020.05.006]
47 **Gupta S**, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, Sutherland A, Puri S, Srivastava A, Leonberg-Yoo A, Shehata AM, Flythe JE, Rashidi A, Schenck EJ, Goyal N, Hedayati SS, Dy R, Bansal A, Athavale A, Nguyen HB, Vijayan A, Charytan DM, Schulze CE, Joo MJ, Friedman AN, Zhang J, Sosa MA, Judd E, Velez JCQ, Mallappallil M, Redfern RE, Bansal AD, Neyra JA, Liu KD, Renaghan AD, Christov M, Molnar MZ, Sharma S, Kamal O, Boateng JO, Short SAP, Admon AJ, Sise ME, Wang W, Parikh CR, Leaf DE; STOP-COVID Investigators. AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19. *J Am Soc Nephrol* 2021; **32**: 161-176 [PMID: 33067383 DOI: 10.1681/ASN.2020060897]
48 **Fominskiy EV**, Scandroglio AM, Monti G, Calabrò MG, Landoni G, Dell'Acqua A, Beretta L, Moizo E, Ravizza A, Monaco F, Campochiaro C, Pieri M, Azzolini ML, Borghi G, Crivellari M, Conte C, Mattioli C, Silvani P, Mucci M, Turi S, Tentori S, Baiardo Redaelli M, Sartorelli M, Angelillo P, Belletti A, Nardelli P, Nisi FG, Valsecchi G, Barberio C, Ciceri F, Serpa Neto A, Dagna L, Bellomo R, Zangrillo A; COVID-BioB Study Group. Prevalence, Characteristics, Risk Factors, and Outcomes of Invasively Ventilated COVID-19 Patients with Acute Kidney Injury and Renal Replacement Therapy. *Blood Purif* 2021; **50**: 102-109 [PMID: 32659757 DOI: 10.1159/000508657]
49 **Chen YT**, Shao SC, Hsu CK, Wu IW, Hung MJ, Chen YC. Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. *Crit Care* 2020; **24**: 346 [PMID: 32546191 DOI: 10.1186/s13054-020-03009-y]
50 **Fisher M**, Neugarten J, Bellin E, Yunes M, Stahl L, Johns TS, Abramowitz MK, Levy R, Kumar N, Mokrzycki MH, Coco M, Dominguez M, Prudhvi K, Golestaneh L. AKI in Hospitalized Patients with and without COVID-19: A Comparison Study. *J Am Soc Nephrol* 2020; **31**: 2145-2157 [PMID: 32669322 DOI: 10.1681/asn.2020040509]
51 **Kunutsor SK**, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. *Ann Med* 2020; **52**: 345-353 [PMID: 32643418 DOI: 10.1080/07853890.2020.1790643]
52 **Jewell PD**, Bramham K, Galloway J, Post F, Norton S, Teo J, Fisher R, Saha R, Hutchings S, Hopkins P, Smith P, Joslin J, Jayawardene S, Mackie S, Mudhaffer A, Holloway A, Kibble H, Akter M, Zuckerman B, Palmer K, Murphy C, Iatropoulou D, Sharpe CC, Lioudaki E. COVID-19-related acute kidney injury; incidence, risk factors and outcomes in a large UK cohort. *BMC Nephrol* 2021; **22**: 359 [PMID: 34719384]
53 **Chan L**, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I, Somani S, Richter F, Miotto R, Lala A, Kia A, Timsina P, Li L, Freeman R, Chen R, Narula J, Just AC, Horowitz C, Fayad Z, Cordon-Cardo C, Schadt E, Levin MA, Reich DL, Fuster V, Murphy B, He JC, Charney AW, Böttinger EP, Glicksberg BS, Coca SG, Nadkarni GN; Mount Sinai COVID Informatics Center (MSCIC). AKI in Hospitalized Patients with COVID-19. *J Am Soc Nephrol* 2021; **32**: 151-160 [PMID: 32883700 DOI: 10.1681/asn.2020050615]
54 **Shemies RS**, Nagy E, Younis D, Sheashaa H. Renal replacement therapy for critically ill patients with COVID-19-associated acute kidney injury: A review of current knowledge. *Ther Apher Dial* 2022; **26**: 15-23 [PMID: 34378870 DOI: 10.1111/1744-9987.13723]
55 **Pei G**, Zhang Z, Peng J, Liu L, Zhang C, Yu C, Ma Z, Huang Y, Liu W, Yao Y, Zeng R, Xu G. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. *J Am Soc Nephrol* 2020; **31**: 1157-1165 [PMID: 32345702 DOI: 10.1681/asn.2020030276]
56 **Nadim MK**, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, Rimmelé T, Zarbock A, Bell S, Bihorac A, Cantaluppi V, Hoste E, Husain-Syed F, Germain MJ, Goldstein SL, Gupta S, Joannidis M, Kashani K, Koyner JL, Legrand M, Lumlertgul N, Mohan S, Pannu N, Peng Z, Perez-Fernandez XL, Pickkers P, Prowle J, Reis T, Srisawat N, Tolwani A, Vijayan A, Villa G, Yang L, Ronco C, Kellum JA. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol* 2020; **16**: 747-764 [PMID: 33060844 DOI: 10.37473/fic/10.1038/s41581-020-00372-5]
57 **Costa RLD**, Sória TC, Salles EF, Gerecht AV, Corvisier MF, Menezes MAM, Ávila CDS, Silva ECF, Pereira SRN, Simvoulidis LFN. Acute kidney injury in patients with Covid-19 in a Brazilian ICU: incidence, predictors and in-hospital mortality. *J Bras Nefrol* 2021; **43**: 349-358 [PMID: 33570081 DOI: 10.1590/2175-8239-jbn-2020-0144]
58 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]
59 **Piñeiro GJ**, Molina-Andújar A, Hermida E, Blasco M, Quintana LF, Rojas GM, Mercadal J, Castro P, Sandoval E, Andrea R, Fernández J, Badia JR, Soriano A, Poch E; Hospital Clínic Critical Care COVID-19 working group (CCCC). Severe acute kidney injury in critically ill COVID-19 patients. *J Nephrol* 2021; **34**: 285-293 [PMID: 33387345 DOI: 10.1007/s40620-020-00918-7]
60 **Ferrando C**, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, Adalia R, Zattera L, Ramasco F, Monedero P, Maseda E, Martínez A, Tamayo G, Mercadal J, Muñoz G, Jacas A, Ángeles G, Castro P, Hernández-Tejero M, Fernandez J, Gómez-Rojo M, Candela Á, Ripollés J, Nieto A, Bassas E, Deiros C, Margarit A, Redondo FJ, Martín A, García N, Casas P, Morcillo C, Hernández-Sanz ML; de la Red de UCI Española para COVID-19. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study. *Rev Esp Anestesiol Reanim (Engl Ed)* 2020; **67**: 425-437 [PMID: 32800622 DOI: 10.1016/j.redare.2020.07.001]
61 **Pourfridoni M**, Abbasnia SM, Shafaei F, Razaviyan J, Heidari-Soureshjani R. Fluid and Electrolyte Disturbances in COVID-19 and Their Complications. *Biomed Res Int* 2021; **2021**: 6667047 [PMID: 33937408 DOI: 10.1155/2021/6667047]
62 **Rondon-Berrios H**, Agaba EI, Tzamaloukas AH. Hyponatremia: pathophysiology, classification, manifestations and management. *Int Urol Nephrol* 2014; **46**: 2153-2165 [PMID: 25248629 DOI: 10.1007/s11255-014-0839-2]
63 **STORMONT JM**, WATERHOUSE C. Severe hyponatremia associated with pneumonia. *Metabolism* 1962; **11**: 1181-

1186 [PMID: 13984434 DOI: 10.5999/aps.2020.01697.s003]
64 **Aggarwal S**, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. *Diagnosis (Berl)* 2020; **7**: 91-96 [PMID: 32352401 DOI: 10.1515/dx-2020-0046]
65 **Atila C**, Sailer CO, Bassetti S, Tschudin-Sutter S, Bingisser R, Siegemund M, Osswald S, Rentsch K, Rueegg M, Schaerli S, Kuster GM, Twerenbold R, Christ-Crain M. Prevalence and outcome of dysnatremia in patients with COVID-19 compared to controls. *Eur J Endocrinol* 2021; **184**: 409-418 [PMID: 33449918 DOI: 10.1530/EJE-20-1374]
66 **Fajri M**, Essafti M, Aloua R, Mouaffak Y. Severe case of COVID -19 pneumonia complicated by SIADH. *Ann Med Surg (Lond)* 2022; **73**: 103153 [PMID: 34900244 DOI: 10.1016/j.amsu.2021.103153]
67 **Goodman RB**, Pugin J, Lee JS, Matthay MA. Cytokine-mediated inflammation in acute lung injury. *Cytokine Growth Factor Rev* 2003; **14**: 523-535 [PMID: 14563354 DOI: 10.1016/s1359-6101(03)00059-5]
68 **Gheorghe G**, Ilie M, Bungau S, Stoian AMP, Bacalbasa N, Diaconu CC. Is There a Relationship between COVID-19 and Hyponatremia? *Medicina (Kaunas)* 2021; **57** [PMID: 33435405 DOI: 10.3390/medicina57010055]
69 **Khan AA**, Ata F, Munir W, Yousaf Z. Fluid Replacement Versus Fluid Restriction in COVID-19 Associated Hyponatremia. *Cureus* 2020; **12**: e9059 [PMID: 32782878 DOI: 10.7759/cureus.9059]
70 **Mallow PJ**, Belk KW, Topmiller M, Hooker EA. Outcomes of Hospitalized COVID-19 Patients by Risk Factors: Results from a United States Hospital Claims Database. *J Health Econ Outcomes Res* 2020; **7**: 165-174 [PMID: 33043063 DOI: 10.36469/jheor.2020.17331]
71 **Alfano G**, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E, Magistroni R, Venturi G, Pederzoli S, Margiotta G, Romeo M, Piccinini F, Franceschi G, Volpi S, Faltoni M, Ciusa G, Bacca E, Tutone M, Raimondi A, Menozzi M, Franceschini E, Cuomo G, Orlando G, Santoro A, Di Gaetano M, Puzzolante C, Carli F, Bedini A, Milic J, Meschiari M, Mussini C, Cappelli G, Guaraldi G; Modena Covid-19 Working Group (MoCo19). Hypokalemia in Patients with COVID-19. *Clin Exp Nephrol* 2021; **25**: 401-409 [PMID: 33398605 DOI: 10.1007/s10157-020-01996-4]
72 **Unwin RJ**, Luft FC, Shirley DG. Pathophysiology and management of hypokalemia: a clinical perspective. *Nat Rev Nephrol* 2011; **7**: 75-84 [PMID: 21278718 DOI: 10.1038/nrneph.2010.175]
73 **Nathan L**, Lai AL, Millet JK, Straus MR, Freed JH, Whittaker GR, Daniel S. Calcium Ions Directly Interact with the Ebola Virus Fusion Peptide To Promote Structure-Function Changes That Enhance Infection. *ACS Infect Dis* 2020; **6**: 250-260 [PMID: 31746195 DOI: 10.1021/acsinfecdis.9b00296]
74 **Millet JK**, Whittaker GR. Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. *Virology* 2018; **517**: 3-8 [PMID: 29275820 DOI: 10.1016/j.virol.2017.12.015]
75 **Martha JW**, Wibowo A, Pranata R. Hypocalcemia is associated with severe COVID-19: A systematic review and meta-analysis. *Diabetes Metab Syndr* 2021; **15**: 337-342 [PMID: 33493853 DOI: 10.1016/j.dsx.2021.01.003]
76 **Liu J**, Han P, Wu J, Gong J, Tian D. Prevalence and predictive value of hypocalcemia in severe COVID-19 patients. *J Infect Public Health* 2020; **13**: 1224-1228 [PMID: 32622796 DOI: 10.1016/j.jiph.2020.05.029]
77 **Di Filippo L**, Formenti AM, Rovere-Querini P, Carlucci M, Conte C, Ciceri F, Zangrillo A, Giustina A. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. *Endocrine* 2020; **68**: 475-478 [PMID: 32533508 DOI: 10.1007/s12020-020-02383-5]
78 **di Filippo L**, Allora A, Locatelli M, Rovere Querini P, Frara S, Banfi G, Giustina A. Hypocalcemia in COVID-19 is associated with low vitamin D levels and impaired compensatory PTH response. *Endocrine* 2021; **74**: 219-225 [PMID: 34586582 DOI: 10.1007/s12020-021-02882-z]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 293-299

DOI: 10.5501/wjv.v11.i5.293

ISSN 2220-3249 (online)

MINIREVIEWS

Rhino-orbital-cerebral mucormycosis as a complication of coronavirus disease 2019

Raid M Al-Ani

Specialty type: Otorhinolaryngology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Apiratwarakul K, Thailand; Meena DS, India

Received: April 17, 2022
Peer-review started: April 17, 2022
First decision: May 12, 2022
Revised: May 13, 2022
Accepted: August 12, 2022
Article in press: August 12, 2022
Published online: September 25, 2022

Raid M Al-Ani, Department of Surgery/Otolaryngology, University of Anbar, College of Medicine, Ramadi 31001, Anbar, Iraq

Corresponding author: Raid M Al-Ani, MBChB, Academic Research, Full Professor, Senior Editor, Surgeon, Department of Surgery/Otolaryngology, University of Anbar, College of Medicine, Al-Thaela, Ramadi 31001, Anbar, Iraq. med.raed.alani2003@uoanbar.edu.iq

Abstract

Coronavirus disease 2019 is a highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2. This disease as well as its various treatments like steroids, antivirals, and antibacterials can alter the immune state of the affected individuals and result in secondary infections such as mucormycosis. Mucormycosis is a well-known opportunistic fungal infection that affects immunocompromised subjects, particularly those with diabetes mellitus, prolonged antibiotic or steroid use, and patients with organ transplantation, neutropenia, and hematological malignancies. Rhino-orbital-cerebral mucormycosis is an aggressive disease owing to its ability to invade the blood vessels by fungal hyphae, leading to necrosis of the involved structures. Large cases were reported from India, indicating that this clinical entity shows a geographical variation. The affected patients are suffering on a clinical spectrum depending on the stage of the disease. Radiological assessment, including computerized tomography and magnetic resonance imaging, is necessary to evaluate the stage of the disease and choose the appropriate surgical treatment. A multidisciplinary approach is required to treat rhino-orbital-cerebral mucormycosis and includes local or intravenous antifungal drugs, debridement of the dead tissues, and appropriate management of any predisposing conditions. The disease has a very poor prognosis with a death rate of 50%. This review aimed to sum-marize the demographic and clinical risk factors, investigations, treatments, and outcomes of coronavirus disease 2019 patients with rhino-orbital-cerebral mucormycosis.

Key Words: Rhino-orbital-cerebral mucormycosis; Mucormycosis; Nose and paranasal sinuses; Orbit; Cerebrum; COVID-19

Core Tip: Rhino-orbital-cerebral mucormycosis is an aggressive, opportunistic fungal infection. There is an increment in cases of this condition in the era of coronavirus disease 2019, particularly in India. It usually affects the severe or critical types of the COVID-19 and those with a history of diabetes mellitus, corticosteroid therapy, and mechanical ventilation. Early diagnosis with prompt treatment carries a better outcome. The treatment consists of intravenous or local amphotericin B, surgical debridement, and reversal of any immunocompromised conditions. However, this disease has a poor prognosis with a high rate of morbidity and mortality.

Citation: Al-Ani RM. Rhino-orbital-cerebral mucormycosis as a complication of coronavirus disease 2019. *World J Virol* 2022; 11(5): 293-299
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/293.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.293

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a peculiar disease owing to having many characteristics. First, although the disease affects mainly the respiratory system, it can affect any part of the body. Therefore, there is a diversity of clinical manifestations. These manifestations are either classical (fever, cough, headache, dyspnea, and olfactory and gustatory abnormalities) or non-classical (gastrointestinal symptoms, dysphonia, facial palsy, *etc*). Second, long-standing features, either due to the disease itself or its treatment, such as parosmia, dysphonia, sudden sensorineural hearing loss, and mucormycosis are debilitating manifestations of the disease. Third, there is a geographical variation of the COVID-19 manifestations such as rhino-orbital-cerebral mucormycosis (ROCM) that affects mainly the Indian population. Fourth, the clinical features might be related to the pandemic wave and a variant of the virus as ROCM appeared in the second wave in India and was caused by the delta variant[1,2].

COVID-19 can impair the immune status of the patients. This process is aggravated more in patients with a history of other immunocompromised conditions like diabetes mellitus (DM) or those who are on long-term steroids or antibiotic therapy. Furthermore, COVID-19 subjects are more prone to get superadded infections in certain patients with low pulmonary preserve or who need mechanical ventilation[3]. It was reported that secondary bacterial and fungal infections in hospitalized patients were approaching the rate of 8%[3,4]. Moreover, fungal infections were occurring more in a severe or critical COVID-19 stage[5].

One of the fungal-related COVID-19 infections is mucormycosis. It occurs mainly in the region of the head and neck, and the most common site is rhino-orbital-cerebral. It is an aggressive disease and carries a high death rate (approximately 50%) even if it is treated early[6]. The aim of this narrative review was to summarize the demographic and clinical characteristics, diagnostic tools, treatments, and outcomes in patients with ROCM-related COVID-19.

EPIDEMIOLOGY

Geographical distribution

In the pre-COVID-19 period, the incidence of mucormycosis in India (0.14/1000 population) was 80 times higher than what was reported in the world (0.005-1.7/million population)[7]. This means that India is the highest-burden country on the healthcare services regarding mucormycosis[8]. Despite India being the second country regarding the number of COVID-19 patients (43088118) (WHO Coronavirus COVID-19 Dashboard on 5-5-2022, https://covid19.who.int/table), most of the large case series of ROCM-related COVID-19 came from India[1,2,9]. Small case series or reported cases came from other countries like Turkey[10], Egypt[11], Iran[12,13], Honduras[14], and Peru[15]. This indicates that mucormycosis is an endemic disease in India in pre- and during COVID-19 periods.

Age

ROCM-related COVID-19 could affect any age. The median age is mostly in the sixth decade[1].

Gender distribution

Males are two to three times more affected than females[1,9].

CAUSATIVE AGENTS

Mucormycosis, previously known as zygomycosis, is a group of diseases caused by a fungal infection. The causative agent belongs to the order *Mucorales*. The *Rhizopus* specie is the commonest type[7] followed by, in descending order, *Mucor, Cunninghamella, Apophysomyces, Lichtheimia* (formerly *Absidia), Saksenaea, Rhizomucor*, and other species[10]. These fungi release a huge amount of spores into the surrounding air. Even though all human beings inhale these fungi, only individuals with impaired immunity from DM, organ transplantation, prolonged use of steroids or antibiotics, cytotoxic drugs, and malignancies are affected by the disease[16]. The disease is characterized by rapid progression from the nose to the orbit and then to the brain owing to the direct invasion of the blood vessels, which results in tissue necrosis[10].

PREDISPOSING FACTORS

Patients with any medical condition or those who use certain drugs such as steroids, which affect the immune system, are capable of initiating opportunistic infections like mucormycosis[17]. A history of DM and corticosteroid therapy are among the commonest predisposing factors of ROCM-related COVID-19[1,9,18]. Around 70% of patients with this disease have a history of DM.

PATHOPHYSIOLOGY

The correlation between COVID-19 and ROCM is well established in the literature[1,10]. There are several mechanisms by which COVID-19 enhances the possibility of mucormycosis. First of all, there is a dramatic reduction in T cells, including CD4+ and CD8+, particularly in the severe form of COVID-19. As a result, the immunocompromised condition will develop that might predispose to mucormycosis [19].

Second, in the severe COVID-19 state, there is a sudden rise in certain inflammatory markers like IL-6, IL-10, IL-2R, and TNF-alpha that results in a "cytokine storm"[19]. This storm increases ferritin levels and decreases iron export. Therefore, iron deposits inside cells. The high level of iron causes tissue necrosis and the free iron passes to the blood. The high environmental level of iron is a good medium for mucormycosis because the iron is essential for the growth of the fungi and spreading in the body [20].

Third, there is a higher prevalence of DM and diabetic ketoacidosis in patients with COVID-19 in comparison with the general population[21]. There are two causes of new-onset DM due to COVID-19; the use of steroids and the disease itself are similar to the severe acute respiratory syndrome coronavirus 1[22]. Also, there are two reasons for the diabetogenic nature of COVID-19: expression of angiotensin-converting enzyme 2 receptors in the pan-creatic islets as well as increased insulin resistance due to the cytokine storm[23]. There is more iron released into the circulation because the excessive glucose occupies the iron-binding site of ferritin and transferrin in patients with hyperglycemia and diabetic ketoacidosis allowing more iron to reach the blood. The high tissue iron level is a favorable medium for the growth of the fungi[24].

Lastly, endotheliitis as a sequel of COVID-19 might increase the risk of mucormycosis[25]. Damage to the endothelial tissue enhances angio-invasion and dissemination of mucormycosis. Besides, low pH in COVID-19 induces hyperglycemia, and high iron concentration contributes to the expression of two receptors: glucose regulatory protein 78 of endothelium cells and fungal ligand spore coating homolog protein. These mediate the adhesion and penetration of *Mucorales* into the tissues[26].

CLINICAL FEATURES

The onset of the ROCM from the time of COVID-19 diagnosis ranged from 0 to 90 d with 56% of the cases presenting within 14 d[1]. Hence, it is necessary to advise the liable patients with this disease to look for any of the warning symptoms (nasal stuffiness or obstruction, bad odor smell, epistaxis, mucopurulent or blood-stained nasal discharge, pain in the teeth, sinuses, or orbit, worsening headache, facial pain, diplopia, proptosis, fever, facial paresthesia or anesthesia, facial palsy, sudden loss of vision, sudden ptosis, altered conscious level, and focal seizures) to catch the diagnosis early[27]. These symptoms occur almost always on one side. Fever could be a warning sign during or following the course of COVID-19 if the cause of the fever is not obvious or not detected. In such cases, a nasal examination is important to detect if there is a possibility of an early stage of mucormycosis or not.

Thereafter, a thorough examination is essential and should include endoscopic nasal, ophthalmological, and neurological examinations. In a large case series of 2826 patients with this disease, the authors reported the following signs: periocular/facial edema (33%); loss of vision (21%); ptosis (12%);

proptosis (11%); nasal discharge (10%); nasal ulcer/eschar (5.7%); diplopia/ocular movement restriction (3%); periocular/facial discoloration (2.3%); periocular hypoesthesia (1.3%); oral or palatal ulcer/eschar (0.6%); facial palsy (0.2%); and altered sensorium (0.1%)[1].

STAGING SYSTEM

Adopting a staging system is crucial in the management of ROCM-related COVID-19. Owing to the huge number of cases found in India, the Indian ophthalmologist Honavar create a very useful staging system[27]. It is a simple system and depends on anatomical location from the starting point in the nose, then to the paranasal sinuses, orbit, and intracranial structures. In addition, the system considers the severity of each site. Furthermore, this system contains the specific symptoms and signs and useful investigations for each stage. As a next step, it is logical to check its validity, suggest the best option of treatment for each stage, and estimate the treatment outcomes.

DIAGNOSIS

A high index of clinical suspicion is crucial for early diagnosis. Involved tissue biopsy and potassium hydroxide mount fungal staining is the cornerstone of the diagnosis. Culture and sensitivity are used to determine the fungal species. However, it is necessary to start with amphotericin B until the laboratory result is achieved. Radiological imaging in the form of computerized tomography and magnetic resonance imaging of the nose and paranasal sinuses is used to support the diagnosis and to evaluate the stage of the disease[1].

TREATMENT

It is of utmost importance in the management of ROCM-related COVID-19 to use a multidisciplinary team including a specialist doctor in infectious diseases, internal medicine, intensive care, otolaryngology, ophthalmology, neuromedicine, and/or neurosurgery[2].

In general, the treatment consists of three steps: intravenous or local antifungals therapy; appropriate surgical debridement; and reversal of the immunosuppressive conditions[28].

Initiation of antifungal therapy within the first 5 d of the diagnosis improves the survival rate to 83%, which is much larger than the survival rate of 49% if the antifungal treatment started at ≥ 6 d[29]. Amphotericin B is considered the drug of choice as a monotherapy, while posaconazole or isavuconazole can be used as a salvage antifungal drug. A combination of amphotericin B and posaconazole can be used in refractory cases of mucormycosis[4]. In the largest case series in the world from India of 2826 patients with ROCM-related COVID-19, intravenous amphotericin B was used in 73% and intraorbital injection of amphotericin B in 22% of the patients. The study showed a satisfactory result with the use of amphotericin B[1]. Also, in another study from India of 58 patients, parenteral amphotericin B and surgical debridement were used in all patients[9]. In a case report study from Peru, isavuconazole was used, owing to the unavailability of amphotericin B, in a 66-year-old woman with this disease. The study revealed that the isavuconazole was effective and without adverse effects over 10 mo[15].

Of note, antifungal therapies have several shortcomings such as adverse effects related to infusion, optimal dosage, and nephrotoxicity. Nowadays, nanomedicine is an alternative promising solution, in which the intravenous route of the amphotericin B is shifted to other routes like through the mouth, local, and pulmonary routes. This system is under further development[30].

Surgical debridement has two advantages. It reduces the fungal load as well as provides sufficient tissue for histopathological evaluation. The process of debridement continues until the appearance of normal tissue that bleeds profusely. Removal of the palate, endoscopic nasal approach, and orbital decompression or exenteration are undertaken depending on the stage of the disease[28].

Correction of the hyperglycemic state, hypoxia, acidosis, and electrolyte disturbances are essential. We must take the opinion of relevant specialists concerning decreasing or discontinuing immunosuppressive or antibiotic therapy. Furthermore, the use of granulocyte colony-stimulating factors might increase the white cell count and improve host immunity[28].

PREVENTION

A golden rule in medicine is that "prevention is better than treatment." This is particularly true in serious diseases like mucormycosis. Many measures should be taken to avoid such a sinister pathology:

judicious and supervised use of systemic corticosteroids in compliance with the current preferred practice guidelines; judicious and supervised use of tocilizumab in compliance with the current preferred practice guidelines; strict monitoring and control of DM; aggressive aseptic precautions while administering oxygen (sterile water for the humidifier, daily change of the sterilized humidifier and the tubes); personal and environmental hygiene: use of betadine as a mouth gargle, barrier mask covering the mouth and nose, and consideration of prophylactic oral posaconazole in high-risk subjects (> 3 wk of mechanical ventilation, > 3 wk of supplemental oxygen, > 3 wk of systemic corticosteroids, poorly or uncontrolled DM with or without ketoacidosis, history of chronic rhinosinusitis, and immunocompromised conditions)[27].

PROGNOSIS

Although ROCM-related COVID-19 is a relatively uncommon condition, it is an aggressive disease with a high rate of morbidity and mortality[17]. One of the disaster complications is a loss of vision. In a large retrospective observational study from India of 2826 COVID-19 patients, there were 289 (16%) cases that ended with orbital exenteration[1]. The death rate is approaching 50%[18]. A recent study from Egypt reported a mortality rate of 21.4% (3/14)[31], which was considered low if one compares it with the mortality rate from India (31% to 49%)[32,33]. The fatality rate might range from 30% to 90% in patients with cerebral involvement[34]. It is of utmost importance to consider the staging system of the ROCM-related COVID-19 adopted by Honavar to determine the severity of the disease and survival rate[27]. It was reported in the literature that the delay in starting treatment even 6 d increases the 1-mo fatality from 35% to 66%[35]. Comorbidities and the immunosuppressive state of the patients will increase the aggressiveness of the disease and increase the morbidity and mortality rates. Early diagnosis and prompt treatment improve the outcomes.

CONCLUSION

ROCM-related COVID-19 is an opportunistic serious fungal infection. The commonest causative agents are from the *Rhizopus* specie. It occurs as one of the complications of COVID-19, particularly in diabetic patients and those on corticosteroid therapy or mechanical ventilation. The disease affects mostly the Indian population. Angio-invasion with tissue destruction is the hallmark of the disease. A high index of clinical suspicion, early diagnosis, intravenous or local amphotericin B, and surgical debridement lead to better outcomes. However, it carries a high rate of morbidity and mortality.

FOOTNOTES

Author contributions: Raid M Al-Ani performed all aspects of this manuscript's generation.

Conflict-of-interest statement: The author declares that there is no conflict of interest.

Country/Territory of origin: Iraq

ORCID number: Raid M Al-Ani 0000-0003-4263-9630.

S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

REFERENCES

1 **Sen M**, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, Sharma M, Sachdev M, Grover AK, Surve A, Budharapu A, Ramadhin AK, Tripathi AK, Gupta A, Bhargava A, Sahu A, Khairnar A, Kochar A, Madhavani A, Shrivastava AK, Desai AK, Paul A, Ayyar A, Bhatnagar A, Singhal A, Nikose AS, Tenagi AL, Kamble A, Nariani A, Patel B, Kashyap B, Dhawan B, Vohra B, Mandke C, Thrishulamurthy C, Sambare C, Sarkar D, Mankad DS, Maheshwari D, Lalwani D,

Kanani D, Patel D, Manjandavida FP, Godhani F, Agarwal GA, Ravulaparthi G, Shilpa GV, Deshpande G, Thakkar H, Shah H, Ojha HR, Jani H, Gontia J, Mishrikotkar JP, Likhari K, Prajapati K, Porwal K, Koka K, Dharawat KS, Ramamurthy LB, Bhattacharyya M, Saini M, Christy MC, Das M, Hada M, Panchal M, Pandharpurkar M, Ali MO, Porwal M, Gangashetappa N, Mehrotra N, Bijlani N, Gajendragadkar N, Nagarkar NM, Modi P, Rewri P, Sao P, Patil PS, Giri P, Kapadia P, Yadav P, Bhagat P, Parekh R, Dyaberi R, Chauhan RS, Kaur R, Duvesh RK, Murthy R, Dandu RV, Kathiara R, Beri R, Pandit R, Rani RH, Gupta R, Pherwani R, Sapkal R, Mehta R, Tadepalli S, Fatima S, Karmarkar S, Patil SS, Shah S, Dubey S, Gandhi S, Kanakpur S, Mohan S, Bhomaj S, Kerkar S, Jariwala S, Sahu S, Tara S, Maru SK, Jhavar S, Sharma S, Gupta S, Kumari S, Das S, Menon S, Burkule S, Nisar SP, Kaliaperumal S, Rao S, Pakrasi S, Rathod S, Biradar SG, Kumar S, Dutt S, Bansal S, Ravani SA, Lohiya S, Ali Rizvi SW, Gokhale T, Lahane TP, Vukkadala T, Grover T, Bhesaniya T, Chawla U, Singh U, Une VL, Nandedkar V, Subramaniam V, Eswaran V, Chaudhry VN, Rangarajan V, Dehane V, Sahasrabudhe VM, Sowjanya Y, Tupkary Y, Phadke Y; members of the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol* 2021; **69**: 1670-1692 [PMID: 34156034 DOI: 10.4103/ijo.IJO_1565_21]

2 **Selarka L**, Sharma S, Saini D, Batra A, Waghmare VT, Dileep P, Patel S, Shah M, Parikh T, Darji P, Patel A, Goswami G, Shah A, Shah S, Lathiya H, Sharma P, Chopra S, Gupta A, Jain N, Khan E, Sharma VK, Sharma AK, Chan ACY, Ong JJY. Mucormycosis and COVID-19: An epidemic within a pandemic in India. *Mycoses* 2021; **64**: 1253-1260 [PMID: 34255907 DOI: 10.1111/myc.13353]

3 **Mehta S**, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. *Cureus* 2020; **12**: e10726 [PMID: 33145132 DOI: 10.7759/cureus.10726]

4 **Rawson TM**, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. *Clin Infect Dis* 2020; **71**: 2459-2468 [PMID: 32358954 DOI: 10.1093/cid/ciaa530]

5 **Song G**, Liang G, Liu W. Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China. *Mycopathologia* 2020; **185**: 599-606 [PMID: 32737747 DOI: 10.1007/s11046-020-00462-9]

6 **Werthman-Ehrenreich A**. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med* 2021; **42**: 264.e5-264.e8 [PMID: 32972795 DOI: 10.1016/j.ajem.2020.09.032]

7 **Jeong W**, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SC. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clin Microbiol Infect* 2019; **25**: 26-34 [PMID: 30036666 DOI: 10.1016/j.cmi.2018.07.011]

8 **Prakash H**, Chakrabarti A. Global Epidemiology of Mucormycosis. *J Fungi (Basel)* 2019; **5** [PMID: 30901907 DOI: 10.3390/jof5010026]

9 **Dave TV**, Gopinathan Nair A, Hegde R, Vithalani N, Desai S, Adulkar N, Kamal S, Mittal R, Bradoo RA. Clinical Presentations, Management and Outcomes of Rhino-Orbital-Cerebral Mucormycosis (ROCM) Following COVID-19: A Multi-Centric Study. *Ophthalmic Plast Reconstr Surg* 2021; **37**: 488-495 [PMID: 34314399 DOI: 10.1097/IOP.0000000000002030]

10 **Bayram N**, Ozsaygılı C, Sav H, Tekin Y, Gundogan M, Pangal E, Cicek A, Özcan İ. Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. *Jpn J Ophthalmol* 2021; **65**: 515-525 [PMID: 34057620 DOI: 10.1007/s10384-021-00845-5]

11 **Fouad YA**, Abdelaziz TT, Askoura A, Saleh MI, Mahmoud MS, Ashour DM, Ashour MM. Spike in Rhino-Orbital-Cerebral Mucormycosis Cases Presenting to a Tertiary Care Center During the COVID-19 Pandemic. *Front Med (Lausanne)* 2021; **8**: 645270 [PMID: 34124087 DOI: 10.3389/fmed.2021.645270]

12 **Pakdel F**, Ahmadikia K, Salehi M, Tabari A, Jafari R, Mehrparvar G, Rezaie Y, Rajaeih S, Alijani N, Barac A, Abdollahi A, Khodavaisy S. Mucormycosis in patients with COVID-19: A cross-sectional descriptive multicentre study from Iran. *Mycoses* 2021; **64**: 1238-1252 [PMID: 34096653 DOI: 10.1111/myc.13334]

13 **Avatef Fazeli M**, Rezaei L, Javadirad E, Iranfar K, Khosravi A, Amini Saman J, Poursabbagh P, Ghadami MR, Parandin MM, Dehghani A, Ahmadi Jouybari T, Mahdavian B, Eivazi N, Rezaei S, Rezaei A, Emami B, Haqgou M, Bozorgomid A, Sayad B. Increased incidence of rhino-orbital mucormycosis in an educational therapeutic hospital during the COVID-19 pandemic in western Iran: An observational study. *Mycoses* 2021; **64**: 1366-1377 [PMID: 34252988 DOI: 10.1111/myc.13351]

14 **Palou EY**, Ramos MA, Cherenfant E, Duarte A, Fuentes-Barahona IC, Zambrano LI, Muñoz-Lara F, Montoya-Ramirez SA, Cardona-Ortiz AF, Valle-Reconco JA, Montenegro-Idrogo JJ, Bonilla-Aldana DK, Paniz-Mondolfi AE, Rodriguez-Morales AJ. COVID-19 Associated Rhino-Orbital Mucormycosis Complicated by Gangrenous and Bone Necrosis-A Case Report from Honduras. *Vaccines (Basel)* 2021; **9** [PMID: 34451951 DOI: 10.3390/vaccines9080826]

15 **Ponce-Rosas L**, Gonzales-Zamora J, Diaz-Reyes N, Alarco-Cadillo O, Alave-Rosas J. Rhino-Orbital-Cerebral Mucormycosis in a Post-COVID-19 Patient from Peru. *Case Rep Infect Dis* 2022; **2022**: 2537186 [PMID: 35299936 DOI: 10.1155/2022/2537186]

16 **Hirabayashi KE**, Idowu OO, Kalin-Hajdu E, Oldenburg CE, Brodie FL, Kersten RC, Vagefi MR. Invasive Fungal Sinusitis: Risk Factors for Visual Acuity Outcomes and Mortality. *Ophthalmic Plast Reconstr Surg* 2019; **35**: 535-542 [PMID: 30893189 DOI: 10.1097/IOP.0000000000001357]

17 **Sarkar S**, Gokhale T, Choudhury SS, Deb AK. COVID-19 and orbital mucormycosis. *Indian J Ophthalmol* 2021; **69**: 1002-1004 [PMID: 33727483 DOI: 10.4103/ijo.IJO_3763_20]

18 **Revannavar SM**, P S S, Samaga L, V K V. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world? *BMJ Case Rep* 2021; **14** [PMID: 33906877 DOI: 10.1136/bcr-2021-241663]

19 **Chen G**, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: 32217835 DOI: 10.1172/JCI137244]

20 **Perricone C**, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y, Gerli R. COVID-19 as part of the

hyperferritinemic syndromes: the role of iron depletion therapy. *Immunol Res* 2020; **68**: 213-224 [PMID: 32681497 DOI: 10.1007/s12026-020-09145-5]

21 **Goldman N**, Fink D, Cai J, Lee YN, Davies Z. High prevalence of COVID-19-associated diabetic ketoacidosis in UK secondary care. *Diabetes Res Clin Pract* 2020; **166**: 108291 [PMID: 32615280 DOI: 10.1016/j.diabres.2020.108291]

22 **Yang JK**, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010; **47**: 193-199 [PMID: 19333547 DOI: 10.1007/s00592-009-0109-4]

23 **Kothandaraman N**, Rengaraj A, Xue B, Yew WS, Velan SS, Karnani N, Leow MKS. COVID-19 endocrinopathy with hindsight from SARS. *Am J Physiol Endocrinol Metab* 2021; **320**: E139-E150 [PMID: 33236920 DOI: 10.1152/ajpendo.00480.2020]

24 **Ibrahim AS**, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. *Clin Infect Dis* 2012; **54** Suppl 1: S16-S22 [PMID: 22247441 DOI: 10.1093/cid/cir865]

25 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

26 **Sabirli R**, Koseler A, Goren T, Turkcuer I, Kurt O. High GRP78 levels in Covid-19 infection: A case-control study. *Life Sci* 2021; **265**: 118781 [PMID: 33220289 DOI: 10.1016/j.lfs.2020.118781]

27 **Honavar SG**. Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-Orbito-Cerebral Mucormycosis in the Setting of COVID-19. *Indian J Ophthalmol* 2021; **69**: 1361-1365 [PMID: 34011699 DOI: 10.4103/ijo.IJO_1165_21]

28 **AK AK**, Gupta V. Rhino-orbital Cerebral Mucormycosis. 2022 Apr 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 32491361]

29 **Girdhar D**, Manocha E. A Comprehensive Review on the Management of COVID-19-Associated Mucormycosis (CAM): The New Basics. BioMed. 2022;2(2):181-198.

30 **Sahu RK**, Salem-Bekhit MM, Bhattacharjee B, Almoshari Y, Ikbal AMA, Alshamrani M, Bharali A, Salawi A, Widyowati R, Alshammari A, Elbagory I. Mucormycosis in Indian COVID-19 Patients: Insight into Its Patho-Genesis, Clinical Manifestation, and Management Strategies. *Antibiotics (Basel)* 2021; **10** [PMID: 34572661 DOI: 10.3390/antibiotics10091079]

31 **Alloush TK**, Mansour O, Alloush AT, Roushdy T, Hamid E, El-Shamy M, Shokri HM. Rhino-orbito-cerebral mucormycosis during the COVID-19 third wave in 2021: an Egyptian preliminary report from a single tertiary hospital. *Neurol Sci* 2022; **43**: 799-809 [PMID: 34787754 DOI: 10.1007/s10072-021-05740-y]

32 **Prakash H**, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, Pamidimukkala U, Jillwin J, Varma S, Das A, Panda NK, Singh S, Bal A, Chakrabarti A. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. *Med Mycol* 2019; **57**: 395-402 [PMID: 30085158 DOI: 10.1093/mmy/myy060]

33 **Patel A**, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, Singh R, Shastri P, Umabala P, Sardana R, Kindo A, Capoor MR, Mohan S, Muthu V, Agarwal R, Chakrabarti A. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. *Clin Microbiol Infect* 2020; **26**: 944.e9-944.e15 [PMID: 31811914 DOI: 10.1016/j.cmi.2019.11.021]

34 **Prakash H**, Chakrabarti A. Epidemiology of Mucormycosis in India. *Microorganisms* 2021; **9** [PMID: 33806386 DOI: 10.3390/microorganisms9030523]

35 **Spellberg B**, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005; **18**: 556-569 [PMID: 16020690 DOI: 10.1128/CMR.18.3.556-569.2005]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 300-309

DOI: 10.5501/wjv.v11.i5.300

ISSN 2220-3249 (online)

MINIREVIEWS

Role of high dose vitamin C in management of hospitalised COVID-19 patients: A minireview

Deven Juneja, Anish Gupta, Sahil Kataria, Omender Singh

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Barve P, United States; Carlan SJ, United States; Emran TB, Bangladesh; Mrzljak A, Croatia

Received: July 29, 2022
Peer-review started: July 29, 2022
First decision: August 22, 2022
Revised: August 22, 2022
Accepted: September 1, 2022
Article in press: September 1, 2022
Published online: September 25, 2022

Deven Juneja, Anish Gupta, Sahil Kataria, Omender Singh, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, 1 Press Enclave Road, Saket, New Delhi 110017, India. devenjuneja@gmail.com

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as one of the most dreadful viruses the mankind has witnessed. It has caused world-wide havoc and wrecked human life. In our quest to find therapeutic options to counter this threat, several drugs have been tried, with varying success. Certain agents like corticosteroids, some anti-virals and immunosuppressive drugs have been found useful in improving clinical outcomes. Vitamin C, a water-soluble vitamin with good safety profile, has been tried to reduce progression and improve outcomes of patients with coronavirus disease 2019 (COVID-19). Because of its anti-oxidant and immunomodulatory properties, the role of vitamin C has expanded well beyond the management of scurvy and it is increasingly been employed in the treatment of critically ill patients with sepsis, septic shock, acute pancreatitis and even cancer. However, in spite of many case series, observational studies and even randomised control trials, the role of vitamin C remains ambiguous. In this review, we will be discussing the scientific rationale and the current clinical evidence for using high dose vitamin C in the management of COVID-19 patients.

Key Words: Ascorbic acid; COVID-19; SARS-CoV-2; Vitamin C

Core Tip: Vitamin C has several biochemical effects including anti-oxidant, anti-inflammatory, immuno-modulatory, and anti-viral properties which could make it a possible low-risk, add on to the current therapeutic options for managing coronavirus disease 2019 (COVID-19) patients. As it is a water-soluble vitamin, even high doses have been shown to be safe and only rarely, complications have been reported. In the last couple of years, many case series, observational studies and even randomised control trials have been conducted to evaluate the role of vitamin C in COVID-19, but have shown conflicting results. Hence, as per the current clinical evidence, the role of vitamin C remains ambiguous and it cannot be recommended as a part of routine therapeutic regimen for managing COVID-19 patients.

Citation: Juneja D, Gupta A, Kataria S, Singh O. Role of high dose vitamin C in management of hospitalised COVID-19 patients: A minireview. *World J Virol* 2022; 11(5): 300-309
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/300.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.300

INTRODUCTION

Viruses have always been potential threats and posed challenges to human health. Historically, various respiratory viruses like severe acute respiratory virus (SARS-CoV) in 2002, H1N1 influenza virus in 2009 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 have created havoc and wrecked human life. In December 2019, in Wuhan, China, the first pneumonia outbreak secondary to COVID was reported. It was given an interim name of 2019-nCoV by the World Health Organisation and was later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses.

SARS-CoV-2 is one of the most dreadful viruses faced by mankind which not only led to the COVID outbreak in China but also spread throughout the world infecting more than 528 million people with more than 6.3 million deaths worldwide[1]. This virus led to a disease with a varied clinical spectrum ranging from asymptomatic viral carriers to severe disease characterised by acute respiratory distress syndrome (ARDS)[2,3]. The majority of affected individuals had mild symptoms especially in the initial stages of infection but many patients developed life threatening complications in the later stages with ARDS and consequent multiorgan failure leading to mortality of 7%-10%, especially in the elderly and those with pre-existing comorbidities[2-4].

The primary mechanism by which the virus caused severe disease was the initiation and propagation of a hyperimmune response, which increased pro-inflammatory cytokines and serum biomarkers[5]. The initial viral cytopathic effects were later complicated by a cytokine storm which led to ARDS and other systemic organ involvement[6]. In lieu of this cytokine storm, various anti-inflammatory and immune-modulating medications like corticosteroids, interleukin-6 (IL-6) inhibitors, and Janus kinase (JAK) inhibitors have been tried to prevent, as well as treat this life threatening complication.

Vitamin C was one of the most commonly prescribed medications for all patients of COVID-19, irrespective of the severity of the disease. Vitamin C is an essential water-soluble vitamin which is required in humans for collagen synthesis, wound healing, bone development, various biochemical functions, redox reactions, synthesis of carnitine, adrenal steroids and catecholamines and metabolism of amino acids and cholesterol[7]. Over the years, its clinical role has expanded and is now commonly prescribed to treat myriad of severe diseases including sepsis, septic shock, acute pancreatitis and even cancer[8-10]. However, its role in these disease conditions remain controversial. Vitamin C has also been suggested as a potential therapeutic option in managing COVID-19 patients, with a few reports showing a beneficial role[11]. However, larger trials have reported variable outcomes, precluding definitive conclusions on vitamin C use in COVID-19 patients[12-14].

RATIONALE

The pathophysiology of COVID-19 remains incompletely understood. However, some patho-physiological changes, cytokine storm, micro thrombosis and immune-paralysis, have been described, which may lead to multi-organ dysfunction and death attributable to COVID-19. Another important phenomenon is release of oxygen free radicals (OFRs), causing oxidative damage and end-organ failure. These pathophysiological changes are similar to those seen with sepsis and septic shock, and hence, it was postulated that the use of vitamin C might be clinically beneficial in managing COVID-19.

Vitamin C deficiency

The normal plasma levels of vitamin C have been described above 50 μmol/L[15]. It is further suggested that although these levels may be sufficient to prevent scurvy, higher levels may be required to

strengthen the immune system[16]. However, these levels quickly fall in patients with acute illness, and vitamin C deficiency, defined as levels below 11 μmol/L, is commonly reported among hospitalized patients[17-19].

Studies in critically ill COVID-19 patients have also shown low mean vitamin C levels. In addition, levels were significantly lower among non-survivors as compared with survivors[20]. In a single center study of patients with COVID-19 associated ARDS, more than 90% had almost undetectable serum vitamin C levels[21]. It is postulated that the reason for vitamin C deficiency observed in acute illnesses like infections, trauma, and surgery is the increase in metabolic consumption[22].

Anti-oxidant properties

Vitamin C has well described anti-oxidant properties, which may help in scavenging OFRs by increasing nitric oxide levels. It also prevents production of nitrogen species, improving capillary blood flow[23].

Anti-inflammatory properties

Vitamin C has several anti-inflammatory effects, potentially having clinical benefits in managing COVID-19 induced cytokine storm. It inhibits tumor necrosis factor-α (TNF-α), suppresses activation of nuclear factor kappa-B (NF-kB), reduces pro-inflammatory cytokines and lowers histamine levels[24].

Immune enhancing properties

By affecting lipid synthesis and reinforcing the maintenance of the alveolar epithelial barrier, vitamin C helps in improving innate immunity. Vitamin C potentially helps in immunomodulation by increasing the immunoglobin and complement levels[25]. It also exhibits immunomodulatory properties by promoting T-cell maturation and modulation, improving neutrophil chemotaxis and phagocytosis and by enhancing oxidative killing. In addition, it also promotes lymphocytic proliferation, interferon production and increases antibody production[23,24].

Prevention of micro and macro vascular dysfunction

Vitamin C acts as a co-factor for synthesis of catecholamines (epinephrine, norepinephrine), and vasopressin and increases the sensitivity of vascular musculature to these compounds. Vitamin C also causes inhibition of inducible nitric oxide synthase (iNOS) expression, thereby preventing vasoconstriction. These effects may be particularly helpful in patients with shock and may improve end-organ perfusion[23,24].

Anti-viral properties

Vitamin C has been shown to have direct and indirect effects on viral replication and can inactivate several viruses *in vitro*[26]. High-dose vitamin C may cause viral inactivation by oxidation of viral nucleic acids and damage to viral capsids. Vitamin C can also have indirect effects by promoting interferon production, which may, in-turn affect viral replication by binding to the cell surface. Interferons may also aid in immune-stimulation leading to virus inactivation[27]. Because of these anti-viral properties, vitamin C has been used clinically to manage viral illnesses ranging from common cold to viral ARDS secondary to wide range of viruses like enterovirus/rhinovirus, H1N1, and CHIKV[28-31].

Other miscellaneous effects

By reducing oxidation injury and apoptosis vitamin C plays a role in prevention of mitochondrial dysfunction. In addition, it also prevents septic cardiomyopathy by reducing oxidation injury and apoptosis and by increasing carnitine synthesis[23,24]. Hence, it may prove useful in managing viral myocarditis and improving cardiac dysfunction.

CLINICAL EVIDENCE

The first large randomized clinical trial (RCT) to evaluate the effect of vitamin C in COVID-19 patients was the COVID A to Z trial. It was a multicentre open label RCT which aimed to assess the effect of high dose zinc (50 mg), high dose ascorbic acid (8000 mg per day in 2-3 divided doses, orally) or a combination of both zinc and ascorbic acid on the duration of symptoms of SARS-COV-2. A total of 214 patients were enrolled in the study and randomised equally into 4 groups to receive a 10-d course of either zinc gluconate, ascorbic acid, both or only standard of care. The study's primary end point was the number of days required for a reduction in symptoms (fever, cough, shortness of breath, and fatigue) by 50%. The results of the study did not show any significant decrease in the duration of symptoms as compared to standard of care. Additionally, there was no statistically significant difference in the need for hospitalisation and mortality[32].

Even though vitamin C is widely prescribed in the management of COVID-19 patients, the scientific evidence is primarily derived from case series and retrospective studies (Table 1)[11,14,33-42]. Only a few RCTs have been conducted to evaluate the role of high dose intravenous vitamin C (HDIVC) in hospitalised COVID-19 patients[12,13,43,44]. The largest RCT was a Pakistani study, which included 150 patients, 75 each in study and control groups. Patients in the study group were given 50 mg/kg/d of IV vitamin C and compared to those who received only the standard therapy. The authors reported that the patients who received IV vitamin C became symptom-free earlier and had reduced hospital length of stay (LOS)[13]. However, there was no significant difference in the need for invasive mechanical ventilation (IMV) and mortality. Other RCTs also failed to show any difference in the need for IMV or reduction in mortality rates (Table 1)[12,43,44].

A few studies showed a reduction in inflammatory markers[11,33,35,36,38] but these results were neither consistent nor translated in to improved clinical outcomes[33]. One small retrospective cohort study even reported increased mortality in COVID-19 patients treated with IV vitamin C 1.5 gm every 6th hourly for four days[37].

A few meta-analyses have also been published evaluating the role of vitamin C in COVID-19 (Table 2)[45-47]. Rawat *et al*[47] performed a meta-analysis on the impact of Vitamin C on major clinical outcomes such as mortality, intensive care unit (ICU) admission, duration of hospital stay and need for mechanical ventilation in patients diagnosed with COVID-19. They included 6 RCTs in their analysis encompassing 572 patients. Amongst the 6 studies, 2 were multicenter RCTs, and 4 were single centre studies. Two studies were conducted on non-severe patients, while 4 studies were conducted on severe cases of COVID-19. Both oral (2 studies) and intravenous vitamin C (4 studies) were used, and the dosage ranged from 50 mg/kg/d to 24 g per day of vitamin C. The meta-analysis did not show vitamin C to reduce any major outcomes in COVID-19 patients. Even in a subgroup analysis based on the dose, route of administration and severity of illness, no significant benefit was observed. However, this meta-analysis had multiple limitations including heterogeneity in the study population, variable doses of vitamin C and differences in route of administration. In defense, the subgroup analysis also revealed similar results. Moreover, some studies used combination of vitamin E and melatonin, which may have confounded the results. Also, the standard treatment used in the control groups differed and the data on the adverse effects of vitamin C was lacking[47].

A recently published meta-analysis analysed data from five trials in which only HDIVC, defined as IV vitamin C ≥ 2 gm/d, was prescribed to hospitalised COVID-19 patients. Among the included studies, three were RCTs, and two were retrospective studies, including 374 patients. The authors could not find any statistically significant difference in terms of hospital LOS, mortality or adverse effects when patients were treated with HDIVC[46].

Another larger meta-analysis, including seven trials and 807 patients analysing the role of HDIVC, also failed to show any beneficial results in terms of mortality, hospital or ICU LOS or need for IMV in COVID-19 patients. The authors further noted that all the included trials were of high quality but different dosing regimens were used ranging from 2-24 gm of IV vitamin C per day for 3-7 d[45].

Recognising the lack of clinical evidence, the current National Institutes of Health (NIH) guidelines also does not make any recommendation for or against the use of vitamin C in the management of outpatient or hospitalised COVID-19 patients[48].

DOSING

Both oral and intravenous formulations of vitamin C have shown similar clinical efficacy, but intravenous route is generally preferred in critically ill patients[49,50]. It is suggested that higher doses of vitamin C, 2-3 gm/day, may be required to maintain the normal serum concentrations in patients with acute viral infections[51]. High doses of up to 100 g/d have been tried in the management of sepsis patients[52]. Although there is no consensus, any dose above 2 g/d is arbitrarily considered as high dose[46].

Even though several different dosing regimens have been tried in patients with COVID-19, data regarding dosing regimens are generally extrapolated from the trials on sepsis patients. Six hourly dosing have been shown to rapidly improve serum vitamin C levels, achieve a steady state and maintain therapeutic levels[53,54]. However, no consensus presently exists on the recommended daily dosage regimen for HDIVC.

ADVERSE EFFECTS

Even when used in high doses, vitamin C is considered harmless as it is a water-soluble vitamin. The major trials have mainly concentrated on the efficacy of vitamin C, and the data regarding adverse effects are primarily derived from case reports and series[55]. Most reported adverse effects are mild and reversible (Table 3)[55-57]. Rarely, patients may develop serious adverse effects, including haemolysis, disseminated intravascular coagulation and acute kidney injury (AKI). Adverse effects have

Table 1 Different studies evaluating the role of high dose intravenous Vitamin C in COVID-19

S. No.	Title	Year of publication	Country of origin	Study design	Sample size in the control arm	Sample size in the intervention arm	Intervention summary	Results in brief
1	Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia[14]	2022	Turkey	Retrospective study	170 patients	153 patients	2 g/d IV	No difference in mortality
2	High-dose intravenous vitamin C decreases rates of mechanical ventilation and cardiac arrest in severe COVID-19[33]	2022	USA	Retrospective cohort study	75 patients	25 patients	3 gm 6 hrly for 7 d IV	HDIVC group had a prolonged hospital stay, prolonged ICU stay, and prolonged time to deathCRP levels were lower in the HDIVC group while other inflammatory markers (d-dimer and ferritin) were similar in both groups.HDIVC patients had significantly lower rates of IMV and cardiac arrest
3	Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial[43]	2021	Iran	RCT	11	10	IV vitamin C (2 g, q6hr), oral; melatonin (6 mg, 6 hourly), and oral zinc sulfate (50 mg, 6 hourly) for 10 d	No differences in PaO2/FiO2, CRP, ESR or LDH levels and ICU LOS
4	Pilot trial of high-dose vitamin C in critically ill COVID-19 patients[12]	2021	China	Multi center RCT	29 in control	27 treatment group	12 g of vitamin C/50 ml every 12 h for 7 d at a rate of 12 mL/h IV	No difference in IMV free days at D28; no difference in 28-d mortality. Steady rise in the PaO_2/FiO_2 in vitamin C group
5	No significant benefit of moderate-dose vitamin C on severe COVID-19 cases[34]	2021	China	Retrospective cohort study	327	70	2-4 gm/d	No significant difference in clinical improvement or mortality rate
6	Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition: a retrospective case series study[35]	2021	China	Retrospective case series		12 patients	71 to 350 mg/kg/d for 3 d IV	Reduction in CRPImproved PaO_2/FiO_2 and SOFA score
7	High Dose Intravenous Vitamin C for Preventing The Disease Aggravation of Moderate COVID-19 Pneumonia. A Retrospective Propensity Matched Before-After Study[36]	2021	China	Retrospective before-after study	55 patients	55 patients	100 mg/kg/d IV for 7 d	Significant reduction in progression to severe disease.Reduced levels of CRP, D-dimer and APTT
8	Safety and effectiveness of high-dose vitamin C in patients with COVID-19: A randomized open-label clinical trial[44]	2021	Iran	Randomised open-label study	30 patients	30 patients	6 g/d IV	Reduced temperature and improved SaO2 in HDIVC group. No difference in ICU or hospital mortalityLonger hospital LOS in HDIVC group
9	Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection[37]	2021	USA	Retrospective cohort study	24 patients	8 patients	1.5 grams IV vitamin C every 6 h for up to 4 d	HDIVC group had higher rates of hospital mortality and mean SOFA scores post-treatment. No difference in daily vasopressor requirement or ICU LOS
10	High-dose intravenous vitamin C attenuates hyperinflammation in severe coronavirus disease 2019[38]	2021	China	Retrospective cohort study	151	85	100 mg/kg every 6 h for day 1 followed by 100 mg/kg evry 12 h for the next 5 d	Significantly reduced inflammatory markers (hs-CRP, IL-6, TNF-alpha)
11	The efficiency and safety of high-dose	2021	China	Retrospective	30	46	6 g twice a day on day 1	Reduced 28 d mortality. No change in oxygen support

	vitamin C in patients with COVID-19: A retrospective cohort study[39]			cohort study			followed by 6 gm once a day for 4 d IV	
12	High-dose vitamin C ameliorates cardiac injury in COVID-19 pandemic: A retrospective cohort study[40]	2021	China	Retrospective cohort study	62	51	100 mg/kg every 6 h for day 1 followed by 100 mg/kg evry 12 h for the next 5 d	HDIVC can ameliorate cardiac injury through alleviating hyperinflammation
13	The Role of Vitamin C as Adjuvant Therapy in COVID-19[13]	2020	Pakistan	RCT	75 patients	75 patients	50 mg/kg/day of intravenous (IV)	Earlier resolution of symptoms and reduced hospital LOS. No significant difference in the need for IMV and mortality
14	Activities of serum ferritin and treatment outcomes among COVID-19 patients treated with vitamin c and dexamethasone:An uncontrolled single-center observational study[41]	2020	India	Prospective, observational study		50 patients	NA	Mortality 6%
15	The use of IV vitamin C for patients with COVID-19: A case series[11]	2020	USA	Case series		17 patients	1 g every 8 h for 3 d IV	Significant decrease in inflammatory markers. Mortality 12%
16	Application of methylene blue -vitamin C - N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial[42]	2020	Iran	Phase I clinical trial	25 ICU COVID-19 patients. 5 received MCN as last resort	25 healthy individuals	Methylene blue (1 mg/kg) along with vitamin C (1500 mg/kg) and N-acetyl Cysteine (1500 mg/kg) orally or intravenously	Reduced methhemoglobin levels, survival of 4/5 patients

IV: Intravenously; HDIVC: High dose intravenous vitamin C; ICU: Intensive care unit; CRP: C-reactive protein; RCT: Randomised control trial; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; LOS: Length of stay; IMV: Invasive mechanical ventilation; SOFA: Sequential organ failure assessment; APTT: Activated prothrombin time; IL: Interleukin; TNF: Tumour necrosis factor; MCN: Methylene blue; USA: United states; COVID-19: Coronavirus disease 2019; RCT: Randomised control trial; NA: Not available.

been reported with both oral and intravenous preparations and the use of normal doses and high doses of vitamin C. Patients with underlying renal dysfunction and glucose-6-phosphate dehydrogenase (G6PD) deficiency are especially more prone to develop side effects like AKI and haemolysis[55].

FUTURE DIRECTIONS

Almost 50 trials are presently being conducted to evaluate the role of vitamin C in patients with COVID-19 disease. These trials are being conducted in patients with different severity of disease and are trying to assess different clinical outcomes ranging from the need for hospitalisation, resolution of symptoms, need for organ support, need for IMV and mortality. Role of vitamin C is also being explored in combination with other therapies like zinc, quercetin, and curcumin and comparison to other anti-oxidants like vitamin E, melatonin, pentoxifylline, and N-acetyl cysteine. These trials may help us better understand vitamin C's clinical efficacy and safety profile and clarify its potential role in the management of COVID-19 patients. Also, these studies may shed light on the dosing of HDIVC, as most of the studies performed till now have used different dosing regimens, which might have affected their results.

Table 2 Meta-analyses evaluating the role of Vitamin C in COVID-19

S. No.	Title	Year of publication	Country of origin	Included studies	Included sample size	Results in brief
1	Intravenous vitamin C use and risk of severity and mortality in COVID-19: A systematic review and meta-analysis[45]	2022	China	7 studies (3 RCTs, 4 observational studies)	807 patients	IV vitamin C treatment did not affect disease severity or mortality
2	The effectiveness of high-dose intravenous vitamin C for patients withcoronavirus disease 2019: A systematic review and meta-analysis[46]	2022	Korea	5 studies (3 RCTs, 2 retrospective trials)	374 patients (186 HDIVC and 184 control group)	No difference in hospital LOS or mortality
3	Vitamin C and COVID-19 treatment: A systematic review and metaanalysis of randomized controlled trials[47]	2021	India	6 RCTs	572 patients	Vitamin C treatment didn't reducemortality, ICU LOS, hospital LOS or need for invasive mechanical ventilation

RCT: Randomised control trial; IV: Intravenously; HDIVC: High dose intravenous vitamin C; LOS: Length of stay; ICU: Intensive care unit.

Table 3 Adverse effects reported with vitamin C

Item	Description
General	Interference with laboratory tests, phlebitis, nausea, vomiting
Neuro-muscular	Lethargy, fatigue, muscle cramps, headache, altered mental status
Metabolic	Hyperglycemia, hypernatremia
Haematological	Haemolysis, disseminated intravascular coagulation, methemoglobinemia
Renal	Oxalosis, renal stones, acute kidney injury

CONCLUSION

Vitamin C is a relatively safe therapeutic option, and there may be scientific rationale which theoretically may help in the recovery of COVID-19 patients. Many observational studies and some RCTs have been conducted to evaluate its role in COVID-19. However, presently there is dearth of clinical evidence showing its utility in the management of COVID-19 patients; hence, it cannot be recommended for routine use in these patients. Further larger multi-center RCTs are warranted to prove its safety and potential role.

FOOTNOTES

Author contributions: Juneja D, Gupta A, and Kataria S performed the majority of the writing, prepared the tables, and performed data accusation; Singh O provided the input in writing the paper and reviewed the manuscript.

Conflict-of-interest statement: There are no conflicts of interest to report.

Country/Territory of origin: India

ORCID number: Deven Juneja 0000-0002-8841-5678; Anish Gupta 0000-0002-0901-4797; Sahil Kataria 0000-0002-0756-4154; Omender Singh 0000-0002-3847-4645.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **World health organization**. WHO Coronavirus (COVID-19) dashboard. [cited 27 July 2022]. Available from: https://covid19.who.int

2 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

3 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

4 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

5 **Liu F**, Li L, Xu M, Wu J, Luo D, Zhu Y, Li B, Song X, Zhou X. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020; **127**: 104370 [PMID: 32344321 DOI: 10.1016/j.jcv.2020.104370]

6 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

7 **Ströhle A**, Wolters M, Hahn A. Micronutrients at the interface between inflammation and infection--ascorbic acid and calciferol: part 1, general overview with a focus on ascorbic acid. *Inflamm Allergy Drug Targets* 2011; **10**: 54-63 [PMID: 21184650 DOI: 10.2174/187152811794352105]

8 **Marik PE**, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* 2017; **151**: 1229-1238 [PMID: 27940189 DOI: 10.1016/j.chest.2016.11.036]

9 **Gao L**, Chong E, Pendharkar S, Phillips A, Ke L, Li W, Windsor JA. The Challenges and Effects of Ascorbic Acid Treatment of Acute Pancreatitis: A Systematic Review and Meta-Analysis of Preclinical and Clinical Studies. *Front Nutr* 2021; **8**: 734558 [PMID: 34765629 DOI: 10.3389/fnut.2021.734558]

10 **Mussa A**, Mohd Idris RA, Ahmed N, Ahmad S, Murtadha AH, Tengku Din TADAA, Yean CY, Wan Abdul Rahman WF, Mat Lazim N, Uskoković V, Hajissa K, Mokhtar NF, Mohamud R, Hassan R. High-Dose Vitamin C for Cancer Therapy. *Pharmaceuticals (Basel)* 2022; **15** [PMID: 35745630 DOI: 10.3390/ph15060711]

11 **Hiedra R**, Lo KB, Elbashabsheh M, Gul F, Wright RM, Albano J, Azmaiparashvili Z, Patarroyo Aponte G. The use of IV vitamin C for patients with COVID-19: a case series. *Expert Rev Anti Infect Ther* 2020; **18**: 1259-1261 [PMID: 32662690 DOI: 10.1080/14787210.2020.1794819]

12 **Zhang J**, Rao X, Li Y, Zhu Y, Liu F, Guo G, Luo G, Meng Z, De Backer D, Xiang H, Peng Z. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. *Ann Intensive Care* 2021; **11**: 5 [PMID: 33420963 DOI: 10.1186/s13613-020-00792-3]

13 **Kumari P**, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, Sohail H, Kumar B, Memon MK, Rizwan A. The Role of Vitamin C as Adjuvant Therapy in COVID-19. *Cureus* 2020; **12**: e11779 [PMID: 33409026 DOI: 10.7759/cureus.11779]

14 **Suna K**, Melahat UŞ, Murat Y, Figen ÖE, Ayperi Ö. Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia. *Med Clin (Barc)* 2022; **158**: 356-360 [PMID: 34103164 DOI: 10.1016/j.medcli.2021.04.010]

15 **European Food Safety Authority Panel on Dietetic Products**, Nutrition and Allergies. Scientific opinion on dietary reference values for vitamin C. *EFSA J* 2013; 11: 3418 [DOI: 10.2903/j.efsa.2013.3418]

16 **Berger MM**, Bischoff-Ferrari HA, Zimmermann M, Herter I, Spieldenner J, Eggersdorfer M. White Paper on Nutritional Status in Supporting a Well-Functioning Immune System for Optimal Health with a Recommendation for Switzerland; SGE: Bern, Switzerland, 2020. [cited 20 June 2022]. Available from: https://crnusa.org/sites/default/files/SSAC/2020.09.010%20SGE%20Nutritional%20status%20in%20supporting%20a%20well-functioning%20immune%20system%20for%20optimal%20health%20with%20a%20recommendation%20for%20Switzerland.pdf

17 **Evans-Olders R**, Eintracht S, Hoffer LJ. Metabolic origin of hypovitaminosis C in acutely hospitalized patients. *Nutrition* 2010; **26**: 1070-1074 [PMID: 20018480 DOI: 10.1016/j.nut.2009.08.015]

18 **Teixeira A**, Carrié AS, Généreau T, Herson S, Cherin P. Vitamin C deficiency in elderly hospitalized patients. *Am J Med* 2001; **111**: 502 [PMID: 11690581 DOI: 10.1016/s0002-9343(01)00893-2]

19 **Fain O**, Pariés J, Jacquart B, Le Moël G, Kettaneh A, Stirnemann J, Héron C, Sitbon M, Taleb C, Letellier E, Bétari B, Gattegno L, Thomas M. Hypovitaminosis C in hospitalized patients. *Eur J Intern Med* 2003; **14**: 419-425 [PMID: 14614974 DOI: 10.1016/j.ejim.2003.08.006]

20 **Arvinte C**, Singh M, Marik PE. Serum Levels of Vitamin C and Vitamin D in a Cohort of Critically Ill COVID-19 Patients of a North American Community Hospital Intensive Care Unit in May 2020: A Pilot Study. *Med Drug Discov* 2020; **8**: 100064 [PMID: 32964205 DOI: 10.1016/j.medidd.2020.100064]

21 **Chiscano-Camón L**, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Crit Care* 2020; **24**: 522 [PMID: 32847620 DOI: 10.1186/s13054-020-03249-y]

22 **Marik PE**, Hooper MH. Doctor-your septic patients have scurvy! *Crit Care* 2018; **22**: 23 [PMID: 29378661 DOI: 10.1186/s13054-018-1950-z]

23 **Carr AC**, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Crit Care* 2015; **19**: 418 [PMID: 26612352 DOI: 10.1186/s13054-015-1131-2]

24 **Marik PE**. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Ther* 2018; **189**: 63-70 [PMID: 29684467 DOI: 10.1016/j.pharmthera.2018.04.007]

25 **Prinz W**, Bortz R, Bregin B, Hersch M. The effect of ascorbic acid supplementation on some parameters of the human immunological defence system. *Int J Vitam Nutr Res* 1977; **47**: 248-257 [PMID: 914459]

26 **Jariwalla RJ**, Harakeh S. Antiviral and immunomodulatory activities of ascorbic acid. *Subcell Biochem* 1996; **25**: 213-231 [PMID: 8821976]

27 **Murata A**, Uike M. Mechanism of inactivation of bacteriophage MS2 containing single-stranded RNA by ascorbic acid. *J Nutr Sci Vitaminol (Tokyo)* 1976; **22**: 347-354 [PMID: 827603 DOI: 10.3177/jnsv.22.347]

28 **Anderson TW**, Reid DB, Beaton GH. Vitamin C and the common cold: a double-blind trial. *Can Med Assoc J* 1972; **107**: 503-508 [PMID: 5057006]

29 **Uchide N**, Toyoda H. Antioxidant therapy as a potential approach to severe influenza-associated complications. *Molecules* 2011; **16**: 2032-2052 [PMID: 21358592 DOI: 10.3390/molecules16032032]

30 **Gonzalez MJ**, Miranda-Massari JR, Berdiel MJ, Duconge J, Rodríguez-López JL, Hunninghake R, Cobas-Rosario VJ. High Dose Intraveneous Vitamin C and Chikungunya Fever: A Case Report. *J Orthomol Med* 2014; **29**: 154-156 [PMID: 25705076]

31 **Fowler Iii AA**, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R, Fisher BJ, Syed A, DeWilde C, Priday A, Kasirajan V. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. *World J Crit Care Med* 2017; **6**: 85-90 [PMID: 28224112 DOI: 10.5492/wjccm.v6.i1.85]

32 **Thomas S**, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, Il'Giovine ZJ, Mehra R, McWilliams C, Nissen SE, Desai MY. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. *JAMA Netw Open* 2021; **4**: e210369 [PMID: 33576820 DOI: 10.1001/jamanetworkopen.2021.0369]

33 **Hess AL**, Halalau A, Dokter JJ, Paydawy TS, Karabon P, Bastani A, Baker RE, Balla AK, Galens SA. High-dose intravenous vitamin C decreases rates of mechanical ventilation and cardiac arrest in severe COVID-19. *Intern Emerg Med* 2022 [PMID: 35349005 DOI: 10.1007/s11739-022-02954-6]

34 **Zheng S**, Chen Q, Jiang H, Guo C, Luo J, Li S, Wang H, Li H, Zheng X, Weng Z. No significant benefit of moderate-dose vitamin C on severe COVID-19 cases. *Open Med (Wars)* 2021; **16**: 1403-1414 [PMID: 34616916 DOI: 10.1515/med-2021-0361]

35 **Zhao B**, Ling Y, Li J, Peng Y, Huang J, Wang Y, Qu H, Gao Y, Li Y, Hu B, Lu S, Lu H, Zhang W, Mao E. Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition: a retrospective case series study. *Ann Palliat Med* 2021; **10**: 1599-1609 [PMID: 33222462 DOI: 10.21037/apm-20-1387]

36 **Zhao B**, Liu M, Liu P, Peng Y, Huang J, Li M, Wang Y, Xu L, Sun S, Qi X, Ling Y, Li J, Zhang W, Mao E, Qu J. High Dose Intravenous Vitamin C for Preventing The Disease Aggravation of Moderate COVID-19 Pneumonia. A Retrospective Propensity Matched Before-After Study. *Front Pharmacol* 2021; **12**: 638556 [PMID: 33967773 DOI: 10.3389/fphar.2021.638556]

37 **Li M**, Ching TH, Hipple C, Lopez R, Sahibzada A, Rahman H. Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection. *J Pharm Pract* 2021; 8971900211015052 [PMID: 34098784 DOI: 10.1177/08971900211015052]

38 **Xia G**, Fan D, He Y, Zhu Y, Zheng Q. High-dose intravenous vitamin C attenuates hyperinflammation in severe coronavirus disease 2019. *Nutrition* 2021; **91-92**: 111405 [PMID: 34388587 DOI: 10.1016/j.nut.2021.111405]

39 **Gao D**, Xu M, Wang G, Lv J, Ma X, Guo Y, Zhang D, Yang H, Jiang W, Deng F, Xia G, Lu Z, Lv L, Gong S. The efficiency and safety of high-dose vitamin C in patients with COVID-19: a retrospective cohort study. *Aging (Albany NY)* 2021; **13**: 7020-7034 [PMID: 33638944 DOI: 10.18632/aging.202557]

40 **Xia G**, Qin B, Ma C, Zhu Y, Zheng Q. High-dose vitamin C ameliorates cardiac injury in COVID-19 pandemic: a retrospective cohort study. *Aging (Albany NY)* 2021; **13**: 20906-20914 [PMID: 34499050 DOI: 10.18632/aging.203503]

41 **Burugu HR**, Kandi V, Kutikuppala LVS, Suvvari TK. Activities of Serum Ferritin and Treatment Outcomes Among COVID-19 Patients Treated With Vitamin C and Dexamethasone: An Uncontrolled Single-Center Observational Study. *Cureus* 2020; **12**: e11442 [PMID: 33324525 DOI: 10.7759/cureus.11442]

42 **Alamdari DH**, Moghaddam AB, Amini S, Keramati MR, Zarmehri AM, Alamdari AH, Damsaz M, Banpour H, Yarahmadi A, Koliakos G. Application of methylene blue -vitamin C -N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial. *Eur J Pharmacol* 2020; **885**: 173494 [PMID: 32828741 DOI: 10.1016/j.ejphar.2020.173494]

43 **Darban M**, Malek F, Memarian M, Gohari A, Kiani A, Emadi A, et al Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial. J Cell Mol Anesth 2021; 6:164-7 [DOI: 10.22037/jcma.v6i2.32182]

44 **JamaliMoghadamSiahkali S**, Zarezade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, Sekhavati Moghadam E, Abbasian L, Dehghan Manshadi SA, Salehi M, Hasannezhad M, Ghaderkhani S, Meidani M, Salahshour F, Jafari F, Manafi N, Ghiasvand F. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. *Eur J Med Res* 2021; **26**: 20 [PMID: 33573699 DOI: 10.1186/s40001-021-00490-1]

45 **Ao G**, Li J, Yuan Y, Wang Y, Nasr B, Bao M, Gao M, Qi X. Intravenous vitamin C use and risk of severity and mortality in COVID-19: A systematic review and meta-analysis. *Nutr Clin Pract* 2022; **37**: 274-281 [PMID: 35148440 DOI: 10.1002/ncp.10832]

46 **Kwak SG**, Choo YJ, Chang MC. The effectiveness of high-dose intravenous vitamin C for patients with coronavirus disease 2019: A systematic review and meta-analysis. *Complement Ther Med* 2022; **64**: 102797 [PMID: 34953366 DOI: 10.1016/j.ctim.2021.102797]

47 **Rawat D**, Roy A, Maitra S, Gulati A, Khanna P, Baidya DK. Vitamin C and COVID-19 treatment: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Syndr* 2021; **15**: 102324 [PMID: 34739908 DOI:

10.1016/j.dsx.2021.102324]
48 **NIH**. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. [cited 25 July 2022]. Available from: https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_86.pdf
49 **Hemilä H**, Chalker E. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients* 2019; **11** [PMID: 30934660 DOI: 10.3390/nu11040708]
50 **Hemilä H**, Chalker E. Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. *J Intensive Care* 2020; **8**: 15 [PMID: 32047636 DOI: 10.1186/s40560-020-0432-y]
51 **de Grooth HJ**, Manubulu-Choo WP, Zandvliet AS, Spoelstra-de Man AME, Girbes AR, Swart EL, Oudemans-van Straaten HM. Vitamin C Pharmacokinetics in Critically Ill Patients: A Randomized Trial of Four IV Regimens. *Chest* 2018; **153**: 1368-1377 [PMID: 29522710 DOI: 10.1016/j.chest.2018.02.025]
52 **Somagutta MKR**, Pormento MKL, Khan MA, Hamdan A, Hange N, Kc M, Pagad S, Jain MS, Lingarajah S, Sharma V, Kaur J, Emuze B, Batti E, Iloeje OJ. The Efficacy of vitamin C, thiamine, and corticosteroid therapy in adult sepsis patients: a systematic review and meta-analysis. *Acute Crit Care* 2021; **36**: 185-200 [PMID: 34185986 DOI: 10.4266/acc.2021.00108]
53 **Fowler AA 3rd**, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S; Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014; **12**: 32 [PMID: 24484547 DOI: 10.1186/1479-5876-12-32]
54 **Hudson EP**, Collie JT, Fujii T, Luethi N, Udy AA, Doherty S, Eastwood G, Yanase F, Naorungroj T, Bitker L, Abdelhamid YA, Greaves RF, Deane AM, Bellomo R. Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock. *Crit Care Resusc* 2019; **21**: 236-242 [PMID: 31778629]
55 **Juneja D**, Jain R, Nasa P. Vitamin C-induced Hemolysis: Meta-summary and Review of Literature. *Indian J Crit Care Med* 2022; **26**: 224-227 [PMID: 35712748 DOI: 10.5005/jp-journals-10071-24111]
56 **Padayatty SJ**, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS One* 2010; **5**: e11414 [PMID: 20628650 DOI: 10.1371/journal.pone.0011414]
57 **Yanase F**, Fujii T, Naorungroj T, Belletti A, Luethi N, Carr AC, Young PJ, Bellomo R. Harm of IV High-Dose Vitamin C Therapy in Adult Patients: A Scoping Review. *Crit Care Med* 2020; **48**: e620-e628 [PMID: 32404636 DOI: 10.1097/CCM.0000000000004396]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 310-320

DOI: 10.5501/wjv.v11.i5.310

ISSN 2220-3249 (online)

MINIREVIEWS

COVID-19 and hemolysis, elevated liver enzymes and thrombocytopenia syndrome in pregnant women - association or causation?

Prashant Nasa, Deven Juneja, Ravi Jain, Ruchi Nasa

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D, D, D
Grade E (Poor): 0

P-Reviewer: Mehri-Ghahfarrokhi A, Iran; Mukhopadhyay A, India; Shariati MBH, Iran; Valipour M, Iran

Received: August 12, 2022
Peer-review started: August 12, 2022
First decision: August 29, 2022
Revised: September 7, 2022
Accepted: September 13, 2022
Article in press: September 13, 2022
Published online: September 25, 2022

Prashant Nasa, Department of Critical Care Medicine, NMC Specialty Hospital, Dubai 7832, United Arab Emirates

Prashant Nasa, Department of Internal Medicine, College of Medicine and Health Sciences, Al Ain 17666, Abu Dhabi, United Arab Emirates

Deven Juneja, Institute of Critical Care Medicine, Max Super Specialty Hospital Saket, New Delhi 110017, India

Ravi Jain, Department of Critical Care Medicine, Mahatma Gandhi Medical College and Hospital, Jaipur 302001, India

Ruchi Nasa, Department of Pathology, Fakeeh University Hospital, Dubai 00000, United Arab Emirates

Corresponding author: Prashant Nasa, MD, Chief Doctor, Department of Critical Care Medicine, NMC Specialty Hospital, Amman Street, Al Nahda 2, Dubai 7832, United Arab Emirates. dr.prashantnasa@hotmail.com

Abstract

Pregnant women are among the high-risk population for severe coronavirus disease 2019 (COVID-19) with unfavorable peripartum outcomes and increased incidence of preterm births. Hemolysis, the elevation of liver enzymes, and low platelet count (HELLP) syndrome and severe preeclampsia are among the leading causes of maternal mortality. Evidence supports a higher odd of pre-eclampsia in women with COVID-19, given overlapping pathophysiology. Involvement of angiotensin-converting enzyme 2 receptors by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the entry to the host cells and its downregulation cause dysregulation of the renin-angiotensin-aldosterone system. The overexpression of Angiotensin II mediated *via* p38 Mitogen-Activated Protein Kinase pathways can cause vasoconstriction and uninhibited platelet aggregation, which may be another common link between COVID-19 and HELLP syndrome. On PubMed search from January 1, 2020, to July 30, 2022, we found 18 studies on of SARS-COV-2 infection with HELLP Syndrome. Most of these studies are case reports or series, did not perform histopathology analysis of the placenta, or measured biomarkers linked to pre-eclampsia/HELLP syndrome. Hence, the relationship between SARS-CoV-2 infection and HELLP syndrome is inconclusive

in these studies. We intend to perform a mini-review of the published literature on HELLP syndrome and COVID-19 to test the hypothesis on association *vs* causation, and gaps in the current evidence and propose an area of future research.

Key Words: SARS-CoV-2; Preeclampsia; Hypertension; Pregnancy-induced; Liver dysfunction; Pregnancy-induced

Core Tip: Observational studies showed an increased prevalence of preeclampsia and hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome in pregnant women with coronavirus disease 2019 (COVID-19). Despite a possible pathophysiology linkage between COVID-19 and HELLP syndrome, the evidence on temporality to prove a causal association between infection with severe acute respiratory syndrome coronavirus 2 and HELLP syndrome is lacking.

Citation: Nasa P, Juneja D, Jain R, Nasa R. COVID-19 and hemolysis, elevated liver enzymes and thrombocytopenia syndrome in pregnant women - association or causation? *World J Virol* 2022; 11(5): 310-320
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/310.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.310

INTRODUCTION

With immense knowledge on the pathogenesis of coronavirus disease 2019 (COVID-19), the viral-host immune interaction plays a critical role in multi-system presentation of the disease. Most of the patients, infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), develop a non-severe illness. However, those patients with specific comorbidities are predisposed to advanced stages of severe COVID-19 infection. Some of the prevalently-reported comorbidities are as follows; age above 75 years, male gender, pre-existing cardiovascular disease, chronic lung, kidney or liver disease, sickle cell disease, diabetes, active cancer, severe obesity and pregnancy[1,2]. The risk factors that aggravate the development of severe COVID-19 among pregnant women include obesity, smoking history, pre-eclampsia and diabetes mellitus[3]. Though pregnancy, per se, does not increase the susceptibility to SARS-CoV-2 infection, pregnant women are highly prone to developing severe illnesses with SARS-CoV-2 infection compared to non-pregnant women. Further, they are also associated with adverse pregnancy and perinatal outcomes[4].

Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome is an uncommon yet deadly complication that is associated with severe pre-eclampsia. Early diagnosis and termination of pregnancy only have been proved to be effective in treating HELLP syndrome[5]. A meta-analysis, conducted recently, inferred that COVID-19 infected women recorded high levels of pre-eclampsia and HELLP syndrome odds[6]. However, abnormal liver enzymes, thrombocytopenia and hemolysis are not only associated with HELLP syndrome, but are observed in many of the critically-ill patients, as a component of multi-organ dysfunction. This phenomenon occurs especially in case of certain infectious diseases and other pregnancy-related liver disorders, for instance, acute fatty liver of pregnancy[7]. Substantial evidence infers that some of the viral infections, for instance SARS-CoV-2, tend to mimic HELLP syndrome among women during pregnancy[8,9].

Hence, the overlapping laboratory features of SARS-CoV-2 infection and HELLP syndrome may increase the possibilities of misdiagnosis than a causal association. The current review discusses about the pathogenetic linkage between COVID-19 and HELLP syndrome, reviews the evidences available on association or causation between the variables and proposes novel suggestions for future research.

PATHOGENESIS OF PRE-ECLAMPSIA AND HELLP SYNDROME

Pre-eclampsia is a multi-system disorder characterized by *de novo* hypertension that occurs after 20 wk of gestation. Recently, the International Society for the Study of Hypertension in Pregnancy provided a new definition for pre-eclampsia as given herewith; new onset of hypertension (systolic > 140 mmHg and diastolic > 90 mmHg) accompanied by at least one feature as listed below and is developed either at or after 20 wk of gestation: (1) Proteinuria; (2) Maternal organ dysfunction (like liver, kidney, neurological and haematological); and (3) Evidence of uteroplacental dysfunctions like fetal growth restriction or abnormal Doppler waveform findings of uteroplacental blood flow or stillbirth[10].

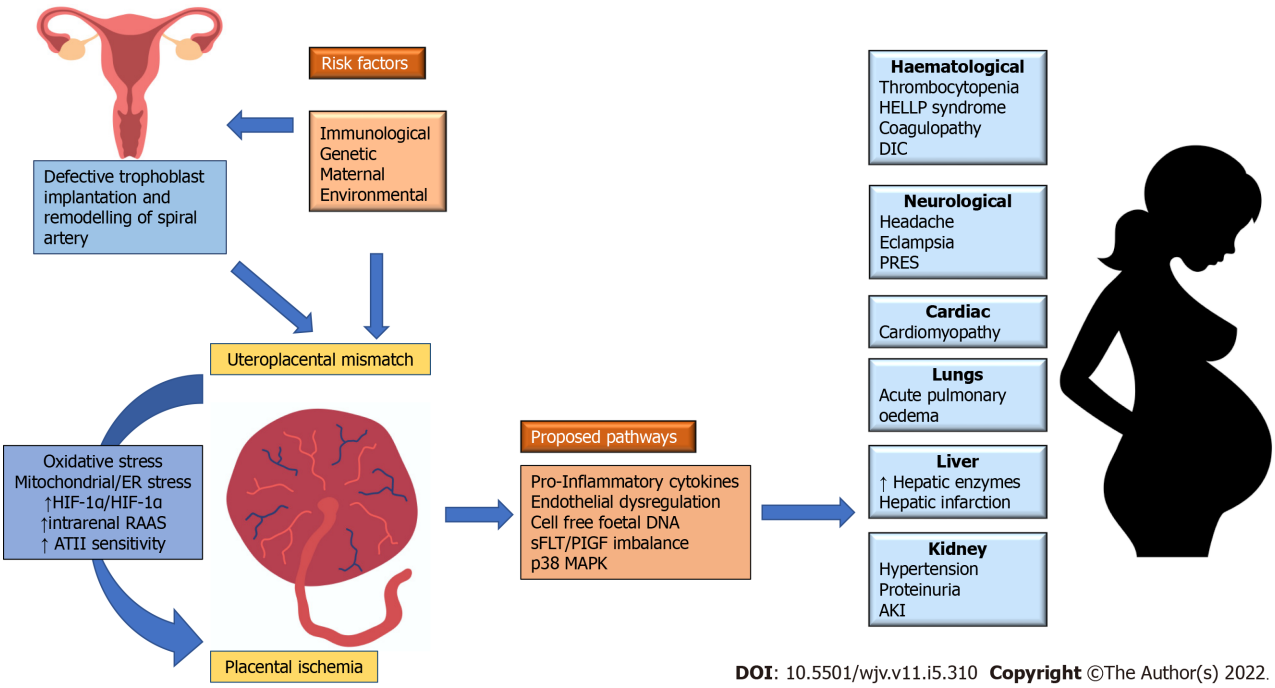
The exact pathogenesis of pre-eclampsia remains uncertain. However, the termination of pregnancy by removing the placenta seems to be an effective therapeutic measure. This method confirms the importance of placenta in the pathophysiology of pre-eclampsia. Two pathogenic phenotypes are established such as early and late pre-eclampsia. The major cause of early pre-eclampsia is placental in nature whereas the late pre-eclampsia is a result of interactions that occur between placental senescence and other factors such as genetics, obesity and nutrition or environmental factors. The oxidative stress upon syncytiotrophoblast, a cell that covers the placental villi on the maternal side, plays a crucial role by getting released into maternal circulation factors like inflammatory cytokines, cell-free fetal DNA, exosomes, and anti-angiogenic agents. This results in the endothelial dysfunction and hypertensive syndrome[11].

Oxidative stress occurs as a result of either uteroplacental hypoperfusion from the defective remodelling of uterine spiral arteries (*i.e.*, early pre-eclampsia) or due to a mismatch between supply and demand in maternal perfusion and placental or foetus requirements (*i.e.*, late pre-eclampsia). Placental stress results in the dysfunction of vascular endothelium which in turn releases the placental factors that cause systemic manifestations of pre-eclampsia. The pathways proposed earlier for the above discussed phenomenon include an increased release of pro-inflammatory cytokines, cell-free fetal DNA, p38 Mitogen-Activated Protein Kinase (MAPK), placental apoptotic debris, soluble receptor for Vascular Endothelial Growth Factor, and soluble fms like tyrosine kinase (sFlt-1)/Placental Growth Factor (PlGF) ratio (Figure 1)[11,12].

The role played by Renin-Angiotensin-Aldosterone System (RAAS) in placenta homeostasis is crucial since it regulates the proliferation of trophoblasts, angiogenesis and blood flow. When RASS is not regulated, it creates an imbalance of vasoactive peptides due to high production of angiotensin II (ATII) and low vasodilatory angiotensin 1-7. ATII is a pro-inflammatory, pro-thrombotic element that induces vascular constriction, endothelial injury and vascular smooth cell proliferation which altogether contribute to pre-eclampsia[13]. Recent evidence suggests that ATII actions are mediated through the MAPK pathway. MAPK is a cellular signaling pathway existing in three forms, p38 MAPK, extracellular signal-regulated kinase, and Janus kinase. p38 MAPK critical component in immune functions as well as stress response pathways, mediates the cellular response to pathogenic microbes, pro-inflammatory cytokines and environmental stress (oxidate stress). p38 MAPK can be stimulated by intrauterine oxidate stress, with exact function unknown. Available evidence supports p38 MAPK is linked to normal embryonic development and maintaining parturition, and premature activation, or overexpression may lead to adverse perinatal and pregnancy outcomes[14]. The upregulated p38 MAPK pathway is linked with increased pro-inflammatory cytokines like NF-κB, Tumour Necrosis Factor (TNF)-α, interleukin (IL)-6 and IL-1β, and COX-2. The activation of NF-κB with p38 MAPK overexpression is found in various tissues, but in uterine tissue, its role is unclear. On the other hand, Angiotensin 1-7 is vasodilatory, attenuate this inflammation, atrophy, and fibrosis by simulating the Mas receptor. Hence, the dysregulation of RASS and high ATII levels lead to uninhibited feedback loop to p38 MAPK pathway which in turn causes untamed inflammation observed in pre-eclampsia[15,16].

The association between pre-eclampsia and HELLP syndrome is unclear. According to a few experts, HELLP syndrome is nothing but an extended manifestation of severe pre-eclampsia. However, a few others argue that HELLP syndrome is an independent entity since it exists without the classical features of pre-eclampsia like proteinuria and oedema. A few resemblances exist between the pathogenesis of pre-eclampsia and HELLP syndrome such as endothelial dysfunction, platelet aggregation and consumption, vasospasm, and end-organ ischemia. However, immune dysregulation with maternal immunological intolerance to fetal tissues is considered as a prominent pathway in HELLP syndrome. This immunological maladaptation has been proved in literature *via* the high levels of fetal mRNA and HLA-DR in the blood of women with HELLP syndrome, who was compared with women with pre-eclampsia[16,17]. One of the recent studies demonstrated that those patients with HELLP syndrome, had a high titer of agonist antibodies to Type I ATII receptor (AT1r-AA), when compared with patients with pre-eclampsia. The agonist antibodies can simulate the ATII effect upon the receptor[18].

Women with HELLP syndrome possess high levels of other types of anti-angiogenesis factors such as endoglin and Fas ligand than the women with pre-eclampsia. These two factors are responsible for vascular endothelial injury and intense inflammation in HELLP syndrome. The role played by p38 MAPK pathway, in the pathogenesis of HELLP syndrome, is hypothesized to be an angiogenic response for environmental hypoxia. The elevated serum levels of p38 MAPK increase the serum vascular permeability and it has the potential to aggravate edema in different tissues including the brain. A recent study that compared the serum levels of p38 MAPK among patients with HELLP syndrome and pre-eclampsia found that the serum levels were significantly higher in HELLP syndrome patients than their counterpart. The authors also recommended to use serum p38 MAPK in the diagnosis of HELLP syndrome[19]. As per the literature, patients with HELLP syndrome exhibit high serum levels of p38 MAPK and low expression in placental p38 MAPK[20,21]. The future researchers must explore this relationship which may shed more insights about the role played by p38 MAPK in the pathophysiology of HELLP syndrome. Furthermore, the activation of immune complexes, $C_{5b\text{-}9}$complement pathway, anaphylatoxins like C3a and C5a and the release of inflammatory cytokines, TNF-α and active von Willebrand factor from leucocytes, macrophages and platelets also cause endothelial injury. In turn, endothelial injury contributes to multiple activities such as hemolysis, platelet aggregation and



DOI: 10.5501/wjv.v11.i5.310

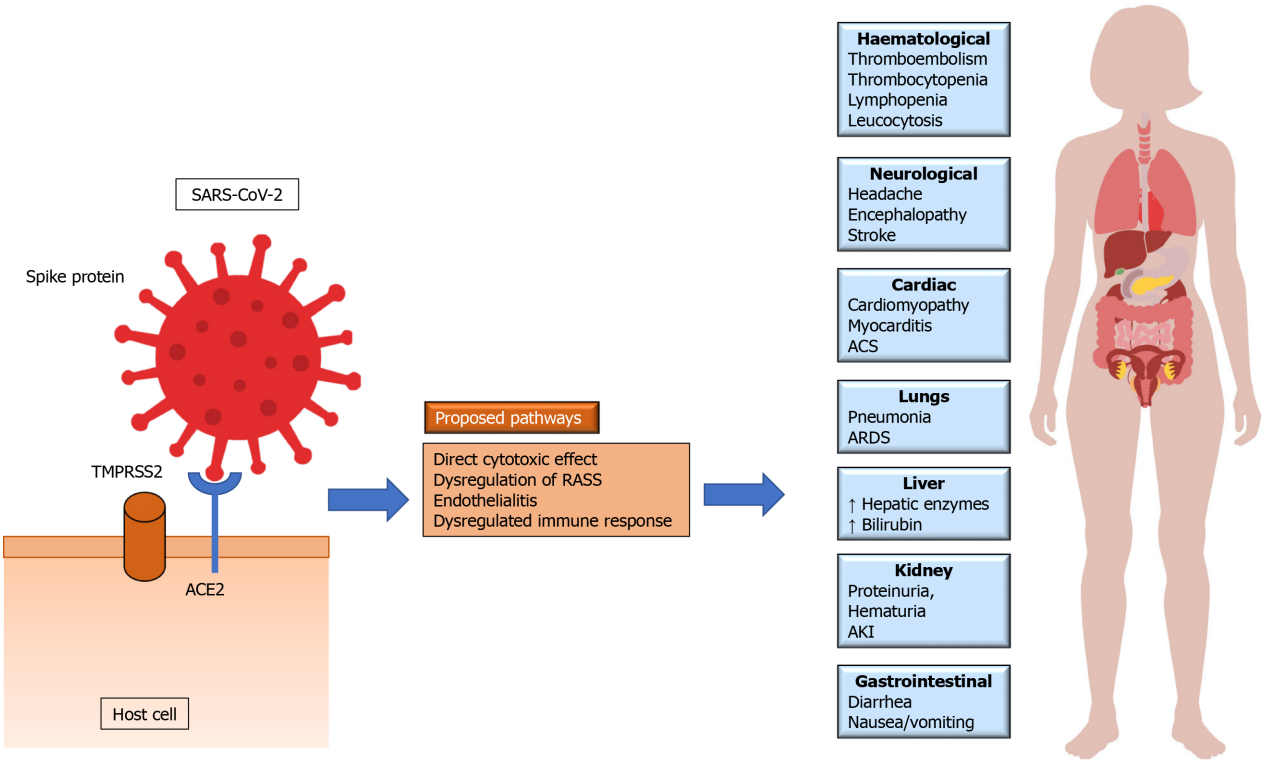
Figure 1 Pathogenesis of hemolysis, elevated liver enzymes and low platelet syndrome. Placenta ischemia is central mechanism which is suspected to play a central role in hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome. Abnormal trophoblast implantation and remodelling of uterine arteries along with genetic, environmental, nutritional, or maternal risk factors cause uteroplacental perfusion mismatch. Various pathways proposed for systemic manifestations of HELLP syndrome include, releases of inflammatory cytokines, endothelial dysfunction, release of cell-free fetal DNA, imbalance of soluble fms-like tyrosine kinase to placental growth factor ratio (sFLT/PIGF ratio). HELLP: Hemolysis, elevated liver enzymes and low platelet; ATII: Angiotensin II; HIF: Hypoxia inducible factor 1 alpha; RAAS: Renin angiotensin aldosterone system; sFlt/PlGF: Soluble fms-like tyrosine kinase and platelet growth factor ratio; ↑: Increased.

consumption (causing thrombocytopenia), intraluminal fibrin deposition, vasospasm and end-organ ischemia (causing hepatitis) that are generally observed in HELLP syndrome[21].

Conventional pre-eclampsia screening includes a periodic assessment and an early detection of hypertension and proteinuria. But, the precision of pre-eclampsia screening has increased tremendously, thanks to the measurement of circulating biomarkers and Doppler assessment of uteroplacental circulation. sFlt-1/PlGF ratio is a potential and a highly-accurate marker that can be used in the prediction of pre-eclampsia and fetal growth restriction[22]. In the prediction of early pre-eclampsia and the complications associated with it, a combination of multiple factors such as demographic risk factors with periodic blood pressure measurement, doppler assessment of uterine artery and the measurements of biomarkers is found to be highly accurate[23].

PATHOGENESIS OF COVID-19

The internalization of SARS-CoV-2, within the host cell, occurs by binding the S-spike protein of the virus with Angiotensin-Converting-Enzyme 2 (ACE2) present on the cell surface and is supplemented by Transmembrane Serine Protease 2 (TMPRSS2) on the host cell. Though ACE2 is found in multiple tissues, it is predominantly expressed in lung and heart tissues. This phenomenon may explain the high incidence of acute respiratory distress syndrome and myocarditis among patients with COVID-19 and the primary cause behind the high mortality rate. ACE2 is an integral part of RAAS and is directly associated in the conversion of ATII to Angiotensin 1-7. Like SARS-CoV, when SARS-CoV-2 interacts with ACE2 receptor, the receptor gets downregulated, thus potentiating RAAS and ATII. All three MAPK pathways are involved in the pathogenesis of COVID-19. The interaction between SARS-CoV-2 and ACE2, like many other viruses, is associated with upregulation of p38 MAPK through the interaction with ACE2 receptors and its direct activation[16,24]. The upregulated ATII through its effect on ATII Type 1 receptor causes an intense vasoconstriction and inflammation. As discussed earlier, the effect of ATII in heart and lung tissues are mediated by p38 MAPK pathway. The crosstalk between p38 MAPK and NF-κB is also found to be involved in the pathophysiology of COVID-19. SARS-CoV and SARS-CoV-2 infection activates p38 MAPK pathway and induces phosphorylation of various down-stream proteins involved in the transcription of various inflammatory cytokines. The upregulation of p38 MAPK is linked with excessive vasoconstriction, production of pro-inflammatory cytokines such as IL6, TNF-α and IL-1β. Hence, an unrestrained p38 MAPK results in hyperinflammation, vasoconstriction



DOI: 10.5501/wjv.v11.i5.310

Figure 2 Pathogenesis of coronavirus disease 2019. Severe acute respiratory syndrome coronavirus 2 entry into the host cell is mediated through its binding with angiotensin converting enzyme 2 receptor and transmembrane serine protease 2 enzyme. The pathogenetic pathways include direct cytotoxicity, endothelialitis, (endothelial damage), dysregulated host-immune response and renin-angiotensin aldosterone system. Respiratory system is the primary target organ, but other systems are involved either with direct invasion or in response of systemic dysregulated immune response. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; RAAS: Renin angiotensin aldosterone system; ACS: Acute coronary syndrome; AKI: Acute kidney injury.

and thrombosis, a hallmark of COVID-19 (Figure 2)[16]. Recently, various agents like emetine, chelerythrine and papaverine regulating the p38 MAPK signaling pathway are found to have therapeutic potential in the management of COVID-19[25-27].

The role played by virus-host immune interplays is crucial in the pathogenesis of COVID-19. Various pro-inflammatory cytokines like IL-6, IL-10, TNF-α, granulocyte-colony stimulating factors and monocyte chemoattract protein 1 mediate lungs and other systemic manifestations of SARS-CoV-2 infection. Though respiratory system is the primary target site of SARS-CoV-2 infection, COVID-19 can be characterized as a multi-system disease that affects heart, kidneys, brain, liver, gastrointestinal and haematological systems and skin (Figure 2)[28].

COVID-19 patients generally exhibit different biochemical manifestations of pre-eclampsia and HELLP syndrome such as thrombocytopenia, raised liver enzymes, proteinuria, coagulopathy, acute kidney injury, and increased lactate dehydrogenase[8,29]. Mild thrombocytopenia (the count of platelets stands at 100-150 × 10^9/L) is observed among 20%-36% patients with COVID-19 whereas severe thrombocytopenia (< 50 × 10^9/L) is uncommon[30].

EVIDENCE ON COVID-19 AND HELLP SYNDROME

A total of 11 studies was found by the authors when PubMed database was mined using the following keywords; "COVID-19" OR "SARS-CoV-2" AND "HELLP syndrome" between 01st January 2020 to 30th July 2022. When a broader keyword *i.e.*, "HELLP syndrome" was used within the same period, a total of 361 studies was found. Out of the total studies filtered, 18 studies were finalized and critically analyzed after excluding non-COVID-19 studies and non-English literature (Table 1)[6,31-47].

Inference from the evidence

Out of the 18 studies considered for final analysis, 13 were case reports or series in which 23 patients were included[31-38,40,42,44,45,47]. Maternal and fetal mortality rates were 8.6% (2) and 21.7% (5) respectively, with the development of severe COVID-19 in three patients. Mendoza *et al*[31] authored a case series in which five patients were suspected with pre-eclampsia and HELLP syndrome whereas

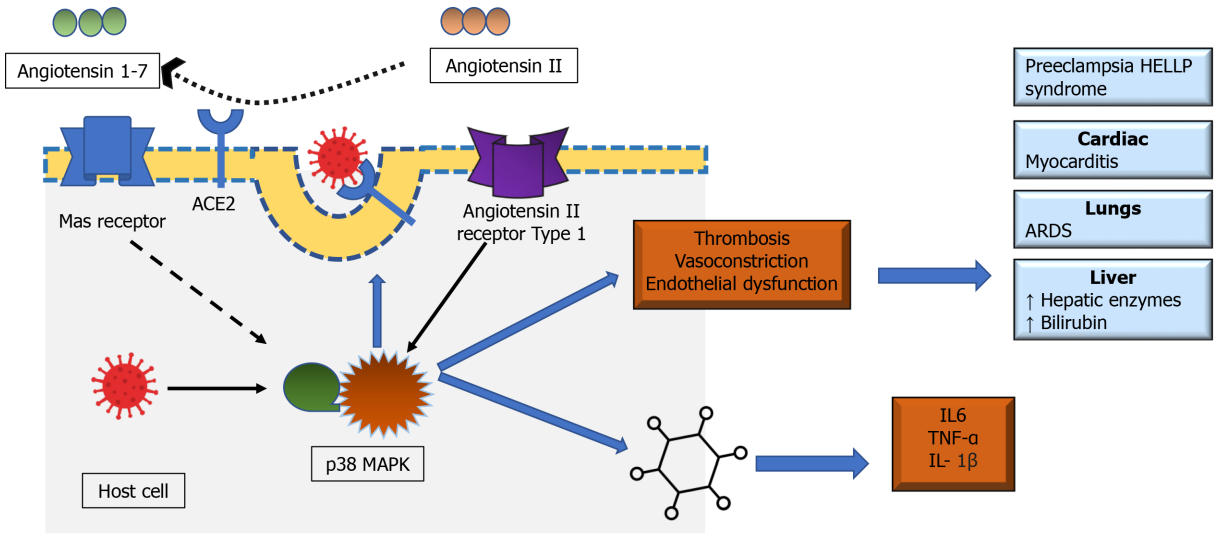
Table 1 Published studies on coronavirus disease 2019 and hemolysis, elevated liver enzymes, and low platelet count syndrome

Ref.	Type of study	Age (yr), gestation (wk)	Number of patients	Main results	Conclusion
Mendoza *et al* [31], 2020	Case series		5 cases with severe PE and/or HELLP syndrome	Out of 8 cases with severe COVID-19, 5 developed PE, proteinuria, elevated liver enzymes and hypertension. One developed platelet less than 150000. However, only one patient had PE based on the uterine artery pulsatility index, sFlt-1/PlGF ratio and LDH	PE like clinical features can develop with severe COVID-19. It can be distinguished from true by PE by sFlt-1/PlGF, LDH and UtAPI measurement
Braga *et al*[32], 2020	Case report	31, 31	1	Multiple pregnancy (dichorionic twins) with PE and partial HELLP syndrome. Moderate COVID-19 with HRCT showing ground-glassing. Underwent caesarean delivery for HELLP syndrome. One of the foetus died on day 16 due to intracranial hemorrhage. Both women and other foetus survived	There is a possible synergism between the pathophysiology of COVID-19 and PE/HELLP syndrome
Federici *et al* [33], 2020	Case report	33, 23.5	1	Multigravida, severe COVID-19 with ARDS requiring mechanical ventilation develop features of PE and HELLP syndrome. The serum sFlt-1/PlGF ratio was normal. Pregnancy continued and laboratory abnormalities resolved spontaneously with removal of mechanical ventilation after 10 d and discharge on day 19. Mother delivered spontaneously a live foetus at 33.4 wk	Severe COVID-19 can mimic PE and HELLP syndrome. Pregnancy can be continued in absence of complications with strict surveillance
Ahmed *et al* [34], 2020	Case report	26, 37	1	Family history of PE, atypical HELLP syndrome with acute kidney injury. Vaginal delivery with induction Postpartum day 3, developed abdominal hematoma requiring laparotomy and blood transfusions. Moderate respiratory symptoms with foetus and mother survived	Severe SARS-CoV-2 infection may be a risk factor for hypertensive disorders of pregnancy
Ronnje *et al* [35], 2020	Case report	26, 32.6	1	Underwent emergency caesarean. Both mother and foetus survived	Possible association of HELLP syndrome and COVID-19 was proposed
Coronado-Arroyo *et al* [36], 2021	Case series	Mean: 29 yr, gestation 31 wk	14 out of 20 patients with severe PE including 5 with HELLP syndrome	One out of 5 women was multipara. Two were asymptomatic and remaining had mild severity COVID-19. Four required caesarean delivery and two had still-birth. No maternal mortality	SARS-CoV-2 infection, can predisposes pregnant female to a greater severity of PE, irrespective of the severity of respiratory symptoms
Norooznezhad *et al*[37], 2021	Case report	24, 29	1	Primigravida, emergency caesarean for HELLP syndrome. Ostelmavir, lopinavir/ritonavir, chloroquine and 0.5 gm/d of methylprednisolone was used. Moderate respiratory symptoms. Both foetus and mother survived	Association between COVID-19 and HELLP syndrome cannot be concluded but deliver and methylprednisolone caused improvement in the condition
Farahani *et al* [38], 2021	Case report	28, 38	1	Multigravida, vaginal delivery for HELLP syndrome. Postpartum developed seizure, lopinavir/ritonavir and dexamethasone was used for treatment. Moderate respiratory symptoms. Both mother and foetus survived	COVID-19 in pregnant women can resemble PE and with possible CNS involvement
Aydın *et al*[39], 2021	Observational retrospective study	Case 1: 22, 31 Case 2: 25, 28	167 pregnant with COVID-19. 20 patients had PE and two (1.2%) had HELLP syndrome.	Case 1: Pregnancy with IVF. Need invasive mechanical ventilation, underwent caesarean delivery for HELLP syndrome and postpartum developed arterial thrombosis. Case 2: Vaginal delivery with preterm foetus. Both patients survived	No significant difference was observed in adverse pregnancy outcomes such as PE, preterm birth, and foetal growth restriction, gestational diabetes mellitus and HELLP syndrome according to the gestational age
Vaezi *et al*[40], 2021	Case series	36, 28	24 patients, 1 with HELLP syndrome	Delivery by caesarean section, performed for HELLP syndrome, preterm foetus admitted to NICU. Both mother and foetus survived	-
Jering *et al*[41], 2021	Retrospective cohort study		406 446 women hospitalized for childbirth. Among women with HELLP syndrome, 989 (0.2%) were without COVID-19 and 33	Unadjusted and adjusted OR for HELLP syndrome with COVID-19 was 2.10 (95%CI-1.48-2.97) and 1.96 (1.36-2.81), $P < 0.001$	In large US cohort of women admitted for childbirth during the pandemic, patients with COVID-19 had higher risk of in-hospital mortality, pre-eclampsia, VTE and HELLP syndrome

			(0.5%) with COVID-19		
Bhardwaj *et al* [42], 2022	Case report	33, 36	1	Underwent caesarean delivery. Both mother and foetus survived	COVID-19 and HELLP overlap and associations are puzzling to clinicians
Conde-Agudelo *et al* [6], 2022	Meta-analysis of observational studies		28 studies, 790954 patients including One study for HELLP syndrome	SARS-CoV-2 infection during pregnancy was associated with significant increase in the odd ratio of PE (1.58, 95%CI- 1.39-1.8), severe PE (1.76, 95%CI 1.18-2.63), eclampsia (1.97, 95%CI 1.01-3.84) and HELLP syndrome (2.76, 95%CI 1.48-2.97)	SARS-CoV-2 infection during pregnancy is associated with significantly higher odds of PE
Madaan *et al* [43], 2022	Case series	Case 1: 32, 34 Case 2: 29, 37 Case 3: 26, 39	3	All three cases had HELLP syndrome and ground glassing opacities on HRCT with RT-PCR positive for SARS-COV-2. Case 1: Severe COVID-19, mother survived, baby still born by caesarean section. Case 2: Patient developed eclampsia and required mechanical ventilation, died on day -8, baby delivered vaginally Case 3: Patient survived and discharged day 15, baby delivered alive by caesarean section due to transverse lie	Authors proposed a synergism in the pathophysiology of COVID-19 and HELLP Syndrome. and combination of both can cause morbidity or mortality risk to fetus and the mother
Takahashi *et al* [44], 2022	Case report	27, 37	1	Underwent caesarean delivery for infection control measures. Postpartum HELLP syndrome. Both mother and foetus survived	Overlap of clinical features with COVID-19 and HELLP syndrome is plausible explanation
Guida *et al*[45], 2022	Nested case-control analysis	-	203 women with COVID-19, including 21 with PE and 2 HELLP syndrome	There was no difference in the rate of PE and HELLP syndrome in women with or without COVID-19. However, imminent eclampsia was more frequent complication and overall maternal perinatal outcomes were worse with patients with PE and COVID-19	Prevalence of PE among women with COVID-19 was around 10%. Chronic hypertension and obesity were more likely associated with PE. High caesarean rate and NICU admissions due to prematurity in women with COVID-19
Snelgrove *et al* [46], 2022	Retrospective cohort study	-	157779 patients during the pandemic compared to 563859 patients delivered between March 2015-september 2019 (historical group)	There was no difference in the rate of PE/HELLP (879, 0.6%) syndrome and severe maternal morbidity (SMM) between the pandemic and historical group (3119, 0.6%). No difference between primiparous and multiparous on severe maternal morbidity and risk of PE/HELLP syndrome. Maternal age, rurality, preexisting comorbidities and use of artificial reproduction therapy were associated with increased risk of PE/HELLP syndrome	Changes in obstetrical care during the pandemic have not increased the risk the PE/HELLP syndrome and adverse maternal outcomes
Arslan[47], 2022	Case report	30, 32	1	Mutigravida pregnancy, emergency Caeserian delivery. Foetus tested positive for SARS-CoV-2 and died 5 d after delivery. Mother had severe COVID-19, required invasive mechanical ventilation and died, 10 d after delivery	Severe COVID-19 as etiological causation of HELLP syndrome is presumptive

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HELLP: Hemolysis, elevated liver enzymes, low platelet count; PE: Pre-eclampsia; LDH: Lactate dehydrogenase; HRCT: High-resolution computed tomography; OR: Odds ratio; CI: Confidence intervals; ARDS: Acute respiratory distress syndrome; NICU: Neonatal intensive care unit; IVF: *In vitro* fertilization.

only one had actual pre-eclampsia features based on the Doppler assessment of uterine artery pulsatility index, sFlt-1/PlGF ratio and lactate dehydrogenase. However, another case report failed to find the elevated sFlt-1/PlGF ratio in a patient who exhibited the biochemical features of HELLP syndrome. The patient was managed conservatively and her biochemical abnormalities were resolved spontaneously while the patient achieved a good perinatal outcome[33]. Most of the studies confirmed the existence of a linkage between HELLP syndrome and COVID-19. However, the inference from individual cases without a case-control remains highly biased. Two retrospective cohort studies, in which women with and without COVID-19 were compared, reported conflicting results on the increased incidence of HELLP syndrome with COVID-19[41,46]. In a population-based study authored by Snelgrove JW *et al* [46], no increased incidence of pre-eclampsia and HELLP syndrome was observed among women infected with SARS-CoV-2 compared to historical controls. On the other hand, in a large registry developed upon hospitalized women for childbirth in the United States, highly-adjusted odds of pre-eclampsia [1.21, 95% confidence interval (CI) 1.11-1.33] and HELLP syndrome (1.96, 95%CI 1.36-2.81) were found in pregnant women with COVID-19 compared to those without COVID-19, during the same duration[41]. A recent meta-analysis, in which 28 studies were included which covered a total of 790954



DOI: 10.5501/wjv.v11.i5.310

Figure 3 Pathophysiological linkage between coronavirus disease 2019 and Hemolysis, elevated liver enzymes and low platelets syndrome. The binding of severe acute respiratory syndrome coronavirus 2 to angiotensin converting enzyme 2 (ACE2) allows its entry to host cells and, subsequently, downregulation. ACE2 also converts angiotensin II (ATII) to angiotensin 1-7. The downregulation of ACE2 increases the concentration of AT II, which causes activation of the p38 mitogen activated protein kinase (MAPK) pathway. p38 MAPK stimulates the production of inflammatory cytokines, platelet aggregation and thrombosis. Renin-angiotensin-aldosterone system and ATII are also involved in the pathogenesis of pre-eclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Serum levels of p38 MAPK are elevated in the HELLP syndrome. ACE2: Angiotensin converting enzyme 2; IL: Interleukin; TNF: Tumour necrosis factor; HELLP: Hemolysis, elevated liver enzymes, and low platelet count;ARDS: Acute respiratory distress syndrome. Solid black arrow- stimulation (positive feedback), Dashed black arrow- inhibition (negative feedback), blue arrow: Effects of p38 MAPK overexpression.

pregnant women, reported a significantly-high risk of pre-eclampsia (pooled odd ratio (OR) 1.62, 95%CI 1.45-1.82, $P < 0.00001$, 26 studies) with SARS-CoV-2 infection compared to non-infected individuals[6]. A single study outcomes from Jering *et al*[41], reported highly-unadjusted odds of HELLP syndrome (2.10, 95%CI 1.48-2.97), in pregnant women with SARS-CoV-2 infection.

Pathophysiology linkage between COVID-19 and HELLP syndrome

Recent evidences confirm the worst clinical outcomes for pregnant women with COVID-19 in terms of high incidence of pre-eclampsia, preterm birth and the need for caesarean delivery[48,49].

ACE2 receptors and TMPRSS2, which are required for the entry of SARS-CoV-2 into human cells, are expressed in placental components including villous cytotrophoblasts, syncytiotrophoblasts and extravillous trophoblasts[50]. This makes the placenta, predisposed to SARS-CoV-2 infection. When S-spike protein of SARS-CoV-2 binds with ACE2 receptor, it results in the downregulation of the receptor, dysfunction of RAAS and triggering of local placental inflammation. Further, ATII type I -receptor and sFlt-1 are also heavily produced from the infected placenta. The increased serum levels of AT1r-AA, found in cases of SARS-CoV-2 infection, can be observed in pre-eclampsia and HELLP syndrome too[7].

Some evidence supports the presence of high levels of placental ACE2 in women with COVID-19. This may explain the increased association between pre-eclampsia and preterm birth[51]. Another study showed that ACE2 receptors and the expression of protease are dependent upon each other during gestational age. The increased levels of expression is prevalent during the first trimester compared to the rest of the trimesters in pregnancy[52]. In a molecular linkage study by Beys-da-Silva *et al*[53], SARS-CoV-2 infection was found to interact with multiple pathways that are involved in pre-eclampsia and HELLP syndrome pathogenesis like upregulation of sFlt-1 and endoglin, angiogenesis, the balance between vasoconstrictive peptides and nitric oxide modulators, hypoxia and inflammation and prothrombotic-related molecules.

There exist a few similarities in the pathophysiology of COVID-19 and HELLP syndrome. The interaction between ATII and p38 MAPK is a plausible linkage among COVID-19, preeclampsia and HELLP (Figure 3)[16]. The upregulation of p38 MAPK pathway is also linked with endothelial injury which in turn causes platelet aggregation and arterial thrombosis. This scenario reveals the systemic manifestations of COVID-19 like thrombocytopenia and raised liver enzymes[54]. However, it is still unclear whether the above-discussed biochemical abnormalities are manifestations of COVID-19 or HELLP syndrome. There is a lack of temporal studies in this domain that can establish a causal relationship between COVID-19 and HELLP syndrome. The studies conducted earlier that can prove that exposure occurred before the outcome (HELLP syndrome) establishing the temporality are missing. So, it is crucial to identify the causal association since immediate termination of the pregnancy is the only successful treatment used for HELLP syndrome, a predominant placental pathology, so far.

However, an expectant and a watchful continuation of pregnancy with better perinatal outcomes may be considered in selected cases of COVID-19[33].

Future studies should explore this linkage using the principle of temporality and circulatory biomarkers like serum p38 MAPK, sFlt-1/PIGF ratio and/or doppler assessment of uteroplacental hypoxia to identify any causal association between COVID-19 and HELLP syndrome.

CONCLUSION

There exists an association among SARS-CoV-2 infection during pregnancy, pre-eclampsia and HELLP syndrome. Evidence accepts the plausible overlap in the pathogenesis of COVID-19 and HELLP syndrome through ACE2 and RAAS dysregulation that involve ATII and p38 MAPK pathways. However, no prospective studies are available based on screening biomarkers and temporality to prove the causal relationship in this domain. Future studies should establish a temporal relationship between SARS-CoV-2 infection and the development of HELLP syndrome including circulatory biomarkers and tissue or radiological documentation of uteroplacental insufficiency.

FOOTNOTES

Author contributions: Nasa P conceptualized and designed the article; Nasa P, Juneja D, Jain R, and Nasa R performed acquisition of data, analysis and interpretation of data, and drafted the article; Juneja D and Jain R revised the article; all authors have read and approve the final manuscript.

Conflict-of-interest statement: Prashant Nasa declared to be on the advisory board of Edwards life sciences. Other authors do not declare any conflict of interest.

Country/Territory of origin: United Arab Emirates

ORCID number: Prashant Nasa 0000-0003-1948-4060; Deven Juneja 0000-0002-8841-5678; Ravi Jain 0000-0001-9260-479X; Ruchi Nasa 0000-0002-4817-6983.

S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

REFERENCES

1 **Gao YD**, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, Gan H, Sun YL, Fu W, Li W, Liang HL, Cao YY, Yan Q, Cao C, Gao HY, Brüggen MC, van de Veen W, Sokolowska M, Akdis M, Akdis CA. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy* 2021; **76**: 428-455 [PMID: 33185910 DOI: 10.1111/all.14657]

2 **Booth A**, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, Labrique A, Mohan D. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. *PLoS One* 2021; **16**: e0247461 [PMID: 33661992 DOI: 10.1371/journal.pone.0247461]

3 **Lassi ZS**, Ana A, Das JK, Salam RA, Padhani ZA, Irfan O, Bhutta ZA. A systematic review and meta-analysis of data on pregnant women with confirmed COVID-19: Clinical presentation, and pregnancy and perinatal outcomes based on COVID-19 severity. *J Glob Health* 2021; **11**: 05018 [PMID: 34221361 DOI: 10.7189/jogh.11.05018]

4 **Allotey J**, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qiu X, Yuan M, Coomar D, Sheikh J, Lawson H, Ansari K, van Wely M, van Leeuwen E, Kostova E, Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Mofenson L, Zamora J, Thangaratinam S; for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* 2020; **370**: m3320 [PMID: 32873575 DOI: 10.1136/bmj.m3320]

5 **van Lieshout LCEW**, Koek GH, Spaanderman MA, van Runnard Heimel PJ. Placenta derived factors involved in the pathogenesis of the liver in the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP): A review. *Pregnancy Hypertens* 2019; **18**: 42-48 [PMID: 31494464 DOI: 10.1016/j.preghy.2019.08.004]

6 **Conde-Agudelo A**, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2022; **226**: 68-89.e3 [PMID: 34302772 DOI: 10.1016/j.ajog.2021.07.009]

7 **Sathiya R**, Rajendran J, Sumathi S. COVID-19 and Preeclampsia: Overlapping Features in Pregnancy. *Rambam Maimonides Med J* 2022; **13** [PMID: 35089126 DOI: 10.5041/RMMJ.10464]

8 **Talwani R**, Gilliam BL, Howell C. Infectious diseases and the liver. *Clin Liver Dis* 2011; **15**: 111-130 [PMID: 21111996 DOI: 10.1016/j.cld.2010.09.002]

9 **Nasa P**, Alexander G. COVID-19 and the liver: What do we know so far? *World J Hepatol* 2021; **13**: 522-532 [PMID: 34131467 DOI: 10.4254/wjh.v13.i5.522]

10 **Brown MA**, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension* 2018; **72**: 24-43 [PMID: 29899139]

11 **Burton GJ**, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. *BMJ* 2019; **366**: l2381 [PMID: 31307997 DOI: 10.1136/bmj.l2381]

12 **Yagel S**, Cohen SM, Goldman-Wohl D. An integrated model of preeclampsia: a multifaceted syndrome of the maternal cardiovascular-placental-fetal array. *Am J Obstet Gynecol* 2022; **226**: S963-S972 [PMID: 33712272 DOI: 10.1016/j.ajog.2020.10.023]

13 **Lumbers ER**, Delforce SJ, Arthurs AL, Pringle KG. Causes and Consequences of the Dysregulated Maternal Renin-Angiotensin System in Preeclampsia. *Front Endocrinol (Lausanne)* 2019; **10**: 563 [PMID: 31551925 DOI: 10.3389/fendo.2019.00563]

14 **Sheller-Miller S**, Richardson L, Martin L, Jin J, Menon R. Systematic review of p38 mitogen-activated kinase and its functional role in reproductive tissues. *Am J Reprod Immunol* 2018; **80**: e13047. [PMID: 30178469 DOI: 10.1111/aji.13047]

15 **Crowley SD**, Rudemiller NP. Immunologic Effects of the Renin-Angiotensin System. *J Am Soc Nephrol* 2017; **28**: 1350-1361 [PMID: 28151411 DOI: 10.1681/ASN.2016101066]

16 **Grimes JM**, Grimes KV. p38 MAPK inhibition: A promising therapeutic approach for COVID-19. *J Mol Cell Cardiol* 2020; **144**: 63-65 [PMID: 32422320 DOI: 10.1016/j.yjmcc.2020.05.007]

17 **Bu S**, Wang Y, Sun S, Zheng Y, Jin Z, Zhi J. Role and mechanism of AT1-AA in the pathogenesis of HELLP syndrome. *Sci Rep* 2018; **8**: 279 [PMID: 29321548 DOI: 10.1038/s41598-017-18553-x]

18 **Petca A**, Miron BC, Pacu I, Dumitrașcu MC, Mehedințu C, Șandru F, Petca RC, Rotar IC. HELLP Syndrome-Holistic Insight into Pathophysiology. *Medicina (Kaunas)* 2022; **58** [PMID: 35208649 DOI: 10.3390/medicina58020326]

19 **Efendi L**, Chalid MT, Upik AM, Syakib B. Comparison of p38 MAPK, soluble endoglin and endothelin-1 Level in severe preeclampsia and HELLP syndrome patients. *Asian Pac J Reprod* 2019; **8**: 83-88 [DOI: 10.4103/2305-0500.254650]

20 **Corradetti A**, Saccucci F, Emanuelli M, Vagnoni G, Cecati M, Sartini D, Giannubilo SR, Tranquilli AL. The role of p38alpha mitogen-activated protein kinase gene in the HELLP syndrome. *Cell Stress Chaperones* 2010; **15**: 95-100 [PMID: 19565356 DOI: 10.1007/s12192-009-0125-x]

21 **Abildgaard U**, Heimdal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. *Eur J Obstet Gynecol Reprod Biol* 2013; **166**: 117-123 [PMID: 23107053 DOI: 10.1016/j.ejogrb.2012.09.026]

22 **Liu N**, Guo YN, Gong LK, Wang BS. Advances in biomarker development and potential application for preeclampsia based on pathogenesis. *Eur J Obstet Gynecol Reprod Biol* × 2021; **9**: 100119 [PMID: 33103113 DOI: 10.1016/j.eurox.2020.100119]

23 **McLaughlin K**, Zhang J, Lye SJ, Parker JD, Kingdom JC. Phenotypes of Pregnant Women Who Subsequently Develop Hypertension in Pregnancy. *J Am Heart Assoc* 2018; **7** [PMID: 30007936 DOI: 10.1161/JAHA.118.009595]

24 **Griego SD**, Weston CB, Adams JL, Tal-Singer R, Dillon SB. Role of p38 mitogen-activated protein kinase in rhinovirus-induced cytokine production by bronchial epithelial cells. *J Immunol* 2000; **165**: 5211-5220 [PMID: 11046054 DOI: 10.4049/jimmunol.165.9.5211]

25 **Valipour M**, Irannejad H, Emami S. Application of emetine in SARS-CoV-2 treatment: regulation of p38 MAPK signaling pathway for preventing emetine-induced cardiac complications. *Cell Cycle* 2022; 1-8 [PMID: 35852390 DOI: 10.1080/15384101.2022.2100575]

26 **Valipour M**, Zarghi A, Ebrahimzadeh MA, Irannejad H. Therapeutic potential of chelerythrine as a multi-purpose adjuvant for the treatment of COVID-19. *Cell Cycle* 2021; **20**: 2321-2336 [PMID: 34585628 DOI: 10.1080/15384101.2021.1982509]

27 **Valipour M**, Irannejad H, Emami S. Papaverine, a promising therapeutic agent for the treatment of COVID-19 patients with underlying cardiovascular diseases (CVDs). *Drug Dev Res* 2022; 10.1002/ddr.21961 [PMID: 35706384 DOI: 10.1002/ddr.21961]

28 **Azer SA**. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New Microbes New Infect* 2020; **37**: 100738 [PMID: 32834902 DOI: 10.1016/j.nmni.2020.100738]

29 **Agbuduwe C**, Basu S. Haematological manifestations of COVID-19: From cytopenia to coagulopathy. *Eur J Haematol* 2020; **105**: 540-546 [PMID: 32663356 DOI: 10.1111/ejh.13491]

30 **Fan BE**, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P, Ong KH. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol* 2020; **95**: E131-E134 [PMID: 32129508 DOI: 10.1002/ajh.25774]

31 **Mendoza M**, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, Lopez-Martinez RM, Balcells J, Fernandez-Hidalgo N, Carreras E, Suy A. Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study. *BJOG* 2020; **127**: 1374-1380 [PMID: 32479682 DOI: 10.1111/1471-0528.16339]

32 **Braga LFB**, Sass N. Coronavirus 2019, Thrombocytopenia and HELLP Syndrome: Association or Coincidence? *Rev Bras Ginecol Obstet* 2020; **42**: 669-671 [PMID: 33129222 DOI: 10.1055/s-0040-1718437]

33 **Federici L**, Picone O, Dreyfuss D, Sibiude J. Successful continuation of pregnancy in a patient with COVID-19-related ARDS. *BMJ Case Rep* 2020; **13** [PMID: 32788159 DOI: 10.1136/bcr-2020-237511]

34 **Ahmed I**, Eltaweel N, Antoun L, Rehal A. Severe pre-eclampsia complicated by acute fatty liver disease of pregnancy,

HELLP syndrome and acute kidney injury following SARS-CoV-2 infection. *BMJ Case Rep* 2020; **13** [PMID: 32784239 DOI: 10.1136/bcr-2020-237521]

35 **Ronnje L**, Länsberg JK, Vikhareva O, Hansson SR, Herbst A, Zaigham M. Complicated COVID-19 in pregnancy: a case report with severe liver and coagulation dysfunction promptly improved by delivery. *BMC Pregnancy Childbirth* 2020; **20**: 511 [PMID: 32887569 DOI: 10.1186/s12884-020-03172-8]

36 **Coronado-Arroyo JC**, Concepción-Zavaleta MJ, Zavaleta-Gutiérrez FE, Concepción-Urteaga LA. Is COVID-19 a risk factor for severe preeclampsia? *Eur J Obstet Gynecol Reprod Biol* 2021; **256**: 502-503 [PMID: 32958322 DOI: 10.1016/j.ejogrb.2020.09.020]

37 **Norooznezhad AH**, Nurzadeh M, Darabi MH, Naemi M. Coronavirus disease 2019 (COVID-19) in a pregnant women with treatment resistance thrombocytopenic purpura with and suspicion to HELLP syndrome: a case report. *BMC Pregnancy Childbirth* 2021; **21**: 567 [PMID: 34407793 DOI: 10.1186/s12884-021-04030-x]

38 **Farahani M**, Azadi K, Hashemnejad M, Agoushi A, Nirouei M. Ruled out of preeclampsia-like syndrome due to COVID-19: A case study. *Clin Case Rep* 2021; **9**: e05195 [PMID: 34934502 DOI: 10.1002/ccr3.5195]

39 **Aydın GA**, Ünal S, Özsoy HGT. The effect of gestational age at the time of diagnosis on adverse pregnancy outcomes in women with COVID-19. *J Obstet Gynaecol Res* 2021; **47**: 4232-4240 [PMID: 34585464 DOI: 10.1111/jog.15051]

40 **Vaezi M**, Mirghafourvand M, Hemmatzadeh S. Characteristics, clinical and laboratory data and outcomes of pregnant women with confirmed SARS-CoV-2 infection admitted to Al-Zahra tertiary referral maternity center in Iran: a case series of 24 patients. *BMC Pregnancy Childbirth* 2021; **21**: 378 [PMID: 34001013 DOI: 10.1186/s12884-021-03764-y]

41 **Jering KS**, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, Solomon SD. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19. *JAMA Intern Med* 2021; **181**: 714-717 [PMID: 33449067 DOI: 10.1001/jamainternmed.2020.9241]

42 **Bhardwaj Y**, Chakole V, Singam A, Madaan S. Anesthetic Management in a Post-COVID Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) Patient in Rural Central India: A Close Shave. *Cureus* 2022; **14**: e24196 [PMID: 35602790 DOI: 10.7759/cureus.24196]

43 **Madaan S**, Talwar D, Kumar S, Jaiswal A, Acharya N, Acharya S. HELLP Syndrome and COVID-19; association or accident: A case series. *J Family Med Prim Care* 2022; **11**: 802-806 [PMID: 35360752 DOI: 10.4103/jfmpc.jfmpc_1136_21]

44 **Takahashi K**, Sato T, Kamide T, Hoshina T, Kanuka H, Kumazawa K, Tanabe Y, Samura O, Okamoto A. Perinatal management of a pregnant woman with COVID-19: A case report from Japan. *Taiwan J Obstet Gynecol* 2022; **61**: 378-381 [PMID: 35361406 DOI: 10.1016/j.tjog.2022.02.033]

45 **Guida JP**, Cecatti JG, Souza RT, Pacagnella RC, Ribeiro-do-Valle CC, Luz AG, Lajos GJ, Surita FG, Nobrega GM, Griggio TB, Charles CM, Miele MJ, Ferreira SB, Tedesco RP, Fernandes KG, Martins-Costa SHA, Ramos JGL, Peret FJA, Feitosa FE, Traina E, Cunha-Filho EV, Vettorazzi J, Haddad SM, Andreucci CB, Correa-Junior MD, Mayrink J, Dias MAB, Oliveira LG, Melo-Junior EF, da Luz MGQ, Costa ML; REBRACO Study Group. Preeclampsia among women with COVID-19 during pregnancy and its impact on maternal and perinatal outcomes: Results from a national multicenter study on COVID in Brazil, the REBRACO initiative. *Pregnancy Hypertens* 2022; **28**: 168-173 [PMID: 35568019 DOI: 10.1016/j.preghy.2022.05.005]

46 **Snelgrove JW**, Simpson AN, Sutradhar R, Everett K, Liu N, Baxter NN. Preeclampsia and Severe Maternal Morbidity During the COVID-19 Pandemic: A Population-Based Cohort Study in Ontario, Canada. *J Obstet Gynaecol Can* 2022; **44**: 777-784 [PMID: 35395419 DOI: 10.1016/j.jogc.2022.03.008]

47 **Arslan E**. COVID-19: A Cause of HELLP Syndrome? *Int J Womens Health* 2022; **14**: 617-623 [PMID: 35506047 DOI: 10.2147/IJWH.S362877]

48 **Jafari M**, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, Basirjafari S, Mohammadi M, Rasmussen-Ivey C, Razizadeh MH, Nouri-Vaskeh M, Zarei M. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. *Rev Med Virol* 2021; **31**: 1-16 [PMID: 33387448 DOI: 10.1002/rmv.2208]

49 **Gesaka SR**, Obimbo MM, Wanyoro A. Coronavirus disease 2019 and the placenta: A literature review. *Placenta* 2022; **126**: 209-223 [PMID: 35872511 DOI: 10.1016/j.placenta.2022.07.007]

50 **Verma S**, Joshi CS, Silverstein RB, He M, Carter EB, Mysorekar IU. SARS-CoV-2 colonization of maternal and fetal cells of the human placenta promotes alteration of local renin-angiotensin system. *Med (N Y)* 2021; **2**: 575-590.e5 [PMID: 33870242 DOI: 10.1016/j.medj.2021.04.009]

51 **Lu-Culligan A**, Chavan AR, Vijayakumar P, Irshaid L, Courchaine EM, Milano KM, Tang Z, Pope SD, Song E, Vogels CBF, Lu-Culligan WJ, Campbell KH, Casanovas-Massana A, Bermejo S, Toothaker JM, Lee HJ, Liu F, Schulz W, Fournier J, Muenker MC, Moore AJ; Yale IMPACT Team, Konnikova L, Neugebauer KM, Ring A, Grubaugh ND, Ko AI, Morotti R, Guller S, Kliman HJ, Iwasaki A, Farhadian SF. Maternal respiratory SARS-CoV-2 infection in pregnancy is associated with a robust inflammatory response at the maternal-fetal interface. *Med (N Y)* 2021; **2**: 591-610.e10 [PMID: 33969332 DOI: 10.1016/j.medj.2021.04.016]

52 **Bloise E**, Zhang J, Nakpu J, Hamada H, Dunk CE, Li S, Imperio GE, Nadeem L, Kibschull M, Lye P, Matthews SG, Lye SJ. Expression of severe acute respiratory syndrome coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and transmembrane protease serine 2, in the placenta across gestation and at the maternal-fetal interface in pregnancies complicated by preterm birth or preeclampsia. *Am J Obstet Gynecol* 2021; **224**: 298.e1-298.e8 [PMID: 32853537 DOI: 10.1016/j.ajog.2020.08.055]

53 **Beys-da-Silva WO**, da Rosa RL, Santi L, Tureta EF, Terraciano PB, Guimarães JA, Passos EP, Berger M. The risk of COVID-19 for pregnant women: Evidences of molecular alterations associated with preeclampsia in SARS-CoV-2 infection. *Biochim Biophys Acta Mol Basis Dis* 2021; **1867**: 165999 [PMID: 33137411 DOI: 10.1016/j.bbadis.2020.165999]

54 **Chen X**, Tao T, Wang H, Zhao H, Lu L, Wu F. Arterial Thrombosis Is Accompanied by Elevated Mitogen-Activated Protein Kinase (MAPK) and Cyclooxygenase-2 (COX-2) Expression *via* Toll-Like Receptor 4 (TLR-4) Activation by S100A8/A9. *Med Sci Monit* 2018; **24**: 7673-7681 [PMID: 30367682 DOI: 10.12659/MSM.909641]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 321-330

DOI: 10.5501/wjv.v11.i5.321

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Retrospective Study

Manifestations of COVID-19 infection in children with malignancy: A single-center experience in Jordan

Mousa Ahmad Qatawneh, Moath Altarawneh, Ruba Alhazaimeh, Mais Jazazi, Omaiema Jarrah, Alaa Shorman, Laila Alsadah, Maher Mustafa

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ahmed S, Pakistan; Virarkar M, United States

Received: February 19, 2022
Peer-review started: February 19, 2022
First decision: June 16, 2022
Revised: June 28, 2022
Accepted: September 2, 2022
Article in press: September 2, 2022
Published online: September 25, 2022

Mousa Ahmad Qatawneh, Moath Altarawneh, Ruba Alhazaimeh, Mais Jazazi, Omaiema Jarrah, Maher Mustafa, Department of Hematology and Medical Oncology and Stem Cell Transplantation Unit, Queen Rania Children's Hospital, Royal Medical Services, Amman 11183, Jordan

Alaa Shorman, Department of Neonatology, Queen Rania Children's Hospital, Royal Medical Services, Amman 11183, Jordan

Laila Alsadah, Department of General Pediatrics, Queen Rania Children's Hospital, Royal Medical Services, Amman 11183, Jordan

Corresponding author: Mousa Ahmad Qatawneh, MD, Consultant Physician-Scientist, Staff Physician, Department of Hematology and Medical Oncology and Stem Cell Transplantation Unit, Queen Rania Children's Hospital, Royal Medical Services, Dabouq, Amman 11183, Jordan.
dr_m_qatawneh@yahoo.com

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of COVID-19 cases. Few data are available regarding the clinical course, disease severity, and mode of treatment in children with malignancy and COVID-19.

AIM

To evaluate the treatment plan and outcome of children with malignancy who contracted COVID-19.

METHODS

A retrospective study of the medical files of patients with malignancy who contracted COVID-19 between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan, and outcome. Eligible patients were those with malignancy who tested positive for COVID-19 by reverse transcription polymerase chain reaction.

RESULTS

A total of 40 patients who had malignancy contracted COVID-19 from July 1, 2020 to June 1, 2021. Their primary diseases were as follows: 34 patients (85%) had hematological malignancies (30 had acute lymphoblastic leukemia, 2 had acute myeloblastic leukemia, and 2 had Hodgkin lymphoma), whereas 6 patients (15%) had solid tumors (2 had neuroblastoma, 2 had rhabdomyosarcoma, and 2 had central nervous system tumors). Twelve patients (30%) did not need hospitalization and underwent home isolation only, whereas twenty-eight patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 were admitted in the pediatric intensive care unit).

CONCLUSION

COVID-19 with malignancy in the pediatric age group has a benign course and does not increase the risk of having severe infection compared to other children.

Key Words: COVID-19; Malignancy; Disease severity score; Children; Jordan

Core Tip: Coronavirus disease 2019 (COVID-19) has caused a global health crisis since the end of 2019. This retrospective study describes the manifestation of COVID-19 in our oncology patients who were treated at Queen Rania Children's Hospital between July 2021 and June 2021, focusing on the initial presentation, clinical course and management plan and comparing these results with the international data worldwide to determine the optimal way to care for oncology patients during the COVID-19 crisis.

Citation: Qatawneh MA, Altarawneh M, Alhazaimeh R, Jazazi M, Jarrah O, Shorman A, Alsadah L, Mustafa M. Manifestations of COVID-19 infection in children with malignancy: A single-center experience in Jordan. *World J Virol* 2022; 11(5): 321-330

URL: https://www.wjgnet.com/2220-3249/full/v11/i5/321.htm

DOI: https://dx.doi.org/10.5501/wjv.v11.i5.321

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused a global health crisis since late 2019[1]. As there were more than 2 million cases of COVID-19 worldwide, the World Health Organization (WHO) declared COVID-19 a pandemic in March 11, 2020[2,3]. By June 1, 2021, a total of 170448610 cases of COVID-19, including 3663570 deaths, had been reported worldwide. In Jordan, a total of 737284 cases of COVID-19 and 9472 deaths had been reported by June 1, 2021[4].

The incubation period of the virus is between 2 and 14 d with an average of 5 d[5,6].The main routes of virus transmission are droplets and close contact[7]. COVID-19 affects all age groups; however, the pediatric population accounts for only 3%-5% of total cases[8]. Oncology patients generally shed respiratory viruses for longer than immunocompetent people and this is mostly true for COVID-19 as well[9]. In children, most cases of COVID-19 are asymptomatic, and studies have revealed that children have less severe symptoms compared to adults[10-12]. However, some patients develop life-threatening complications such as acute respiratory distress syndrome, thrombosis, and multiorgan failure[13-15]. Children with malignancy are frequently immunocompromised because of the therapy they receive, putting them at high risk for severe infections, which are the major cause of mortality in these patients [16-18]. However, there is growing evidence that the mortality rate in pediatric cancer patients with COVID-19 is extremely low[19,20]. The international pediatric oncology community acted quickly in response to the COVID-19 pandemic and made many recommendations to decrease the risk of infection in pediatric cancer patients[21,22].

This study analyzed and evaluated the treatment plans and outcomes of children with malignancy who contracted COVID-19 in Queen Rania Children's Hospital (QRCH; Amman, Jordan), and compared our results with the international results.

MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of the Jordanian Medical Services. The medical records were reviewed of patients at QRCH who had malignancy and tested positive for

COVID-19 between July 2020 and June 2021.

All pediatric oncology patients under 14-years-old who had received anticancer treatment and were diagnosed with COVID-19 by polymerase chain reaction (PCR) nasopharyngeal swab were eligible for this study. The primary endpoint was death, discharge from the hospital, or end of active care for COVID-19 for patients who needed further treatment of their primary disease in the hospital, or 14 d after initial diagnosis of COVID-19 in patients who did not need hospitalization.

Data were collected on primary disease, age, white blood cell count, absolute neutrophil count, lymphocyte count, place of admission, clinical status on admission, mode of treatment, radiological findings, and outcome.

PCR for COVID-19 was done for symptomatic patients, patients who had close contact with a confirmed case of COVID-19, and before any admission to the hospital, as our hospital guidelines recommend PCR for COVID-19 for any patient who needs admission, whatever the cause of admission.

Detailed clinical histories including primary disease, status of the disease, comorbidities, and detailed chemotherapy history were taken from all of our patients. We also performed full physical examinations, investigations, and chest X-rays, and if indicated, a high-resolution chest computed tomography (CT) scan was performed. After obtaining all of these data, researchers assigned patients a "disease severity score" categorizing the severity of their disease into the following categories: asymptomatic, mild, moderate, and severe disease (as described in Table 1).

For patients who needed admission, they were admitted in an isolation room in a specialized ward in the hospital (COVID-19 ward). When they met the criteria for discharge, they were discharged home with precautions and remained in home isolation until 14 d from the day of their COVID-19 diagnosis.

COVID-19 recovery was defined by the disappearance of the clinical symptoms in symptomatic patients or 14 d from the diagnosis of COVID-19 in asymptomatic patients.

RESULTS

About 400 oncology patients were seen in QRCH during the study period between July 2020 and June 2021. A total of 40 oncology patients tested positive for COVID-19 during the same period. Twenty-four patients (60%) were males and sixteen (40%) were females. Twenty-eight patients were below the age of 6 years; they accounted for the majority of our patients in this study (70%). Five patients (12.5%) were between the ages of 6-years-old and 12-years-old whereas seven patients (17.5%) were between the ages of 12-years-old and 14-years-old. Hematological malignancies were the predominant primary disease in this study, as they accounted for about (85%) of the cases. The patients' characteristics are summarized in Table 2.

Upon presentation, full investigations were done for the patients in addition to chest X-rays. A high-resolution chest CT scan was done if there were any chest X-ray abnormalities or moderate to severe respiratory symptoms. Only 10 patients required a chest CT scan. Laboratory and radiological findings are summarized in Table 3.

According to the disease severity score, 10 patients (25%) were asymptomatic, 20 patients (50%) had mild symptoms, and 8 patients (20%) had moderate symptoms whereas just 2 patients (5%) had severe symptoms. Of these patients, 12 (30%) were kept in home isolation whereas 28 patients were treated in the hospital, where 26 patients (65%) were treated in the COVID-19 ward and 2 patients (5%) were treated in the pediatric intensive care unit (PICU). The solid tumor patients were asymptomatic or had mild symptoms, whereas the moderate and severe symptoms were found only in patients with hematological malignancies; however, some patients who had hematological malignancies were asymptomatic or had mild symptoms. The hospital management was case by case and the treatment plan comprised intravenous (IV) antibiotics, azithromycin, dexamethasone, oxygen support, IV immunoglobulin (IVIG) for patients with hypogammaglobulinemia, and vitamins. Details about the clinical course of COVID-19 are summarized in Table 4.

DISCUSSION

Few data are available worldwide regarding the effect of COVID-19 on pediatric oncology patients; however, multiple studies have been published on the COVID-19 clinical course in these patients. In our center, 10% of our oncology patients contracted COVID-19 between July 2020 and June 2021. This percentage of COVID-19-infected oncology patients was higher than that reported in the general pediatric population in Jordan in the same period, which was about 5%-6%[4]. This increase in the percentage of COVID-19 among our oncology patients can be explained by the frequent testing of these patients for COVID-19 even if they were asymptomatic, as they require recurrent admissions to the hospital for different reasons including chemotherapy, fever, blood, and platelet transfusions and surgeries. Screening for COVID-19 was done before each admission as part of our hospital protocol regarding admissions during the era of COVID-19. However, this was not the case for healthy pediatric patients. Screening for COVID-19 was not done for healthy children who did not need hospital

Table 1 Coronavirus disease 2019 disease severity score

Disease severity	Definition
Asymptomatic	No symptoms at all during the course of COVID-19
Mild disease	Symptoms that did not require hospital admission; if hospitalization was required, the indication was for a cause other than the management of COVID-19 associated symptoms or signs
Moderate disease	Symptoms that required inpatient management of COVID-19 associated symptoms, but without the need for PICU care
Severe disease	Symptoms that required PICU care for COVID-19 related signs and symptoms

COVID-19: Coronavirus disease 2019; PICU: Pediatric intensive care unit.

Table 2 Characteristics of pediatric oncology patients with coronavirus disease 2019

Patient characteristics	Number	Percentage (%)
Sex		
Male	24	60
Female	16	40
Age		
1-6 yr	28	70
6-12 yr	5	12.5
12-14 yr	7	17.5
Primary disease		
Acute lymphoblastic leukemia	30	75
Acute myeloid leukemia	2	5
Neuroblastoma	2	5
Rhabdomyosarcoma	2	5
CNS tumors	2	5
Hodgkin lymphoma	2	5

CNS: Central nervous system.

admission unless they were symptomatic or in close contact with a confirmed COVID-19 case.

The median age of our oncology patients at the time of COVID-19 diagnosis was 5 years (range between 1.5 years and 13.5 years). This is similar to what was reported by Millen *et al*[23] in a study done in the United Kingdom involving 54 patients under the age of 16 years with malignancy. The median age in our study was less than that reported by Al Odda *et al*[24] in a study done in al Sulaimani-Kurdisan involving 54 malignancy patients and by Dong *et al*[25] in a Chinese study involving 2143 patients with malignancy, as the median age for these two studies was 7 years. We also reported that the majority of our patients were less than 6 years (70%), followed by patients who were more than 12 years (17.5%), consistent with the study by Navaeian *et al*[26] that was conducted in Iran in 20 oncology patients.

In our study, 24 patients were males (60%) and 16 patients were females (40%). This male predominance was reported in a study done in our center about patients who underwent hematopoietic stem cell transplantation and had COVID-19 infection post-transplant; all of them were males[27]. Madhusoodhan *et al*[28] also reported male predominance in a multicenter retrospective study involving 578 pediatric oncology patients in the New York-New Jersey region; 70% of their patients were males.

The majority of our cases had hematological malignancies (85%); 30 patients (75%) had acute lymphocytic leukemia (ALL), 2 patients (5%) had acute myeloid leukemia, and 2 patients had Hodgkin lymphoma. Solid tumors accounted for a smaller percentage (20%) of the cases. Similar results were reported by most of the international studies done worldwide[10,20,29,30]. This predominance of hematological malignancies among oncology patients who had COVID-19 can be explained by the fact

Table 3 Laboratory and radiological details for coronavirus disease 2019 in our oncology patients

Parameters	Numbers	Percentage (%)
WBC count		
Leukopenia < 4000	16	40
Normal WBC count	20	50
Leukocytosis > 16000	4	10
Lymphocytes count		
Lymphopenia	23	57.5
Normal count	17	42.5
Lymphocytosis	0	0
Neutrophil count		
Severe neutropenia	10	25
Mild-Moderate neutropenia	10	25
Normal count	16	40
Neutrophilia	4	10
CRP titer		
Negative < 6	3	7.5
Positive 6	37	92.5
D-Dimer		
Positive	6	15
Negative	34	85
IgG level		
< 700 mg/dL	9	22.5
> 700 mg/dL	31	77.5
Chest X-ray findings		
Normal chest X-ray	18	45
Perihilar infiltrates	12	30
Bilateral patchy consolidation	10	25
High-resolution chest CT scan findings		
Bilateral infiltration > 25%	8	20
Bilateral infiltration 25%-50%	2	5
Bilateral infiltration > 50%	0	0

CRP: C-reactive protein; CT: Computed tomography; IgG: Immunoglobulin G; WBC: White blood cell.

that hematological malignancies are the most common malignancies in pediatric age groups, and they require longer duration of treatment, especially for ALL patients. Furthermore, the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocyte function compared to solid tumors[31,32].

Regarding our patients, fever was the most common presenting symptom, as 24 patients (60%) had a temperature higher than 37.8 axillary at the time of the COVID-19 test. All of these patients were admitted to the COVID-19 ward in our hospital and were treated with IV antibiotics, as bacterial infection cannot be ruled out and has to be covered by IV antibiotics, especially in neutropenic patients.

Most of the international studies also reported that fever was the most common presenting symptom of COVID-19 in oncology patients[33,34].

Most of our patients had mild symptoms (50%), whereas just 2 patients (5%) had severe symptoms. The moderate and severe symptoms were found exclusively in patients who had hematological malignancies, whereas the patients who had solid tumors were asymptomatic or had mild symptoms.

Table 4 Details of the clinical course of coronavirus disease 2019 in oncology patients

Parameters	Number	Percentage
Presenting symptoms		
Fever	24	60
Cough	15	37.5
Sore throat	3	7.5
Dyspnea	2	5
Diarrhea	2	5
Disease severity		
Asymptomatic	10	25
Mild disease	20	50
Moderate disease	8	20
Severe disease	2	5
Place of care		
Home isolation	12	30
COVID-19 ward	26	65
PICU	2	5
Treatment required		
No treatment	10	25
IV antibiotic	24	60
Azithromycin	30	75
Vitamins	30	75
Dexamethasone	26	65
Oxygen support	4	10
CPAP	2	5
IVIG	9	22.5

COVID-19: Coronavirus disease 2019; CPAP: Continuous positive airway pressure; IVIG: Intravenous immunoglobulin; PICU: Pediatric intensive care unit.

This can be explained by the fact that the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocyte function compared to solid tumors[31,32], in addition to the role of granulocyte-colony stimulating factor (G-CSF) administration after completing chemotherapy in solid tumor patients, which prevents the development of severe neutropenia.

Asymptomatic patients and patients with mild symptoms except fever were discharged home with instructions for strict home isolation and were followed by video and phone calls.

The patients with severe symptoms were treated in the PICU as they required the use of continuous positive airway pressure (CPAP) to maintain oxygen saturation of more than 94%. The primary disease for these 2 patients with severe symptoms was ALL. Both of them were in remission and in the consolidation phase of their treatment; however, these 2 patients had severe neutropenia at the time of COVID-19 infection. The treatment plan for these 2 patients was IVIG, dexamethasone, azithromycin, and IV antibiotics in addition to the CPAP, which was needed for 2 d for the first patient and 3 d for the second patient. Gradual improvement in clinical status was noticed for both of them and they were discharged home without any complications after about 2 wk of admission. As severe neutropenia might have played a major role in the development of severe symptoms of COVID-19 in these 2 patients, modifications of the chemotherapy doses for all of our patients in the hospital were made to prevent severe bone marrow suppression, especially severe neutropenia. Furthermore, we administered G-CSF at 48 h after finishing the chemotherapy protocol for non-hematological malignancies to perform bone marrow rescue.

Patients with moderate symptoms were admitted to the COVID-19 ward and they received dexamethasone and azithromycin. IV antibiotics were also given for patients with fever. IVIG was given

for patients with secondary hypogammaglobulinemia, which may have occurred due to chemotherapy; only 9 of our patients (22.5%) received IVIG.

These results are similar to what was reported by Millen *et al*[23], who reported that 6.6% of their oncology patients had severe symptoms of COVID-19. On the other hand, our results are higher than what was reported by Madhusoodhan *et al*[28], as they reported that only 17 of 578 oncology patients (3%) developed severe symptoms of COVID-19.

However, studies done on COVID-19 in the general pediatric population have shown similar rates of severe symptoms of COVID-19 among children who tested positive for COVID-19. Bellino *et al*[35] reported in a study done in Italy that 4.3% of patients who had COVID-19 developed severe symptoms. Meena *et al*[36] reported in their systematic review and meta-analysis that 4% of pediatric patients who had COVID-19 developed severe symptoms.

These similar results of severe symptoms of COVID-19 among oncology patients compared to the general pediatric population suggest that, even though the oncology patients have more risk factors for developing severe symptoms of COVID-19, children with malignancy who have COIVD-19 are not at greater risk of having severe symptoms of COVID-19.

None of our patients died or developed any of the chronic complications of COVID-19, including multisystem inflammatory syndrome in children, after recovering from the infection. These results may be explained by the role of chemotherapy-related immune suppression in the protection against the development of cytokine release storm[37]. The mortality rate in our study is comparable to the overall death rate reported by Verity *et al*[38], as the estimated rate in their study was 0.66% and decreased to 0.0016% in children under the age of 9 years.

For all of our patients who tested positive for COVID-19, chemotherapy was withheld for at least 10 d, even in asymptomatic patients. We did not notice any increase in the malignancy-related morbidity nor mortality due this delay of chemotherapy.

On the other hand, we did not notice an increase in the incidence of any malignancy groups during the COVID-19 era, which indicates that the virus is not an oncogenic virus, at least in the short term.

As there is a risk of exposure to COVID-19 in both the community and hospital settings, resulting in extreme anxiety in the families of patients with malignancies, standard precautions for basic and respiratory hygiene must be strictly applied to reduce the risk of transmission of COVID-19.

One limitation of this study was the small number of cases, as it included just one institution's experience in a short period of time. Another limitation was the short follow-up period of these patients, which prevented us from detecting the possible long-term complications.

CONCLUSION

Patients with malignancies are more likely to be infected with COVID-19, especially patients with hematological malignancies. However, these patients are not more likely to develop severe symptoms of COVID-19 compared to children in general. Furthermore, mortality and morbidity due to COVID-19 infection are not increased in patients with malignancies. Therefore, chemotherapy should be continued for patients with cancer during the era of COVID-19, provided that the WHO recommendations are strictly applied and that patients are not severely suppressed and have tested negative for COVID-19. However, the prevention of severe neutropenia by administering G-CSF as a bone marrow rescue is mandatory to prevent the moderate to severe symptoms of COVID-19 in malignancy patients.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of cases of COVID-19. Few data are available regarding the clinical course, the severity of the disease, and mode of treatment in children with malignancy and COVID-19.

Research motivation

COVID-19 has caused a global crisis worldwide, with few data available on this new health crisis. Patients with comorbidities are more susceptible to COVID-19 complications, especially oncology patients who are receiving different modalities of treatment making them immunocompromised most of the time. We would like to share our experience in these patients to compare it with the published data worldwide.

Research objectives

The main objective of this study was to evaluate the outcome of oncology patients who contracted COVID-19, compare it with the results of the healthy population in the same age group, and compare the outcomes among different malignancy groups. Also we compared our patients' outcome with the international data published worldwide to share our experience and try to improve our management plan for these patients to provide the best care for them during this health crisis.

Research methods

A retrospective review of the medical files of patients who have malignancy and developed COVID-19 between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan, and outcome. Eligible patients were patients who had malignancy and tested positive for COVID-19 by reverse transcription polymerase chain reaction.

Research results

A total of 40 patients with malignancy who contracted COVID-19 from July 1, 2020 to June 1, 2021. Their primary diseases were as follows: 34 patients (85%) had hematological malignancies (30 of them had acute lymphoblastic leukemia, 2 had acute myeloblastic leukemia, and 2 had Hodgkin lymphoma), whereas 6 (15%) had solid tumors (2 had neuroblastoma, 2 had rhabdomyosarcoma, and 2 had central nervous system tumors). Twelve patients (30%) did not need hospitalization and underwent home isolation only, whereas 28 patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 patients were admitted to the pediatric intensive care unit).

Research conclusions

Children with malignancy who contracted COVID-19 have a benign course and do not have increased risk of severe infection compared to healthy children.

Research perspectives

The findings of this study will help us share our experience worldwide and give an idea of what is occurring in developing countries during this health crisis, especially in oncology patients who need special care.

FOOTNOTES

Author contributions: Qatawneh MA, Jazazi M, and Mutafa M substantially contributed to the conception and design of the work; Altarawneh M, Jazazi M, and Shorman A substantially contributed to the data collection; Alhazaimeh R, Shorman A, and Alsadah L substantially contributed to the acquisition, analysis, or interpretation of the data; Qatawneh MA, Alhazaimeh R, and Jarrah O contributed to drafting or revising the manuscript critically for important intellectual content; Qatawneh MA, Altarawneh M, and Mustafa M gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Institutional review board statement: This retrospective study was approved by the Ethical committee of the Jordanian Medical Services.

Informed consent statement: Informed consent forms were obtained from all the patients.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: The clinical data of this article are available upon reasonable request to the corresponding author.

Country/Territory of origin: Jordan

ORCID number: Mousa Ahmad Qatawneh 0000-0002-5400-8804; Moath Altarawneh 0000-0001-9526-9181; Ruba Alhazaimeh 0000-0002-2579-8915; Mais Jazazi 0000-0003-0400-6840; Omaiema Jarrah 0000-0003-0719-7822; Alaa Shorman 0000-0002-9760-0904; Laila Alsadah 0000-0002-8667-5142; Maher Mustafa 0000-0001-5975-3400.

S-Editor: Zhang H

L-Editor: Filipodia
P-Editor: Zhang H

REFERENCES

1 **Sahu KK**, Mishra AK, Lal A. Coronavirus disease-2019: An update on third coronavirus outbreak of 21st century. *QJM* 2020; **113**: 384-386 [PMID: 32125418 DOI: 10.1093/qjmed/hcaa081]
2 **World Health Organization**. Coronavirus Disease (COVID-19) Situation Reports. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
3 **Worldometer**. Coronavirus update (live): 2,359,332 cases and 161,951 deaths from COVID-19 virus pandemic. Available from: https://www.worldometers.info/coronavirus/?/
4 **Johns Hopkins University**. Coronavirus COVID-19 Global Cases by Johns Hopkins CSSE. 2 May 2020. Available from https://coronavirus.jhu.edu/map.html
5 **Glenthøj A**, Jakobsen LH, Sengeløv H, Ahmad SA, Qvist K, Rewes A, Poulsen CB, Overgaard UM, Mølle I, Severinsen MT, Strandholdt CN, Maibom J, Kodahl AR, Ryg J, Ravn P, Johansen IS, Helsø SN, Jensen-Fangel S, Kisielewicz J, Wiese L, Helleberg M, Kirk O, Clausen MR, Frederiksen H. SARS-CoV-2 infection among patients with haematological disorders: Severity and one-month outcome in 66 Danish patients in a nationwide cohort study. *Eur J Haematol* 2021; **106**: 72-81 [PMID: 32939853 DOI: 10.1111/ejh.13519]
6 **Lattenist R**, Yildiz H, De Greef J, Bailly S, Yombi JC. COVID-19 in Adult Patients with Hematological Disease: Analysis of Clinical Characteristics and Outcomes. *Indian J Hematol Blood Transfus* 2020; **37**: 1-5 [PMID: 32837052 DOI: 10.1007/s12288-020-01318-4]
7 **Wang J**, Du G. COVID-19 may transmit through aerosol. *Ir J Med Sci* 2020; **189**: 1143-1144 [PMID: 32212099 DOI: 10.1007/s11845-020-02218-2]
8 **Dorantes-Acosta E**, Ávila-Montiel D, Klünder-Klünder M, Juárez-Villegas L, Márquez-González H. Survival and Complications in Pediatric Patients With Cancer and COVID-19: A Meta-Analysis. *Front Oncol* 2021; **10**: 608282 [PMID: 33552980 DOI: 10.3389/fonc.2020.608282]
9 **Lehners N**, Tabatabai J, Prifert C, Wedde M, Puthenparambil J, Weissbrich B, Biere B, Schweiger B, Egerer G, Schnitzler P. Long-Term Shedding of Influenza Virus, Parainfluenza Virus, Respiratory Syncytial Virus and Nosocomial Epidemiology in Patients with Hematological Disorders. *PLoS One* 2016; **11**: e0148258 [PMID: 26866481 DOI: 10.1371/journal.pone.0148258]
10 **He W**, Chen L, Yuan G, Fang Y, Chen W, Wu D, Liang B, Lu X, Ma Y, Li L, Wang H, Chen Z, Li Q, Gale RP. COVID-19 in persons with haematological cancers. *Leukemia* 2020; **34**: 1637-1645 [PMID: 32332856 DOI: 10.1038/s41375-020-0836-7]
11 **Foà R**, Bonifacio M, Chiaretti S, Curti A, Candoni A, Fava C, Ciccone M, Pizzolo G, Ferrara F. Philadelphia-positive acute lymphoblastic leukaemia (ALL) in Italy during the COVID-19 pandemic: a Campus ALL study. *Br J Haematol* 2020; **190**: e3-e5 [PMID: 32368790 DOI: 10.1111/bjh.16758]
12 **Cuneo A**, Scarfò L, Reda G, Varettoni M, Quaglia FM, Marchetti M, De Paoli L, Re F, Pietrasanta D, Rigolin GM, Orsucci L, Ibatici A, Gattei V, Mauro FR, Trentin L, Laurenti L, Marasca R, Foà R. Chronic lymphocytic leukemia management in Italy during the COVID-19 pandemic: a Campus CLL report. *Blood* 2020; **136**: 763-766 [PMID: 32559271 DOI: 10.1182/blood.2020006854]
13 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]
14 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
15 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]
16 **Zhang J**, Wang X, Jia X, Li J, Hu K, Chen G, Wei J, Gong Z, Zhou C, Yu H, Yu M, Lei H, Cheng F, Zhang B, Xu Y, Wang G, Dong W. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect* 2020; **26**: 767-772 [PMID: 32304745 DOI: 10.1016/j.cmi.2020.04.012]
17 **Balduzzi A**, Brivio E, Rovelli A, Rizzari C, Gasperini S, Melzi ML, Conter V, Biondi A. Lessons after the early management of the COVID-19 outbreak in a pediatric transplant and hemato-oncology center embedded within a COVID-19 dedicated hospital in Lombardia, Italy. Estote parati. *Bone Marrow Transplant* 2020; **55**: 1900-1905 [PMID: 32313181 DOI: 10.1038/s41409-020-0895-4]
18 **Pathak EB**, Salemi JL, Sobers N, Menard J, Hambleton IR. COVID-19 in Children in the United States: Intensive Care Admissions, Estimated Total Infected, and Projected Numbers of Severe Pediatric Cases in 2020. *J Public Health Manag Pract* 2020; **26**: 325-333 [PMID: 32282440 DOI: 10.1097/PHH.0000000000001190]
19 **André N**, Rouger-Gaudichon J, Brethon B, Phulpin A, Thébault É, Pertuisel S, Gandemer V. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? *Pediatr Blood Cancer* 2020; **67**: e28392 [PMID: 32383827 DOI: 10.1002/pbc.28392]
20 **de Rojas T**, Pérez-Martínez A, Cela E, Baragaño M, Galán V, Mata C, Peretó A, Madero L. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatr Blood Cancer* 2020; **67**: e28397 [PMID: 32383819 DOI:

10.1002/pbc.28397]

21 **Bouffet E**, Challinor J, Sullivan M, Biondi A, Rodriguez-Galindo C, Pritchard-Jones K. Early advice on managing children with cancer during the COVID-19 pandemic and a call for sharing experiences. *Pediatr Blood Cancer* 2020; **67**: e28327 [PMID: 32239747 DOI: 10.1002/pbc.28327]

22 **International Late Effects of Childhood Cancer Guideline Harmonization Group**. IGHG COVID-19 Statement. Available from: https://www.ighg.org/ighg-statement-covid-19/

23 **Millen GC**, Arnold R, Cazier JB, Curley H, Feltbower RG, Gamble A, Glaser AW, Grundy RG, Lee LYW, McCabe MG, Phillips RS, Stiller CA, Várnai C, Kearns PR. Severity of COVID-19 in children with cancer: Report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. *Br J Cancer* 2021; **124**: 754-759 [PMID: 33299130 DOI: 10.1038/s41416-020-01181-0]

24 **Al Odda BKA**, Mohamme ZB, Muhealddina DL, Abdullah KM, Qadir AO, Shrif R, Fakrealdeen GA, Al odda ZBK, Al odda GBK. Characteristics of COVID-19 in Pediatric Patients with Malignancy in Sulaymaniyah Governorate, Kurdistan Region of Iraq. *J Corona Virus* 2021; **1**: 1-7 [DOI: 10.47690/jcv.2021.1104]

25 **Dong Y**, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020; **145** [PMID: 32179660 DOI: 10.1542/peds.2020-0702]

26 **Navaeian A**, Mahmoudi S, Pourakbari B, Bakhtiari M, Khodabandeh M, Abdolsalehi MR, Sharari AS, Mamishi S. COVID-19 infection in children with underlying malignancies in Iran. *J Basic Clin Physiol Pharmacol* 2021; **33**: 79-84 [PMID: 34192829 DOI: 10.1515/jbcpp-2021-0057]

27 **Qatawneh M**, Aljazazi M, Altarawneh M, Aljamaen H, Mustafa M, Alqasem A, Sharar AA. Hematopoietic Stem Cell Transplantation During the Era of COVID-19 in Queen Rania Children's Hospital. *Mater Sociomed* 2021; **33**: 131-137 [PMID: 34483742 DOI: 10.5455/msm.2021.33.131-137]

28 **Madhusoodhan PP**, Pierro J, Musante J, Kothari P, Gampel B, Appel B, Levy A, Tal A, Hogan L, Sharma A, Feinberg S, Kahn A, Pinchinat A, Bhatla T, Glasser CL, Satwani P, Raetz EA, Onel K, Carroll WL. Characterization of COVID-19 disease in pediatric oncology patients: The New York-New Jersey regional experience. *Pediatr Blood Cancer* 2021; **68**: e28843 [PMID: 33338306 DOI: 10.1002/pbc.28843]

29 **Borah P**, Mirgh S, Sharma SK, Bansal S, Dixit A, Dolai TK, Lunkad S, Gupta N, Singh G, Jain A, Bansal D, Choudhary D, Khandelwal V, Doval D, Kumar M, Bhargava R, Chakrabarti A, Kalashetty M, Rauthan A, Kazi B, Mandal PK, Jeyaraman P, Naithani R; AIIMS Hematology Alumni Group. Effect of age, comorbidity and remission status on outcome of COVID-19 in patients with hematological malignancies. *Blood Cells Mol Dis* 2021; **87**: 102525 [PMID: 33338697 DOI: 10.1016/j.bcmd.2020.102525]

30 **Carlotti APCP**, Carvalho WB, Johnston C, Rodriguez IS, Delgado AF. COVID-19 Diagnostic and Management Protocol for Pediatric Patients. *Clinics (Sao Paulo)* 2020; **75**: e1894 [PMID: 32321116 DOI: 10.6061/clinics/2020/e1894]

31 **Allegra A**, Pioggia G, Tonacci A, Musolino C, Gangemi S. Cancer and SARS-CoV-2 Infection: Diagnostic and Therapeutic Challenges. *Cancers (Basel)* 2020; **12** [PMID: 32549297 DOI: 10.3390/cancers12061581]

32 **von Lilienfeld-Toal M**, Vehreschild JJ, Cornely O, Pagano L, Compagno F; EHA Infectious Disease Scientific Working Group, Hirsch HH. Frequently asked questions regarding SARS-CoV-2 in cancer patients-recommendations for clinicians caring for patients with malignant diseases. *Leukemia* 2020; **34**: 1487-1494 [PMID: 32358568 DOI: 10.1038/s41375-020-0832-y]

33 **Boulad F**, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in Children With Cancer in New York City. *JAMA Oncol* 2020; **6**: 1459-1460 [PMID: 32401276 DOI: 10.1001/jamaoncol.2020.2028]

34 **Ogimi C**, Englund JA, Bradford MC, Qin X, Boeckh M, Waghmare A. Characteristics and Outcomes of Coronavirus Infection in Children: The Role of Viral Factors and an Immunocompromised State. *J Pediatric Infect Dis Soc* 2019; **8**: 21-28 [PMID: 29447395 DOI: 10.1093/jpids/pix093]

35 **Bellino S**, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, Fabiani M, Boros S, Vescio F, Riccardo F, Bella A, Filia A, Rezza G, Villani A, Pezzotti P; COVID-19 WORKING GROUP. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. *Pediatrics* 2020; **146** [PMID: 32665373 DOI: 10.1542/peds.2020-009399]

36 **Meena J**, Yadav J, Saini L, Yadav A, Kumar J. Clinical Features and Outcome of SARS-CoV-2 Infection in Children: A Systematic Review and Meta-analysis. *Indian Pediatr* 2020; **57**: 820-826 [PMID: 32583808 DOI: 10.1007/s13312-020-1961-0]

37 **Minotti C**, Tirelli F, Barbieri E, Giaquinto C, Donà D. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? *J Infect* 2020; **81**: e61-e66 [PMID: 32335173 DOI: 10.1016/j.jinf.2020.04.026]

38 **Verity R**, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, Cuomo-Dannenburg G, Thompson H, Walker PGT, Fu H, Dighe A, Griffin JT, Baguelin M, Bhatia S, Boonyasiri A, Cori A, Cucunubá Z, FitzJohn R, Gaythorpe K, Green W, Hamlet A, Hinsley W, Laydon D, Nedjati-Gilani G, Riley S, van Elsland S, Volz E, Wang H, Wang Y, Xi X, Donnelly CA, Ghani AC, Ferguson NM. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020; **20**: 669-677 [PMID: 32240634 DOI: 10.1016/S1473-3099(20)30243-7]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 331-340

DOI: 10.5501/wjv.v11.i5.331

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Retrospective Study

Effect of age on computed tomography findings: Specificity and sensitivity in coronavirus disease 2019 infection

Erdal Karavas, Edhem Unver, Sonay Aydın, Gonul Seven Yalcin, Erdem Fatihoglu, Ufuk Kuyrukluyildiz, Yusuf Kemal Arslan, Mustafa Yazici

Specialty type: Radiology, nuclear medicine and medical imaging

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bellini MI, Italy; Wang MK, China

Received: April 24, 2022
Peer-review started: April 24, 2022
First decision: May 12, 2022
Revised: June 1, 2022
Accepted: August 25, 2022
Article in press: August 25, 2022
Published online: September 25, 2022

Erdal Karavas, Sonay Aydın, Erdem Fatihoglu, Department of Radiology, Erzincan Binali Yildirim University, Erzincan 24100, Turkey

Edhem Unver, Gonul Seven Yalcin, Department of Pulmonology, Erzincan Binali Yildirim University, Erzincan 24100, Turkey

Ufuk Kuyrukluyildiz, Department of Anesthesiology and Reanimation, Erzincan Binali Yıldırım University, Erzincan 24100, Turkey

Yusuf Kemal Arslan, Department of Biostatistics, Erzincan Binali Yildirim University, Erzincan 24100, Turkey

Mustafa Yazici, Department of Dermatology, Erzincan Binali Yildirim University, Erzincan 24100, Turkey

Corresponding author: Sonay Aydın, MD, Associate Professor, Department of Radiology, Erzincan Binali Yildirim University, Erzincan Binali Yıldırım Üniversitesi Tıp Fakültesi Dekanlığı Başbağlar Mahallesi 1429, Sokak No:2/1 24100 ERZİNCAN, Erzincan 24100, Turkey. sonay.aydin@erzincan.edu.tr

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a pandemic caused by the severe acute respiratory syndrome coronavirus in 2019. Although the real-time reverse transcription PCR test for viral nucleic acids is the gold standard for COVID-19 diagnosis, computed tomography (CT) has grown in importance.

AIM

To evaluate the sensitivity and specificity of thoracic CT findings of COVID-19 pneumonia according to age groups.

METHODS

PCR and CT results from 411 patients were reviewed. The diagnosis of COVID-19 pneumonia was made by three radiologists. Lymphadenopathy, pericardial effusion, pleurisy, pleural thickening, pleural effusion, location features of the lesions, ground glass, consolidation, air bronchogram, vascular enlargement, bronchial dilatation, halo finding, inverted halo sign, nodularity, air bubble,

subpleural band (curvilinear density), reticular density, crazy paving pattern, and fibrosis findings were recorded. The patients were divided into nine groups by decades while calculating the sensitivity, specificity, and diagnostic efficacy for CT positivity.

RESULTS

The mean age of the cases was 48.1 ± 22.7 years. The CT finding with the highest diagnostic power was ground glass. Vascular enlargement and bronchial dilatation followed ground glass. Pericardial effusion was the finding with the lowest diagnostic accuracy. The incidence of lymphadenopathy, pleurisy, pleural thickening, peripheral localization, bilateral, ground glass, vascular enlargement, bronchial dilatation, subpleural band, reticular density, crazy paving appearance, and fibrosis all increased increase significantly with age in patients with positive real-time reverse transcription PCR test.

CONCLUSION

There are few publications comparing sensitivity and specificity of thoracic CT findings according to age. In cases of COVID-19 pneumonia, there is an increase in the variety and frequency of CT findings with age, and parallel to this the sensitivity and specificity of the findings increase. COVID-19 cases in the pediatric age group have fewer lung findings than adults, and this situation decreases the diagnostic value of CT in pediatric patients.

Key Words: Thoracic computerized tomography; SARS-CoV-2; COVID-19; Diagnosis; Pediatric age

Core Tip: Despite its high sensitivity for identifying coronavirus disease 2019 (COVID-19) pneumonia, the diagnostic potential of computed tomography findings has not been thoroughly investigated, particularly in relation to age subgroups. It is worth noting that the prevalence of COVID-19 pneumonia can vary by age. Even common results, such as ground glass opacities, can be reduced in younger individuals, particularly in the pediatric population. Additionally, the findings of this study may raise awareness about the proper use of computed tomography scans in children and contribute to radiation protection by limiting computed tomography scans in age groups with low sensitivity.

Citation: Karavas E, Unver E, Aydın S, Yalcin GS, Fatihoglu E, Kuyrukluyildiz U, Arslan YK, Yazici M. Effect of age on computed tomography findings: Specificity and sensitivity in coronavirus disease 2019 infection. *World J Virol* 2022; 11(5): 331-340

URL: https://www.wjgnet.com/2220-3249/full/v11/i5/331.htm

DOI: https://dx.doi.org/10.5501/wjv.v11.i5.331

INTRODUCTION

The World Health Organization has declared coronavirus disease 2019 (COVID-19) a pandemic caused by severe acute respiratory syndrome coronavirus 2[1,2]. Although fever and cough are the most common clinical symptoms, other symptoms such as fatigue, shortness of breath, and headache may also be present[3]. However, because all of these symptoms are not unique to the disease and because the disease can progress quickly to severe pneumonia, diagnostic tests are required.

Although the real-time reverse transcription (RT)-PCR test for viral nucleic acids is the gold standard in the diagnosis of COVID-19, computed tomography (CT) has become increasingly important in the diagnosis due to false negative results and the inability to obtain results quickly[4]. Because CT has a sensitivity of 97 %, it is frequently used, and algorithms are developed accordingly[5]. Even if the RT-PCR is negative, treatment and filiation are initiated in close contacts[6]. However, because CT contains ionizing radiation, there is a risk of unintentional use. The expected harms of ionizing radiation are greater in children than in adults. Seeing that, we aim to define the change of the CT findings as well as the sensitivity and the specificity of these findings according to age.

MATERIALS AND METHODS

Study design

The local (33216249-50.01.02-E.25467) medical ethics committee approved this study. The ethics committee waived informed consent as a result of the retrospective nature.

The study included 411 patients with suspected COVID-19 who applied to a tertiary healthcare center. The registration period began on March 15, 2020 and ended on May 15, 2020. All patients had laboratory RT-PCR testing of respiratory secretions obtained *via* nasopharyngeal or oropharyngeal swab. Clinical data from electronic medical records were reviewed.

All patients had a CT scan without intravenous contrast material on the day they were admitted to the hospital (Siemens SOMATOM Sensation 16, Forchheim, Germany). All patients were scanned in the supine position using an adult CT protocol; reconstruction images of the 1.5 mm lung window were obtained using tube voltage = 130kV, effective mAs = 70, slice thickness = 5 mm, collimation = 16 × 1.2, pitch = 0.8. In children, reconstruction images of the lung window of 1.5 mm were obtained with protocol tube voltage = 110kV, effective mAs = 60, slice thickness = 8 mm, collimation = 16 × 1.2, pitch = 0.8 (14 years and younger).

All CT images were reviewed by three thorax imaging experts who were not aware of the RT-PCR test results, and the final decision was reached by consensus. The North American Society of Radiology Expert Consensus Statement on Reporting of Lung CT Findings Related to COVID-19[7] (Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19) was followed in the evaluation for pneumonia caused by COVID-19. Typical and indeterminate appearance were considered positive for COVID-19 infection, whereas atypical appearance and negative for pneumonia were considered negative for infection. Lymphadenopathy, pericardial effusion, pleurisy, pleural thickening, pleural effusion, lesion location features (peripheral-central-diffuse, posterior, bilateral-unilateral, *etc*), ground glass, consolidation, air bronchogram, vascular enlargement, bronchial dilatation, halo sign, reverse halo sign, nodularity, air bubble, subpleural band (curvilinear density), reticular density, crazy paving pattern, and fibrosis findings were recorded.

The patients were divided into nine groups by decades when calculating the sensitivity, specificity, and significance for CT positivity. The ninth group was defined as people aged 80 and up. To avoid decreasing statistical power, the sensitivity, specificity, and significance of the CT findings were divided into three groups determined by the World Health Organization (age group 1: 0-18, age group 2: 18-60, age group 3: 60 and above).

Statistical analysis

IBM SPSS 22 was used for statistical analyses (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, United States: IBM Corp.). The Kolmogorov-Smirnov test was used to determine whether the data conformed to a normal distribution. Numerical variables with a normal distribution were represented as mean and standard deviation values, variables without a normal distribution as median (minimum-maximum) values, and categorical variables as number (*n*) and percentage values (percent) When calculating CT diagnostic accuracy measures, RT-PCR was used as the gold standard. CT sensitivity and specificity were reported along with their 95% confidence intervals. Exact Clopper-Pearson confidence intervals for sensitivity and specificity were calculated. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

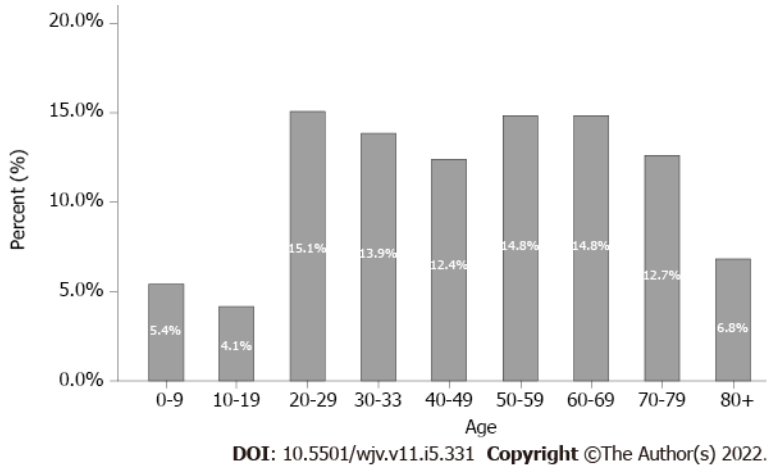
The average age of the 411 cases was 48.1 ± 22.7 years (median: 49, range: 0-99), with 241 (58.8%) males and 170 (41.4%) females. Figure 1 depicts the distribution of the number of patients by decade, while Figure 2 depicts the distribution by group. There were 181 positive RT-PCR results and 230 negative RT-PCR results out of 411 patients, for a positive rate of 41% (181/411). There was no statistically significant difference in age or gender between patients with positive and negative RT-PCR results ($P > 0.05$). There were 141 positive and 40 negative CT findings in 181 cases, for a positive rate of 77.9% (141/181). The overall and age-segregated sensitivity and specificity of CT were calculated and reported based on RT-PCR results. CT sensitivity was found to be 77.9% (95% confidence interval: 71.15 to 83.72) for all patients. However, when the sensitivity value was stratified based on age, it was discovered that it had changed. The findings revealed that the sensitivity of CT increased with age (Table 1, Figures 3 and 4).

Table 2 showed the diagnostic accuracy of the findings recorded in RT-PCR test negative and positive cases across the entire population. According to these findings, ground glass opacity had the highest diagnostic accuracy of 62.5 % (sensitivity 84.4%, specificity 33.7%), followed by vascular enlargement at 58.5% and bronchial dilatation at 58.3% (Figure 5A). With a diagnostic accuracy of 40.0%, pericardial effusion is the finding with the lowest diagnostic accuracy.

Table 1 Diagnostic accuracy measures of the computerized tomography according to age

Age		CT	RT-PCR		Sensitivity, % (95%CI)	Specificity, % (95%CI)
			COVID-19 negative	COVID-19 positive		
Age categories	0-9	Negative	3	8	11.11 (0.28-48.25)	23.08 (5.04-53.81)
		Positive	10	1		
	10-19	Negative	0	3	50.00 (11.81-88.19)	0.00 (0.00-28.49)
		Positive	11	3		
	20-29	Negative	10	9	60.87 (38.54-80.29)	25.64 (13.04-42.13)
		Positive	29	14		
	30-39	Negative	5	10	66.67 (47.19-82.71)	18.52 (6.30-38.08)
		Positive	22	20		
	40-49	Negative	9	2	91.30 (71.96-98.93)	32.14 (15.88-52.35)
		Positive	19	21		
	50-59	Negative	4	3	90.32 (74.25-97.96)	13.33 (3.76-30.72)
		Positive	26	28		
	60-69	Negative	3	2	92.59 (75.71-99.09)	8.82 (1.86-23.68)
		Positive	31	25		
	70-79	Negative	4	3	81.25 (54.35-95.95)	11.11 (3.11-26.06)
		Positive	32	13		
	80+	Negative	4	0	100.00 (79.41-100.0)	33.33 (9.92-65.11)
		Positive	8	16		
Overall		Negative	42	40	77.90 (71.15-83.72)	18.26 (13.49-23.87)
		Positive	188	141		

Diagnostic accuracy measures (sensitivity and specificity) were calculated for computed tomography when real-time reverse transcription PCR was gold standard. CT: Computed tomography; RT-PCR: Real-time reverse transcription PCR; COVID-19: Coronavirus disease 2019; CI: Confidence interval.



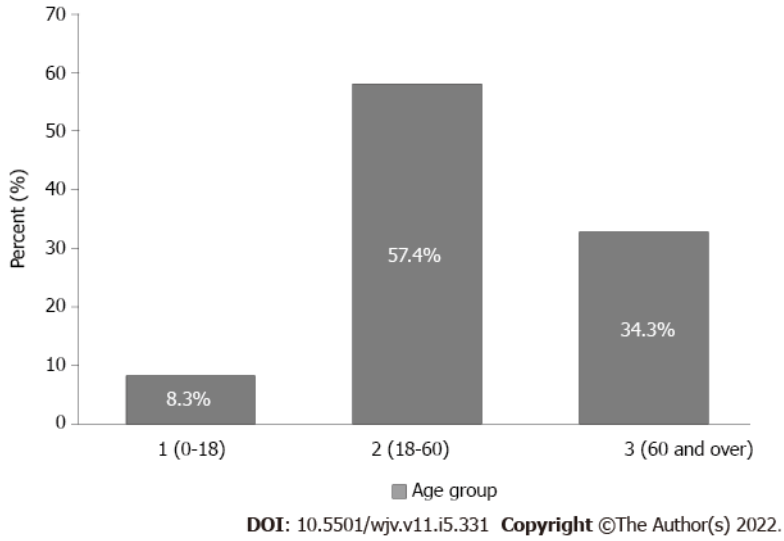
DOI: 10.5501/wjv.v11.i5.331

Figure 1 Age distribution.

Table 3 showed the frequency of findings in cases with positive RT-PCR tests based on age groups. Lymphadenopathy, pleurisy, pleural thickening, peripheral localization, bilateral, ground glass, vascular enlargement, bronchial dilatation, subpleural band, reticular density, crazy paving appearance, and fibrosis all increased with age ($P < 0.05$) (Figure 5B). Although there was a significant difference in consolidation, air bronchogram, and air bubble findings between age groups, it was not related to

Table 2 Diagnostic accuracy of findings across the entire population

Findings	Sensitivity, %	Specificity, %	Diagnostic accuracy, %
Lymphadenopathy	60.3	44.7	46.9
Pleurisy	78.3	45.6	48.0
Pericardial effusion	80.0	40.0	40.0
Pleural thickening	19.3	86.1	48.0
Peripheral location	46.5	53.6	49.6
Posterior location	65.1	22.0	48.5
Bilateral location	69.3	22.0	51.4
Ground glass	84.4	33.7	62.5
Consolidation	45.9	71.1	56.7
Air bronchogram	31.2	81.3	52.8
Vascular enlargement	53.2	65.7	58.5
Bronchial dilatation	50.5	68.7	58.3
Halo sign	28.9	75.3	48.9
Reverse halo sign	1.4	95.8	42.1
Nodularity	37.2	68.1	50.5
Air bubble	16.1	87.3	46.8
Subpleural band	27.1	70.5	45.8
Reticular density	11.9	88.6	45.0
Crazy paving appearance	11.0	97.6	48.4
Fibrosis	15.6	90.3	47.7



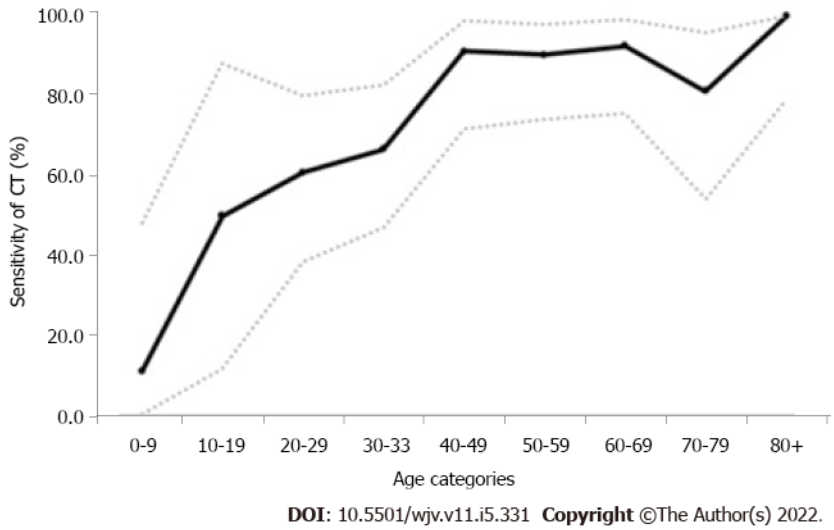
DOI: 10.5501/wjv.v11.i5.331

Figure 2 Age group distribution.

patient age (Figure 5C). There was no significant difference in the rates of bilateral involvement, posterior location, pericardial effusion, halo, reverse halo, and nodularity between the three groups (P > 0.05) (Figure 5D).

Table 3 Frequency of findings according to age groups

Findings	Age group 1, %	Age group 2, %	Age group 3, %	*P* value
Lymphadenopathy	0	8.1	29.8	0.001
Pleurisy	0	2.2	20.8	0.002
Pericardial effusion	0	0.5	3.1	0.092
Pleural thickening	3.0	12.7	27.5	0.005
Peripheral location	36.4	61.5	65.1	0.04
Posterior location	59.1	67.1	74.6	0.09
Bilateral location	50.0	62.1	88.5	0.07
Ground glass	51.5	69.1	94.7	0.007
Consolidation	39.4	29.5	52.7	0.02
Air bronchogram	36.4	18.2	35.1	0.001
Vascular enlargement	30.3	38.2	59.5	0.03
Bronchial dilatation	30.3	36.7	53.4	0.005
Halo sign	24.2	26.8	24.2	0.055
Reverse halo sign	0	2.3	3.8	0.06
Nodularity	36.4	34.1	35.9	0.067
Air bubble	0	0	0.8	0.04
Subpleural band	12.1	21.8	42.8	0.002
Reticular density	0	9.1	18.3	0.001
Crazy paving appearance	3.0	4.1	13.0	0.02
Fibrosis	0	2.7	33.8	0.001

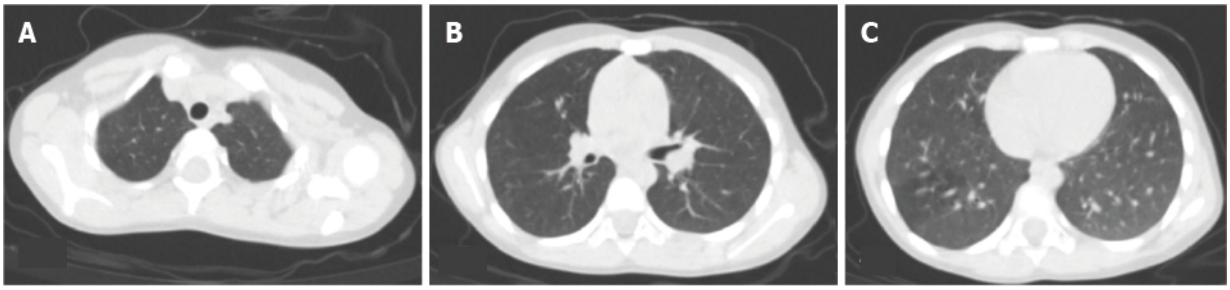


DOI: 10.5501/wjv.v11.i5.331

Figure 3 Sensitivity of computed tomography by age groups. Sensitivity values and their 95% confidence intervals were shown on the graph. CT: Computed tomography.

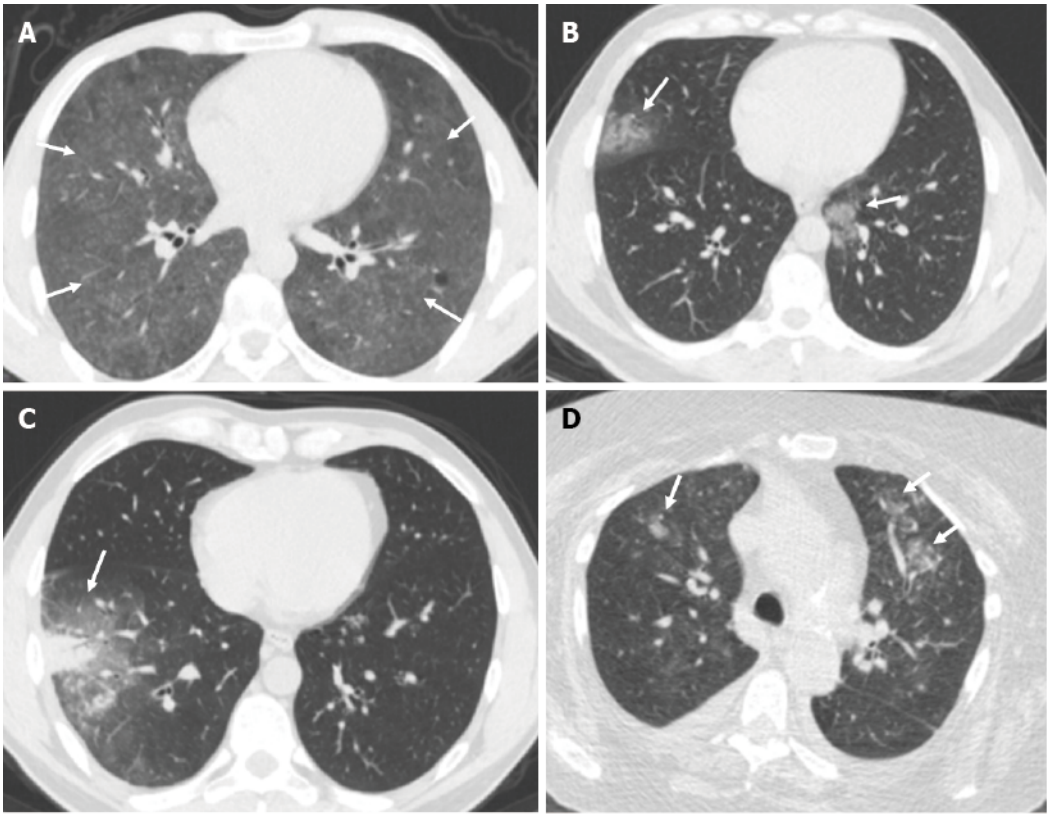
DISCUSSION

On March 11, 2020, the World Health Organization declared COVID-19 a global epidemic. The disease's high contagiousness necessitated the development of a rapid and highly sensitive test. In addition to the low sensitivity of the gold standard RT-PCR test, test results were provided within days or weeks due to a lack of testing centers, particularly in the 1st months of the pandemic. This circumstance has resulted in a more rapid and accessible test requirement. The impact of COVID-19 infection on the lower



DOI: 10.5501/wjv.v11.i5.331

Figure 4 A thoracic computed tomography scan in a 5-year-old female patient. There were no pathological findings in the sections that passed through the upper (A), middle (B), and lower (C) zones.



DOI: 10.5501/wjv.v11.i5.331

Figure 5 Thoracic computed tomography scans in patients. A: A 45-year-old male patient underwent a thoracic computed tomography (CT) scan. Sections passing through the middle zones showed diffuse ground-glass infiltration areas with preservation of subpleural areas in both lungs (arrows); B: A 44-year-old female patient underwent a thoracic CT scan. In the sections passing through the lower zones, infiltration areas of peripheral ground glass density with a mild halo were observed in the medial basal segment on the right and in the upper lobe inferior lingular segment on the left (arrows); C: A 35-year-old male patient underwent a thoracic CT scan. A subpleural consolidation area with air bronchogram and ground-glass density halo could be seen in the lateral basal segment of the right lung lower lobe in sections passing through the lower zones (arrow); D: A 77-year-old female patient underwent a thoracic CT scan. In the sections passing through the upper zones, centrilobular nodular infiltrating areas in the form of a budded tree pattern were observed in the anterior segments of the upper lobes of bilateral lungs, particularly on the left (arrows).

respiratory tract has brought thoracic CT examination to the forefront. Thoracic CT is useful for detecting viral lung infection, determining the nature and extent of pulmonary lesions, and monitoring disease activity[8-11]. In addition, the latest studies revealed that CT perfusion examinations can reveal perfusion deficits in COVID-19 pneumonia[12]. In these circumstances, in addition to the potential for rapid diagnosis of COVID-19 by thoracic CT, identification of pulmonary changes and base images of the cases to be followed may be an added benefit.

Multiple, peripheral, bilateral, irregular, subsegmental or segmental ground glass opacities, mostly bronchovascular bundles, and areas of consolidation scattered throughout the subpleural space are typical COVID-19 chest CT imaging features. The presence of associated intralobular septal thickening in areas of ground glass opacity, crazy paving appearance, consolidation, and air bronchograms with

areas of bronchial wall thickening and less frequently thickening of the adjacent or interlobar pleura as well as a small amount of pleural effusion are also COVID-19 chest CT imaging features[7,13,14]. When all cases were considered in our study, the findings of ground glass density, vascular enlargement, bronchial dilatation, consolidation, and bilaterality stood out for diagnostic accuracy.

In limited studies, pediatric patients with COVID-19 have relatively mild clinical symptoms, a higher prevalence of negative CT scans, and atypical, peribronchial distribution of lung opacities and bronchial wall thickening are more common[15,16]. The incidence of any finding other than an air bronchogram and nodular appearance is not higher in this age group than in other age groups. Posterior location, bilaterality, and ground glass density are the most common findings. Among these findings is that the prevalence of ground glass density is significantly lower in this age group than in other age groups. The sensitivity of CT diagnosis in the 0-9 age group was found to be quite low in our study.

For the diagnosis of COVID-19, various algorithms have been developed. Due to the large number of cases, doctors from fields other than chest diseases or infectious diseases had to play an active role in disease diagnosis in many hospitals. Due to a lack of experience in physical examination, doctors from various fields frequently rely on thoracic CT exam-ination, with the tendency to deviate from algorithms and make an easy and quick diagnosis. RT-PCR may be negative in the early stages of the disease and due to other variants as well as the inadequacy of the RT-PCR test contributes to the overuse of thoracic CT[17,18]. Routine thoracic CT screening for COVID-19 is not recommended, and confirmatory diagnosis is based on RT-PCR. When a low-dose CT scan is required, it is preferable for the pediatric population. Follow-up imaging is only necessary in cases of clinical deterioration and should be kept to a minimum.

The study's most significant limitation is the small number of cases in the 0-18 age range. The main reason for this is that clinical symptoms in this age group are unclear, and pediatricians in our hospital are actively treating patients with suspected COVID-19.

CONCLUSION

Despite its high sensitivity for identifying COVID-19 pneumonia, the diagnostic potential of CT findings has not been thoroughly investigated, particularly in relation to age subgroups. It is worth noting that the prevalence of COVID-19 pneumonia can vary by age. Even common results, such as ground glass opacities, can be reduced in younger individuals, particularly in the pediatric population. Additionally, the findings of this study may raise awareness about the proper use of CT scans in children and contribute to radiation protection by limiting CT scans in age groups with low sensitivity.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) is a pandemic caused by the severe acute respiratory syndrome coronavirus in 2019. Although the real-time reverse transcription (RT)-PCR test for viral nucleic acids is the gold standard for COVID-19 diagnosis, computed tomography (CT) has grown in importance.

Research motivation

There is a risk of unintentional use because CT contains ionizing radiation. Ionizing radiation is expected to cause more harm to children than to adults.

Research objectives

We aim to define the change of the CT findings as well as the sensitivity and the specificity of these findings according to age.

Research methods

The study included 411 patients with suspected COVID-19 who sought treatment at a tertiary healthcare facility. RT-PCR testing of respiratory secretions obtained *via* nasopharyngeal or oropharyngeal swab was performed on all patients. Clinical information from electronic medical records was examined. On the day they were admitted to the hospital, all patients had a CT scan without intravenous contrast material. Three thorax imaging experts who were not aware of the RT-PCR test results reviewed all CT images, and the final decision was reached by consensus. When calculating the sensitivity, specificity, and significance for CT positivity, the patients were divided into nine groups based on decades. The group was defined as people aged 80 and up for the ninth group. The sensitivity, specificity, and significance of CT findings into three groups (age group 1: 0-18, age group 2: 18-60, age group 3: 60 and above) was determined.

Research results

There were 181 positive RT-PCR results and 230 negative RT-PCR results out of 411 patients, for a positive rate of 41% (181/411). There were 141 positive and 40 negative CT findings in 181 cases, for a positive rate of 77.9 % (141/181). CT sensitivity was found to be 77.9 % (95% confidence interval: 71.15 to 83.72) for all patients. The findings revealed that the sensitivity of CT increased with age. Ground glass opacity had the highest diagnostic accuracy of 62.5 %, followed by vascular enlargement at 58.5% and bronchial dilatation at 58.3%. Lymphadenopathy, pleurisy, pleural thickening, peripheral localization, bilateral, ground glass, vascular enlargement, bronchial dilatation, subpleural band, reticular density, crazy paving appearance, and fibrosis all increased with age ($P < 0.05$).

Research conclusions

Due to the large number of cases, doctors from various fields frequently rely on thoracic CT examination, with the tendency to deviate from algorithms and make an easy and quick diagnosis. The inadequacy of the RT-PCR test contributes to the overuse of thoracic CT. The sensitivity of CT diagnosis in the 0-9 age group was found to be quite low in our study. When a low-dose CT scan is required, it is preferable for the pediatric population. Follow-up imaging is only necessary in cases of clinical deterioration and should be kept to a minimum.

Research perspectives

Further research should be conducted to determine the diagnostic potential of COVID-19 CT findings in relation to age subgroups. Additionally, the findings of this study may raise awareness about the proper use of CT scans in children and contribute to radiation protection by limiting CT scans in age groups with low sensitivity.

FOOTNOTES

Author contributions: Karavaş E and Ünver E were responsible for the conceptualization, methodology, and project administration; Karavaş E did the writing-review & editing; Karavaş E, Aydin S, Yalçin GS, Fatihoglu E, Kuyrukluyildiz U, and Yazici M were responsible for the investigation and resources; Aydin S wrote the original draft; Aydin S and Arslan Y performed the data curation and formal analysis.

Institutional review board statement: The study was reviewed and approved by the Erzincan Binali Yildirim University Institutional Review Board (Approval No: 22/06/2020-06/04).

Informed consent statement: The Institutional Ethical Review Board waived informed consent due to the retrospective nature of the study procedure.

Conflict-of-interest statement: The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Data sharing statement: No additional data are available.

Country/Territory of origin: Turkey

ORCID number: Erdal Karavas 0000-0001-6649-3256; Edhem Unver 0000-0002-0322-8102; Sonay Aydın 0000-0002-3812-6333; Gonul Seven Yalcin 0000-0002-7751-3774; Erdem Fatihoglu 0000-0003-4192-6638; Ufuk Kuyrukluyildiz 0000-0001-6820-0699; Yusuf Kemal Arslan 0000-0003-1308-8569; Mustafa Yazici 0000-0002-3808-1788.

S-Editor: Wu YXJ
L-Editor: Filipodia
P-Editor: Wu YXJ

REFERENCES

1 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients

with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
2 **WHO**. Coronavirus disease (COVID-19) pandemic. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
3 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
4 **Majidi H**, Niksolat F. Chest CT in patients suspected of COVID-19 infection: A reliable alternative for RT-PCR. *Am J Emerg Med* 2020; **38**: 2730-2732 [PMID: 32312575 DOI: 10.1016/j.ajem.2020.04.016]
5 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]
6 **Sağlık Bakanlığı TC**. Covid-19 Genel bilgiler, epidemiyoloji ve tanı. *Halk Sağlığı Genel Müdürlüğü* 2020; **19**: 1-32 Available from https://covid19.saglik.gov.tr/
7 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]
8 **Zhao W**, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol* 2020; **214**: 1072-1077 [PMID: 32125873 DOI: 10.2214/AJR.20.22976]
9 **Liu J**, Chen T, Yang H, Cai Y, Yu Q, Chen J, Chen Z, Shang QL, Ma C, Chen X, Xiao E. Clinical and radiological changes of hospitalised patients with COVID-19 pneumonia from disease onset to acute exacerbation: a multicentre paired cohort study. *Eur Radiol* 2020; **30**: 5702-5708 [PMID: 32385648 DOI: 10.1007/s00330-020-06916-4]
10 **Aydin S**, Kantarci M, Fatihoglu E, Yesilyurt H, Karavas E. COVID-19 CT Severity and Handedness: Is There a Relation? *Imaging Interv* 2021; **28**: 1-5 [DOI: 10.5152/iai.2021.21010]
11 **Aydin S**, Unver E, Karavas E, Yalcin S, Kantarci M. Computed tomography at every step: Long coronavirus disease. *Respir Investig* 2021; **59**: 622-627 [PMID: 34210624 DOI: 10.1016/j.resinv.2021.05.014]
12 **Aydin S**, Kantarci M, Karavas E, Unver E, Yalcin S, Aydin F. Lung perfusion changes in COVID-19 pneumonia: a dual energy computerized tomography study. *Br J Radiol* 2021; **94**: 20201380 [PMID: 34415201 DOI: 10.1259/bjr.20201380]
13 **Hani C**, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, Revel MP. COVID-19 pneumonia: A review of typical CT findings and differential diagnosis. *Diagn Interv Imaging* 2020; **101**: 263-268 [PMID: 32291197 DOI: 10.1016/j.diii.2020.03.014]
14 **Dennie C**, Hague C, Lim RS, Manos D, Memauri BF, Nguyen ET, Taylor J. Canadian Society of Thoracic Radiology/Canadian Association of Radiologists Consensus Statement Regarding Chest Imaging in Suspected and Confirmed COVID-19. *Can Assoc Radiol J* 2020; **71**: 470-481 [PMID: 32380844 DOI: 10.1177/0846537120924606]
15 **Chen A**, Huang JX, Liao Y, Liu Z, Chen D, Yang C, Yang RM, Wei X. Differences in Clinical and Imaging Presentation of Pediatric Patients with COVID-19 in Comparison with Adults. *Radiol Cardiothorac Imaging* 2020; **2**: e200117 [PMID: 33778567 DOI: 10.1148/ryct.2020200117]
16 **Duan YN**, Zhu YQ, Tang LL, Qin J. CT features of novel coronavirus pneumonia (COVID-19) in children. *Eur Radiol* 2020; **30**: 4427-4433 [PMID: 32291501 DOI: 10.1007/s00330-020-06860-3]
17 **Erturk SM**. CT of Coronavirus Disease (COVID-19) Pneumonia: A Reference Standard Is Needed. *AJR Am J Roentgenol* 2020; **215**: W20 [PMID: 32302207 DOI: 10.2214/AJR.20.23286]
18 **Bellini MI**, Fresilli D, Lauro A, Mennini G, Rossi M, Catalano C, D'Andrea V, Cantisani V. Liver Transplant Imaging prior to and during the COVID-19 Pandemic. *Biomed Res Int* 2022; **2022**: 7768383 [PMID: 35036437 DOI: 10.1155/2022/7768383]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 341-351

DOI: 10.5501/wjv.v11.i5.341

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Observational Study

Validity of the patient health questionnaires (phq-2 and phq-9) for screening depression among human immunodeficiency virus patients in Lahore, Pakistan

Khunsa Junaid, Iqra Akram, Muhammad Daood, Amjad Khan

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Diaz-Batanero C, Spain; Masaru T, Hungary

Received: March 20, 2022
Peer-review started: March 20, 2022
First decision: April 18, 2022
Revised: May 6, 2022
Accepted: August 26, 2022
Article in press: August 26, 2022
Published online: September 25, 2022

Khunsa Junaid, Muhammad Daood, Department of Community Medicine, King Edward Medical University, Lahore 54000, Punjab Province, Pakistan

Iqra Akram, Department of Pulmonology, General Hospital, Lahore 54000, Punjab Province, Pakistan

Amjad Khan, Department of Public Health and Nutrition, the University of Haripur, Haripur 22781, Khyber Pakhtunkhwa, Pakistan

Corresponding author: Khunsa Junaid, Post-graduate trainee, Department of Community Medicine, King Edward Medical University, Lahore 54000, Punjab Province, Pakistan.
khunsajunaidmir@gmail.com

Abstract

BACKGROUND

Many human immunodeficiency virus (HIV) infected patients suffer from depression, but a little focus is given to detecting and treating depression in primary health care. Detection of depression can be improved by introducing short, reliable, and valid screening instruments.

AIM

To determine the psychometric properties of the patient health questionnaire-2 (PHQ-2) and patient health questionnaire-9 (PHQ-9) for depression screening and diagnosis, and the sensitivity and specificity of the PHQ-2 in HIV infected patients.

METHODS

A cross-sectional study was conducted on 158 HIV-infected patients aged 18 years and above in Lahore, Pakistan. PHQ-2 was implemented to screen depression. PHQ-9 was implemented to diagnose major depressive disorder as a reference standard. Reliability, Validity tests and receiver operating characteristic curve were computed.

RESULTS

The Cronbach's alpha of PHQ-2 and PHQ-9 were 0.732 and 0.759, respectively. The study results showed that the score of 2 on PHQ-2 indicates the highest

Youden's index of 0.924, with both sensitivity and specificity of 0.96, and the area under the curve for PHQ-2 was 0.98 (95%CI: 0.953-0.998).

CONCLUSION
Good psychometric properties for the PHQ-2 and PHQ-9 indicated their significant potential as tools for depression screening and diagnosis in the HIV-infected population.

Key Words: Depression; Validity; Patient health questionnaire-9; Patient health questionnaire-2; HIV/AIDS; Lahore; Pakistan

Core Tip: Many human immunodeficiency virus patients suffer from depression, but a little focus is given to detecting and treating depression in primary healthcare settings. The study aims to assess the psychometric properties of the patient health questionnaire-2 (PHQ-2) and Patient health questionnaire-9 for depression screening and diagnosis and estimate the sensitivity and specificity of the PHQ-2 for depression screening in human immunodeficiency virus infected patients. The study results showed that the score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with both sensitivity and specificity of 0.96, and the area under the curve for PHQ-2 was 0.98.

Citation: Junaid K, Akram I, Daood M, Khan A. Validity of the patient health questionnaires (phq-2 and phq-9) for screening depression among human immunodeficiency virus patients in Lahore, Pakistan. *World J Virol* 2022; 11(5): 341-351
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/341.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.341

INTRODUCTION

People living with human immunodeficiency virus (HIV) infection (PLWHA) seem to be more vulnerable to psychiatric morbidity than the overall population[1,2], with major depressive disorder seems to be the most prevalent psychiatric diagnosis. Suicidal thinking, anxiety, post-traumatic stress disorder, and drug/alcohol use disorders are also frequently documented psychiatric morbidities in HIV patients[3,4]. Around 3.8 percent of the world's population suffers from depression, including 5.0 percent of adults and 5.7 percent of people over 60. Depression affects around 280 million people worldwide[5]. The global HIV/AIDS 2020 research estimated that 37.7 million people were infected with HIV infection. Sub-Saharan Africa was linked to about two-thirds of the world's HIV-positive individuals[6]. In Pakistan, an estimated 183705 people infected with HIV by 2020[7]. Even though the expected prevalence of HIV infection in Pakistan's general population is less than 0.1 percent in 2019, it remains a major public health issue[8].

Depression is a mental health condition defined by a depressed mood, low mood, difficulty concentrating, self-blame or poor self-worth, sleeping or eating difficulties, and impaired focus[9-11]. Depression is associated with several clinical and socio-demographic factors in HIV patients. Some clinical factors, such as AIDS-related stigma, compromised immune status (low CD4 counts), and opportunistic infections[12,13] could be distinctive to HIV patients; however, socio-demographic factors such as gender, low levels of education, and unemployment were linked to depression including both HIV positive and negative populations[14]. Untreated depression causes rapid HIV infection advancement and increases deaths[15]. Inflammatory pathway indicators, such as monocytes and pro-inflammatory cytokines, are recognized as contributing to the higher prevalence of depression in HIV-positive individuals[16]. When a person has HIV infection, their body releases more of the pro-inflammatory cytokines interleukin-6 and tumour necrosis factor. These cytokines promote the spread of viruses and the depletion of CD4 cells[17].

Antidepressants were the most frequently recommended drugs, followed by anxiolytics, antipsychotics and psycho-stimulants[18]. Non-invasive brain stimulation (NIBS) techniques such as repeated trans-cranial magnetic stimulation and trans-cranial direct current stimulation are increasingly being used to improve cognitive function and reduce depressive symptoms in a variety of settings[19]. Given that severe depression is typically associated with cognitive impairments, the NIBS method may be beneficial in enhancing cognition in depressed people[20]. More than half of the patients with a serious depressive illness did not use antidepressants. Effective depression treatment may be crucial for increasing HIV medication adherence and clinical outcomes, possibly in combination with adherence supports[21].

Despite successful pharmacological and psychological treatments, a high proportion of individuals suffering from depression in HIV-infected patients is frequently undiagnosed clinically and is frequently untreated in primary health care settings[22,23]. Several screening questionnaires have been developed as instruments to assist in the timely identification of depression and clinical judgment[24-28]. To generate accurate clinical results, the validity and reliability of the depression screening tools should be good. Screening tools should be easy and quick for successful practical application[29-31]. The Patient Health Questionnaire [patient health questionnaire-2 (PHQ-2) and patient health questionnaire-9 (PHQ-9)] were designed especially as depression screening and diagnostic tools for primary care settings to promote the delivery of evidence-based psychiatric care intervention strategies in regions where specially trained mental health providers are scant[32-34].

A cross-culturally applicable form of PHQ-9 and PHQ-2 is available, but its psychometric properties are still to be validated formally. In many studies, the accuracy of PHQ-9 has been tested by applying it to many chronic disease populations[35-40]. However, the PHQ-9 and PHQ-2 have not yet been validated in HIV patients in Pakistan. Therefore, the present study aimed to measure the (1) psychometric properties of the PHQ-9 and PHQ-2 for the diagnosis of depression; and (2) to estimate PHQ-2 screening accuracy by using PHQ-9 as the reference standard in patients of HIV infection in Lahore, Pakistan.

MATERIALS AND METHODS

Study setting

The study was carried out in the HIV clinic of Jinnah hospital Lahore, Pakistan, from January 2019 to March 2019. HIV clinic in Jinnah hospital Lahore works from Monday to Saturday and serves around 20 to 30 patients per day. The population of Lahore is 11126285, and it is one of the most populated cities in Punjab Province[41]. The current study comprises finding active cases of depression by the use of PHQ-2 for screening, followed by the use of PHQ-9 to detect depression. Patients with a PHQ-9 score of nine or higher were referred to a psychiatrist to confirm the diagnosis of depression.

Study design

An analytical cross-sectional study design was executed to assess the validity and reliability of the Patient Health Questionnaire among HIV patients.

Participants

One hundred and fifty-eight study participants were recruited from the HIV clinic of Jinnah hospital, Lahore, through a non-probability convenience sampling technique. All participants were agreed to participate in the study. Eligibility criteria for study subjects included age more than 18 years, capability to correspond, understand Urdu language, patients must have a diagnosis of HIV based on positive test on an ELISA for HIV anti-bodies, were attending the HIV clinic for medical care, and were available for a 20 min interview. Participants who had other medical disorders unrelated to HIV, such as renal failure, chronic hepatitis, and malignancy determined on history and clinical examination, were excluded.

Measures

PHQ-9: It is a nine-component criterion-based diagnostic instrument for the evaluation of depression that identifies the presence and frequency of nine major symptoms of depression in the participant (as recommended by DSM-IV) for two weeks. PHQ-9 is applied frequently in the western world and in sub-Saharan Africa[35,40]. Scoring varies from 0 to 27, and the patient who scores ten or more on PHQ-9 is said to be suffering from depression and should be treated for it to avoid severe consequences. Studies provide evidence that PHQ-9 is designed for self-administration, but it gives the same outcomes when the researcher takes interviews based on this questionnaire[42].

PHQ-2: It comprises the first two PHQ-9 questions and evaluates the frequency of past two week's spells of despair, boredom, and happiness. Questions are valued from 0-3 (4-point scale), where zero represents the complete absence of symptoms and three shows symptoms of depression on each day of the last two weeks with a total score ranging from zero to six[43]. A cutoff value of 3 or more indicates the presence of depression and is associated with a high level of sensitivity and specificity for screening depression[40]. It is easy to use and can be easily applied by healthcare staff of over-burdened health facilities.

Data collection and study procedures: Prior to the start of data collection, study participants were informed about the study's objective, and verbal informed consent was obtained. The researcher did a face-to-face interview with the PHQ-2 depression screening questionnaire after receiving informed consent. To obtain socio-demographic information, the clinic file of the patient was examined. Due to the study population's poor literacy level, the survey was administered by the interviewer, and

responses were written down. After the screening interview, participants answered the PHQ-9 questionnaire with a second research staff member who was blind to the PHQ-2 results. The interview was conducted by local health care practitioners who had been trained in the use of the PHQ-9 questionnaire. The PHQ-9 was given in the same language as the screening interview, with the help of an interpreter if needed. A good sample size of 200 was chosen due to the restricted availability of staff who can diagnose depression. 158 (79%) of the study participants completed the interview. PHQ-2 items were used to calculate total depression screening scores, and the PHQ-9 items were used to calculate total depression diagnosis scores. Patients with a PHQ-9 score of 9 or above are referred to a psychiatrist to confirm the diagnosis of depression.

Ethical considerations: Ethical approval was obtained from the research ethical review board of the Jinnah hospital Lahore, Pakistan. Before the data collection, informed verbal consent was obtained from each study participant.

HI

Statistical analysis

IBM SPSS version 24 software (Chicago, IL, United States) and the statistical software MedCalc were used to analyze the data. To describe the sociodemographic characteristics of the study participants, descriptive statistics were used. The mean (standard deviation [SD]) was employed to represent continuous data, and the two-sample *t*-test was applied to compare groups. Where applicable, categorical data were evaluated using Pearson's χ^2 test. The overall Cronbach's alpha coefficient was used to assess the internal consistency of PHQ-2 and PHQ-9. Cronbach's alpha was also calculated with each item removed. The criterion validity of PHQ-2 was determined using receiver operating characteristic (ROC) analysis. Using the PHQ-9 as the reference standard, we employed MedCalc 14.8 to evaluate the sensitivity, specificity, and positive and negative predictive values of the PHQ-2 as a screening tool. Statistical significance was evaluated for all tests using a *P* value of 0.05. The area under the curve (AUC) determines the performance of a test, and an AUC of 0.5 indicates a non-discriminating test. In contrast, the value of AUC of 1.0 specifies perfect diagnostic accuracy. In sensitivity analyses, cutoffs scores balancing sensitivity and specificity were found out utilizing the point of convergence between sensitivity and specificity and Youden's index, which was calculated by (sensitivity + specificity– 1)[44,45].

RESULTS

Participant characteristics

In total, 158 study participants were completed the PHQ-2 and PHQ-9. The background characteristics of the study participants are mentioned in Table 1. According to the study results, study participants ranged from 18 to 54 years with a mean age of 30.42 ± 7.11 years (± SD). One hundred and thirty-five study participants (85.4%) were male, while twenty-three (14.5%) were female. The total score of PHQ-9 ranged from 0 to 22, with the mean PHQ-9 score being 9.92 (SD = 4.648). By the present study result, PHQ-9 scores were higher in depressed individuals (mean = 12.81) compared to those without depression (mean = 8.41). In most socio-demographic characteristics, no statistically significant differences were found as evaluated by chi-square and *t*-test for gender, education, residence, and religion by depression. However, age, marital status, and monthly family income of HIV patients showed a statistically significant difference with the depression ($P < 0.05$).

Reliability and item analysis of PHQ-2 and PHQ-9

The reliability coefficient, Cronbach's alpha for PHQ-9 total score was 0.759, indicating a strong internal consistency. The bivariate correlation between nine items of the PHQ-9 was shown in Table 2, with coefficient ranging from 0.559 to 0.301, and all correlations were statistically significant (all 2-tailed *P* values < 0.01). Thoughts that harming yourself or dying would be better and moving and feeling bad about yourself or that you are a failure were the two most frequently endorsed items. On the contrary, Feeling down, depressed, or hopeless was the item least frequently endorsed by HIV patients (Table 2). The PHQ-2 had a Cronbach's alpha of 0.732, indicating that the items of the PHQ-2 were consistent. The corrected inter-total correlation was 0.574 and 0.574, respectively.

Sensitivity and specificity for PHQ-2

Table 3 showed the sensitivity, specificity, predictive values, and Youden's index at different cutoff scores of the PHQ-2 for depression screening. The study results showed that the score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with a sensitivity and specificity of 0.96. The area under

Table 1 Socio demographic characteristics of human immunodeficiency virus positive patients (*n* = 158)

Variables	Non-depression, *n* (%)	Depression, *n* (%)	*P* value
	104 (65.8)	54 (34.1)	
Age (yr)			
mean ± SD	30.42 ± 7.11	43.91 ± 5.133	**0.001**[a]
Gender			
Male	89 (56.3)	46 (29.1)	0.947
Female	15 (9.5)	8 (5.1)	
Education			
No education	62 (39.2)	27 (17.1)	0.377
Up to primary school	11 (7.0)	6 (3.8)	
Up to secondary school	23 (14.6)	14 (8.9)	
Up to college	4 (2.5)	6 (3.8)	
Up to University	4 (2.5)	1 (0.6)	
Marital status			
Married	51 (32.3)	42 (26.6)	**0.001**[a]
Unmarried	47 (29.7)	4 (2.5)	
Separated	1 (0.6)	5 (3.2)	
Divorced	4 (2.5)	2 (1.3)	
Widowed	1 (0.6)	0 (0.6)	
Monthly family income			
Less than 20000 Rs	66 (41.8)	17 (10.8)	**0.001**[a]
Between Rs. 20000-30000	29 (18.4)	25 (15.8)	
More than Rs. 30000	9 (5.7)	12 (7.6)	
Residential status			
Rural	36 (22.8)	25 (15.8)	0.153
Urban	68 (43.0)	29 (18.4)	
Religion			
Muslim	101 (63.9)	50 (31.6)	0.190
Non-Muslim	3 (1.9)	4 (2.5)	

[a]*P* value < 0.05.

the curve for PHQ-2 was 0.98 (95%CI: 0.953-0.998) (Figure 1), which indicates excellent criterion validity of PHQ-2 in distinguishing between HIV/AIDS patients with and without major depression with a PHQ-9 diagnosis of depression. The optimum cutoff for detecting depression was found to be a PHQ-2 score of 2, according to study (Table 3).

Comparison of internal consistency between PHQ-9 and PHQ-2

According to the present study results, Cronbach's alpha was similar but quite greater for PHQ-9 than in PHQ-2. In ROC curve analysis, The AUC (0.98) was in PHQ-2. The score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with a sensitivity and specificity of 0.96. When the score of 2 for PHQ2 was assumed, 35.5% of study subjects were diagnosed with probable depression.

Table 2 Item analysis of patient health questionnaire-9

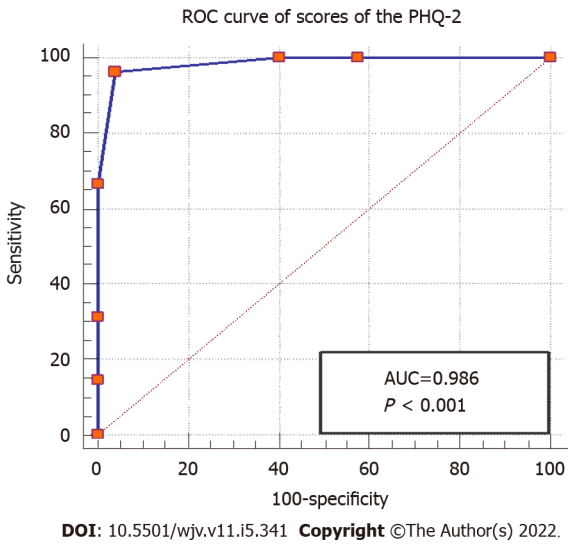
PHQ-9	Mean	SD	Item-total correlation	α if item deleted
Little interest or pleasure in doing things	1.06	1.005	0.432	0.738
Feeling down, depressed, or hopeless	1.01	1.003	0.301	0.761
Trouble falling or staying asleep, or sleeping too much	1.06	0.975	0.422	0.739
Feeling tired or having little energy	1.27	0.803	0.414	0.740
Poor appetite or overeating	1.15	0.797	0.460	0.733
Feeling bad about yourself — or that you are a failure or have let yourself or your family down	1.07	0.775	0.518	0.726
Trouble concentrating on things, such as reading a newspaper or watching television	1.13	0.799	0.381	0.745
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	1.11	0.834	0.496	0.728
Thoughts that you would be better off dead or of hurting yourself in some way	1.06	0.926	0.559	0.716

PHQ-9: Patient health questionnaire-9.

Table 3 Sensitivity, specificity, predictive values, at various cut-off scores of the patient health questionnaire-2

PHQ-2 score	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Youden's index
≥ 1	100.00 (93.4-100.0)	59.62 (49.5-69.1)	21.6 (17.9-25.8)	100.0 (93.4-100.)	**59.62**
≥ 2	96.30 (87.3-99.5)	96.15 (90.4-98.9)	73.6 (51.5-87.9)	99.6 (98.4-99.9)	**92.45**
≥ 3	66.67 (52.5-78.9)	100.(96.5-100.0)	100.0 (96.5-100.0)	96.4(94.9-97.5)	**66.67**
≥ 4	31.48 (96.5-100.0)	100.0 (96.5-100.0)	100.0 (96.5-100.0)	92.9 (91.6-94.0)	**31.48**
≥ 5	14.81 (6.6-27.1)	100.0 (96.5-100.0)	100.0 (96.5-100.0)	91.4 (90.4-92.2)	**14.81**

PHQ-2: Patient health questionnaire-2; PPV: Positive predictive value; NPV: Negative predictive value.



DOI: 10.5501/wjv.v11.i5.341

Figure 1 Receiver operating characteristic curve of Patient Health Questionnaire-2 for depression screening. AUC: Area under the curve.

DISCUSSION

Key findings

The current study concludes that PHQ-9 and PHQ-2 are useful tools for detecting depression in people

affected by HIV living in Lahore, Pakistan. Cronbach's alpha was similar but quite greater for PHQ-9 than in PHQ-2. In ROC curve analysis, The AUC (0.98) was in PHQ-2. The score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with a sensitivity and specificity of 0.96.

Validity and reliability of PHQ-2 and PHQ-9

Based on analysis of indicators like Youden's index, sensitivity, specificity, and AUC, a cutoff score of 2 for PHQ-2 was suggested. Anyhow there are a small number of studies assessing the cutoff of depression based on its severity categories[45,46]. However, there is highly recommended to determine the cutoff scores of depression based on severity categories amid different populations[47,48]. According to the best of our knowledge, this is the first-ever study on validation and calibration of PHQ-2in the Lahore, Pakistan. Patel *et al*[15] suggested that the best cutoff score was designed by considering the best balance between sensitivity and PPV and is required for its suitability to person-based location and use. Such an instrument is especially significant for routine application in developing regions where healthcare staff is over-burdened.

The current research showed a cutoff score of 2 while using PHQ-2, sensitivity and specificity were 0.96, but this result was different from already done studies[49-51]. A score of 2 is suggested to suspect a patient is suffering from depression in patients of HIV infection when using the PHQ-2 questionnaire based on current and previous studies. The sensitivity value of our study for PHQ-2 is found to be lower than previous studies when a cutoff value of 3 or more is employed along with a documented reference standard. This result can be clarified because we used a sample of patients enrolled consecutively or by chance. One limitation is the design of the study, which is cross-sectional. For acquiring the required sensitivity, we need longitudinal studies. Enrollment of recently diagnosed HIV patients in our study can make the study prone to bias by increasing the estimation of detection of depression with precision[52].

The internal consistency or alpha coefficient for PHQ-9 was 0.759. The value of Cronbach's alpha must be at least 0.70 or higher for a self-administered questionnaire to be reliable[53,54]. The value of the alpha coefficient of PHQ-9 for our study was lesser than previous studies, where its value was 0.79-0.89, respectively[55,56]. As far as Cronbach's alpha of PHQ-2 is concerned, it is found to be 0.73, which is remarkably good. This value is also in line with the studies done in various populations[49,57].

Prevalence of depression

PHQ-2 outcomes showed the frequency of depression to be 35%. This value is higher when compared with previous studies which also used PHQ-2[48]. This high prevalence of depression in our study participants is consistent across various measures in the results of both instruments, and this concludes that the prevalence of depression in HIV patients in Pakistan can be remarkably higher than the previous estimate. Hence validation with a reliable diagnostic instrument is required to detect the real prevalence of depression[58]. As already discussed in different studies, it is suggested that the first two questions of PHQ-9 may not be able to detect symptoms of depression experienced by HIV patients accurately. It reveals that a remarkable number of HIV patients could not be detected without employing a full PHQ-9 instrument. So it is recommended that PHQ-2 be used for the initial evaluation of patients, but we cannot reach a true conclusion without applying PHQ-9[58].

Strengths and limitations of the study

It was the first-ever research done to evaluate the diagnostic accuracy of PHQ-2 for screening major and minor depression in HIV patients by using PHQ-9 as a reference standard. We used a standard instrument that is smaller than other analytical instruments to recognize patients with depression, and it is crucial in primary healthcare settings. PHQ-9 has remarkable properties for the detection of depression and has good capability for assessing the severity of depression.

Especially for evaluation of severity, the PHQ-9 and PHQ-2 offers locally adapted thresholds and follows suggestions to adjust the tool to the background and location when it is intended for application. Because of its shortness, simplicity, and ease of application and interpretation, the use of this instrument is continuously increasing in epidemiological research.

There are a few limitations or constraints in our research. The data were obtained from only one clinic, and hence results cannot be generalized to the population. Because of some reasons, we could not perform test-retest reliability in participants. The study used the cross-sectional design the study, and because of this, we could not establish causation between variables used in our research. Another drawback of this study was that information on participants' mental and physical disabilities was not gathered.

Second, we evaluated the PHQ-2's sensitivity and specificity as a depression screening tool using the PHQ-9 as the reference standard. Therefore, a study utilizing a different diagnostic tool than the PHQ-9 is recommended if the sensitivity or specificity of the PHQ-9 is insufficient as it may bias our estimates of the sensitivity and specificity of the PHQ-2. We propose modifying the PHQ-9 to the local context and literacy level of the population because several participants misunderstood a number of the PHQ-9 items.

CONCLUSION

HIV patients are more likely than the general population to develop depression. The PHQ-2 and PHQ-9 showed good psychometric properties, implying that they could be useful as depression screening tools. Due to the substantial health and social burden of depression and need for relatively short, organized, reliable, and valid tools to help healthcare professionals evaluate patients for depression, the PHQ-2 and PHQ-9 would be useful and valuable tools for screening and diagnosing depression in HIV-infected individuals. Moreover, to lessen the global prevalence of psychiatric disorders and improve patient well-being, the instruments can be used in combination with increased access to adequate mental healthcare and therapeutical and non-pharmacological treatments, which are effective in these settings.

ARTICLE HIGHLIGHTS

Research background

People living with human immunodeficiency virus (HIV) infection (PLWHA) seem to be more vulnerable to psychiatric morbidity than the overall population, with major depressive disorder seems to be the most prevalent psychiatric diagnosis. Suicidal thinking, anxiety, post-traumatic stress disorder, and drug/alcohol use disorders are also frequently documented psychiatric morbidities in HIV patients

Research motivation

Many HIV-infected patients suffer from depression, but a little focus is given to detecting and treating depression in primary health care. Detection of depression can be improved by introducing short, reliable, and valid screening instruments.

Research objectives

The current study assessed the psychometric properties of the patient health questionnaire-2 (PHQ-2) and patient health questionnaire-9 (PHQ-9) for depression screening and diagnosis and estimated the sensitivity and specificity of the PHQ-2 for depression screening in HIV-infected patients.

Research methods

A cross-sectional study was conducted on 158 HIV-infected patients aged 18 years and above in Lahore, Pakistan. PHQ-2 was implemented to screen depression. PHQ-9 was implemented to diagnose major depressive disorder as a reference standard. Reliability, Validity tests and receiver operating characteristic curve were computed.

Research conclusions

Due to the substantial health and social liability of depression and need for brief, organized, reliable, and valid tools that can help medical practitioners better assess patients for depression, the PHQ-2 and PHQ-9 would indeed be useful and beneficial instruments for screening and diagnosing depression in HIV-infected persons. Moreover, to lessen the global prevalence of psychiatric disorders and improve patient well-being, the instruments can be used in combination with increased access to adequate mental healthcare and therapeutical and non-pharmacological treatments, which are effective in these settings

Research results

The Cronbach's alpha of PHQ-2 and PHQ-9 were 0.732 and 0.759, respectively. The study results showed that the score of 2 on PHQ-2 indicates the highest Youden's index of 0.924, with both sensitivity and specificity of 0.96, and the area under the curve for PHQ-2 was 0.98 (95%CI: 0.953-0.998).

Research perspectives

HIV patients are more likely than the general population to develop depression. The PHQ-2 and PHQ-9 demonstrated good psychometric properties, implying that they might be helpful as depression screening tools.

ACKNOWLEDGEMENTS

The authors would like to thank all the participants for their cooperation.

FOOTNOTES

Author contributions: All authors contributed to the concept of this study; Junaid K, Akram I conceived the study; Daood M carried out the literature searches; Junaid K distributed the questionnaires and extracted the data; Daood M assessed the study quality; Junaid K and Khan A performed the statistical analysis; Junaid K and Daood M wrote the manuscript; Khan A revised the manuscript; all the authors read the published version of the manuscript and gave their consent.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Jinnah hospital Lahore, Pakistan.

Informed consent statement: Informed consent was obtained from all patients for being included in the study.

Conflict-of-interest statement: All the authors have no conflicts of interest.

Data sharing statement: Participants gave informed consent for data sharing and the presented data are anonymized and the risk of identification is low.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Pakistan

ORCID number: Khunsa Junaid 0000-0002-9959-1407; Iqra Akram 0000-0003-1989-3083; Muhammad Daood 0000-0002-8280-2263; Amjad Khan 0000-0002-9668-0324.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Nanni MG**, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. *Curr Psychiatry Rep* 2015; **17**: 530 [PMID: 25413636 DOI: 10.1007/s11920-014-0530-4]
2 **Remien RH**, Stirratt MJ, Nguyen N, Robbins RN, Pala AN, Mellins CA. Mental health and HIV/AIDS: the need for an integrated response. *AIDS* 2019; **33**: 1411-1420 [PMID: 30950883 DOI: 10.1097/QAD.0000000000002227]
3 **Parcesepe AM**, Bernard C, Agler R, Ross J, Yotebieng M, Bass J, Kwobah E, Adedimeji A, Goulet J, Althoff KN. Mental health and HIV: research priorities related to the implementation and scale up of 'treat all' in sub-Saharan Africa. *J Virus Erad* 2018; **4**: 16-25 [PMID: 30515310]
4 **Wittchen HU**, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**: 655-679 [PMID: 21896369 DOI: 10.1016/j.euroneuro.2011.07.018]
5 **World Health Organization**. Depression: a global public health concern. [Cited 6 June 2021]. Available from: Available from: http:// www.who.int/mental_health/management/depression/en/
6 **Joint United Nations Programme on HIV/AIDS**. AIDS by the numbers. [Cited 26 April 2022]. Available from: Available from: https://www.unaids.org/en
7 **Joint United Nations Programme on HIV/AIDS**. "We must ensure that HIV treatment adherence is not compromised"—keeping people in Pakistan on HIV treatment. [Cited 26 April 2022]. Available from: https://www.unaids.org/en/keywords/pakistan
8 **Ahmed A**, Hashmi FK, Khan GM. HIV outbreaks in Pakistan. *Lancet HIV* 2019; **6**: e418 [PMID: 31204244 DOI: 10.1016/S2352-3018(19)30179-1]
9 **Rotenstein LS**, Ramos MA, Torre M, Segal JB, Peluso MJ, Guille C, Sen S, Mata DA. Prevalence of Depression, Depressive Symptoms, and Suicidal Ideation Among Medical Students: A Systematic Review and Meta-Analysis. *JAMA* 2016; **316**: 2214-2236 [PMID: 27923088 DOI: 10.1001/jama.2016.17324]
10 **Demyttenaere K**, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, de Girolamo G, Morosini P, Polidori G, Kikkawa T, Kawakami N, Ono Y, Takeshima T, Uda H, Karam EG, Fayyad JA, Karam AN, Mneimneh ZN, Medina-Mora ME, Borges G, Lara C, de Graaf R, Ormel J, Gureje O, Shen Y, Huang Y, Zhang M, Alonso J, Haro JM, Vilagut G, Bromet EJ, Gluzman S, Webb C, Kessler RC, Merikangas KR, Anthony JC, Von Korff MR, Wang PS, Brugha TS, Aguilar-Gaxiola S, Lee S, Heeringa S, Pennell BE, Zaslavsky AM, Ustun TB, Chatterji S; WHO World

Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA* 2004; **291**: 2581-2590 [PMID: 15173149 DOI: 10.1001/jama.291.21.2581]

11 **Kohn R**, Levav I, de Almeida JM, Vicente B, Andrade L, Caraveo-Anduaga JJ, Saxena S, Saraceno B. [Mental disorders in Latin America and the Caribbean: a public health priority]. *Rev Panam Salud Publica* 2005; **18**: 229-240 [PMID: 16354419 DOI: 10.1590/s1020-49892005000900002]

12 **Antelman G**, Kaaya S, Wei R, Mbwambo J, Msamanga GI, Fawzi WW, Fawzi MC. Depressive symptoms increase risk of HIV disease progression and mortality among women in Tanzania. *J Acquir Immune Defic Syndr* 2007; **44**: 470-477 [PMID: 17179766 DOI: 10.1097/QAI.0b013e31802f1318]

13 **Liu H**, Zhao M, Ren J, Qi X, Sun H, Qu L, Yan C, Zheng T, Wu Q, Cui Y. Identifying factors associated with depression among men living with HIV/AIDS and undergoing antiretroviral therapy: a cross-sectional study in Heilongjiang, China. *Health Qual Life Outcomes* 2018; **16**: 190 [PMID: 30231885 DOI: 10.1186/s12955-018-1020-x]

14 **Rosengren A**, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S; INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**: 953-962 [PMID: 15364186 DOI: 10.1016/S0140-6736(04)17019-0]

15 **Patel V**, Araya R, Bolton P. Treating depression in the developing world. *Trop Med Int Health* 2004; **9**: 539-541 [PMID: 15117296 DOI: 10.1111/j.1365-3156.2004.01243.x]

16 **Norcini Pala A**, Steca P, Bagrodia R, Helpman L, Colangeli V, Viale P, Wainberg ML. Subtypes of depressive symptoms and inflammatory biomarkers: An exploratory study on a sample of HIV-positive patients. *Brain Behav Immun* 2016; **56**: 105-113 [PMID: 26883521 DOI: 10.1016/j.bbi.2016.02.013]

17 **Musinguzi K**, Obuku A, Nakasujja N, Birabwa H, Nakku J, Levin J, Kinyanda E. Association between major depressive disorder and pro-inflammatory cytokines and acute phase proteins among HIV-1 positive patients in Uganda. *BMC Immunol* 2018; **19**: 1 [PMID: 29298663 DOI: 10.1186/s12865-017-0239-3]

18 **Gokhale RH**, Weiser J, Sullivan PS, Luo Q, Shu F, Bradley H. Depression Prevalence, Antidepressant Treatment Status, and Association with Sustained HIV Viral Suppression Among Adults Living with HIV in Care in the United States, 2009-2014. *AIDS Behav* 2019; **23**: 3452-3459 [PMID: 31367965 DOI: 10.1007/s10461-019-02613-6]

19 **Begemann MJ**, Brand BA, Ćurčić-Blake B, Aleman A, Sommer IE. Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. *Psychol Med* 2020; **50**: 2465-2486 [PMID: 33070785 DOI: 10.1017/S0033291720003670]

20 **Liu S**, Sheng J, Li B, Zhang X. Recent Advances in Non-invasive Brain Stimulation for Major Depressive Disorder. *Front Hum Neurosci* 2017; **11**: 526 [PMID: 29163106 DOI: 10.3389/fnhum.2017.00526]

21 **Ormel J**, Petukhova M, Chatterji S, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, Bromet EJ, Burger H, Demyttenaere K, de Girolamo G, Haro JM, Hwang I, Karam E, Kawakami N, Lépine JP, Medina-Mora ME, Posada-Villa J, Sampson N, Scott K, Ustün TB, Von Korff M, Williams DR, Zhang M, Kessler RC. Disability and treatment of specific mental and physical disorders across the world. *Br J Psychiatry* 2008; **192**: 368-375 [PMID: 18450663 DOI: 10.1192/bjp.bp.107.039107]

22 **Mogga S**, Prince M, Alem A, Kebede D, Stewart R, Glozier N, Hotopf M. Outcome of major depression in Ethiopia: population-based study. *Br J Psychiatry* 2006; **189**: 241-246 [PMID: 16946359 DOI: 10.1192/bjp.bp.105.013417]

23 **Gureje O**, Kola L, Afolabi E. Epidemiology of major depressive disorder in elderly Nigerians in the Ibadan Study of Ageing: a community-based survey. *Lancet* 2007; **370**: 957-964 [PMID: 17869636 DOI: 10.1016/S0140-6736(07)61446-9]

24 **Hughes J**, Jelsma J, Maclean E, Darder M, Tinise X. The health-related quality of life of people living with HIV/AIDS. *Disabil Rehabil* 2004; **26**: 371-376 [PMID: 15204489 DOI: 10.1080/09638280410001662932]

25 **Smit J**, Myer L, Middelkoop K, Seedat S, Wood R, Bekker LG, Stein DJ. Mental health and sexual risk behaviours in a South African township: a community-based cross-sectional study. *Public Health* 2006; **120**: 534-542 [PMID: 16684549 DOI: 10.1016/j.puhe.2006.01.009]

26 **Mokkink LB**, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, Bouter LM, de Vet HC. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-745 [PMID: 20494804 DOI: 10.1016/j.jclinepi.2010.02.006]

27 **Gilbody S**, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J Gen Intern Med* 2007; **22**: 1596-1602 [PMID: 17874169 DOI: 10.1007/s11606-007-0333-y]

28 **Kroenke K**, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606-613 [PMID: 11556941 DOI: 10.1046/j.1525-1497.2001.016009606.x]

29 **Pence BW**, Gaynes BN, Atashili J, O'Donnell JK, Tayong G, Kats D, Whetten R, Whetten K, Njamnshi AK, Ndumbe PM. Validity of an interviewer-administered patient health questionnaire-9 to screen for depression in HIV-infected patients in Cameroon. *J Affect Disord* 2012; **143**: 208-213 [PMID: 22840467 DOI: 10.1016/j.jad.2012.05.056]

30 **Kroenke K**, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007; **146**: 317-325 [PMID: 17339617 DOI: 10.7326/0003-4819-146-5-200703060-00004]

31 **Manea L**, Gilbody S, McMillan D. A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *Gen Hosp Psychiatry* 2015; **37**: 67-75 [PMID: 25439733 DOI: 10.1016/j.genhosppsych.2014.09.009]

32 **Kiely KM**, Butterworth P. Validation of four measures of mental health against depression and generalized anxiety in a community based sample. *Psychiatry Res* 2015; **225**: 291-298 [PMID: 25578983 DOI: 10.1016/j.psychres.2014.12.023]

33 **Zimmerman M**, Martinez JH, Friedman M, Boerescu DA, Attiullah N, Toba C. Speaking a more consistent language when discussing severe depression: a calibration study of 3 self-report measures of depressive symptoms. *J Clin Psychiatry* 2014; **75**: 141-146 [PMID: 24345406 DOI: 10.4088/JCP.13m08458]

34 **Arroll B**, Goodyear-Smith F, Crengle S, Gunn J, Kerse N, Fishman T, Falloon K, Hatcher S. Validation of PHQ-2 and

PHQ-9 to screen for major depression in the primary care population. *Ann Fam Med* 2010; **8**: 348-353 [PMID: 20644190 DOI: 10.1370/afm.1139]

35 **Wang W**, Bian Q, Zhao Y, Li X, Wang W, Du J, Zhang G, Zhou Q, Zhao M. Reliability and validity of the Chinese version of the Patient Health Questionnaire (PHQ-9) in the general population. *Gen Hosp Psychiatry* 2014; **36**: 539-544 [PMID: 25023953 DOI: 10.1016/j.genhosppsych.2014.05.021]

36 **Fann JR**, Bombardier CH, Dikmen S, Esselman P, Warms CA, Pelzer E, Rau H, Temkin N. Validity of the Patient Health Questionnaire-9 in assessing depression following traumatic brain injury. *J Head Trauma Rehabil* 2005; **20**: 501-511 [PMID: 16304487 DOI: 10.1097/00001199-200511000-00003]

37 **Bombardier CH**, Richards JS, Krause JS, Tulsky D, Tate DG. Symptoms of major depression in people with spinal cord injury: implications for screening. *Arch Phys Med Rehabil* 2004; **85**: 1749-1756 [PMID: 15520969 DOI: 10.1016/j.apmr.2004.07.348]

38 **Williams LS**, Brizendine EJ, Plue L, Bakas T, Tu W, Hendrie H, Kroenke K. Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke* 2005; **36**: 635-638 [PMID: 15677576 DOI: 10.1161/01.STR.0000155688.18207.33]

39 **Akena D**, Joska J, Obuku EA, Stein DJ. Sensitivity and specificity of clinician administered screening instruments in detecting depression among HIV-positive individuals in Uganda. *AIDS Care* 2013; **25**: 1245-1252 [PMID: 23398282 DOI: 10.1080/09540121.2013.764385]

40 **Pakistan Bureau of statistics**. Population Census. [Cited 10 September 2021]. Available from: http://www.pbs.gov.pk/content/population-census

41 **Pinto-Meza A**, Serrano-Blanco A, Peñarrubia MT, Blanco E, Haro JM. Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? *J Gen Intern Med* 2005; **20**: 738-742 [PMID: 16050884 DOI: 10.1111/j.1525-1497.2005.0144.x]

42 **Kroenke K**, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry* 2010; **32**: 345-359 [PMID: 20633738 DOI: 10.1016/j.genhosppsych.2010.03.006]

43 **Haddad M**, Walters P, Phillips R, Tsakok J, Williams P, Mann A, Tylee A. Detecting depression in patients with coronary heart disease: a diagnostic evaluation of the PHQ-9 and HADS-D in primary care, findings from the UPBEAT-UK study. *PLoS One* 2013; **8**: e78493 [PMID: 24130903 DOI: 10.1371/journal.pone.0078493]

44 **Urtasun M**, Daray FM, Teti GL, Coppolillo F, Herlax G, Saba G, Rubinstein A, Araya R, Irazola V. Validation and calibration of the patient health questionnaire (PHQ-9) in Argentina. *BMC Psychiatry* 2019; **19**: 291 [PMID: 31533674 DOI: 10.1186/s12888-019-2262-9]

45 **Dadfar M**, Kalibatseva Z, Lester D. Reliability and validity of the Farsi version of the Patient Health Questionnaire-9 (PHQ-9) with Iranian psychiatric outpatients. *Trends Psychiatry Psychother* 2018; **40**: 144-151 [PMID: 29995159 DOI: 10.1590/2237-6089-2017-0116]

46 **Kendrick T**, Dowrick C, McBride A, Howe A, Clarke P, Maisey S, Moore M, Smith PW. Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data. *BMJ* 2009; **338**: b750 [PMID: 19299475 DOI: 10.1136/bmj.b750]

47 **Nolan CP**, O'Donnell PJM, Desderius BM, Mzombwe M, McNairy ML, Peck RN, Kingery JR. Depression screening in HIV-positive Tanzanian adults: comparing the PHQ-2, PHQ-9 and WHO-5 questionnaires. *Glob Ment Health (Camb)* 2018; **5**: e38 [PMID: 30637111 DOI: 10.1017/gmh.2018.31]

48 **Yu X**, Stewart SM, Wong PT, Lam TH. Screening for depression with the Patient Health Questionnaire-2 (PHQ-2) among the general population in Hong Kong. *J Affect Disord* 2011; **134**: 444-447 [PMID: 21665288 DOI: 10.1016/j.jad.2011.05.007]

49 **Yeung A**, Fung F, Yu SC, Vorono S, Ly M, Wu S, Fava M. Validation of the Patient Health Questionnaire-9 for depression screening among Chinese Americans. *Compr Psychiatry* 2008; **49**: 211-217 [PMID: 18243896 DOI: 10.1016/j.comppsych.2006.06.002]

50 **Suzuki K**, Kumei S, Ohhira M, Nozu T, Okumura T. Screening for major depressive disorder with the Patient Health Questionnaire (PHQ-9 and PHQ-2) in an outpatient clinic staffed by primary care physicians in Japan: a case control study. *PLoS One* 2015; **10**: e0119147 [PMID: 25789476 DOI: 10.1371/journal.pone.0119147]

51 **Rice DB**, Thombs BD. Risk of Bias from Inclusion of Currently Diagnosed or Treated Patients in Studies of Depression Screening Tool Accuracy: A Cross-Sectional Analysis of Recently Published Primary Studies and Meta-Analyses. *PLoS One* 2016; **11**: e0150067 [PMID: 26919313 DOI: 10.1371/journal.pone.0150067]

52 **Streiner DL**, Norman GR. Scaling responses. Health Measurement Scales: a practical guide to their development and use. 2nd ed. Oxford: Oxford University Press; 1995

53 **Huang FY**, Chung H, Kroenke K, Delucchi KL, Spitzer RL. Using the Patient Health Questionnaire-9 to measure depression among racially and ethnically diverse primary care patients. *J Gen Intern Med* 2006; **21**: 547-552 [PMID: 16808734 DOI: 10.1111/j.1525-1497.2006.00409.x]

54 **Lee PW**, Schulberg HC, Raue PJ, Kroenke K. Concordance between the PHQ-9 and the HSCL-20 in depressed primary care patients. *J Affect Disord* 2007; **99**: 139-145 [PMID: 17049999 DOI: 10.1016/j.jad.2006.09.002]

55 **Williams KG**, Sanderson M, Jette N, Patten SB. Validity of the Patient Health Questionnaire-9 in neurologic populations. *Neurol Clin Pract* 2020; **10**: 190-198 [PMID: 32642320 DOI: 10.1212/CPJ.0000000000000748]

56 **Monahan PO**, Shacham E, Reece M, Kroenke K, Ong'or WO, Omollo O, Yebei VN, Ojwang C. Validity/reliability of PHQ-9 and PHQ-2 depression scales among adults living with HIV/AIDS in western Kenya. *J Gen Intern Med* 2009; **24**: 189-197 [PMID: 19031037 DOI: 10.1007/s11606-008-0846-z]

57 **Cholera R**, Gaynes BN, Pence BW, Bassett J, Qangule N, Macphail C, Bernhardt S, Pettifor A, Miller WC. Validity of the Patient Health Questionnaire-9 to screen for depression in a high-HIV burden primary healthcare clinic in Johannesburg, South Africa. *J Affect Disord* 2014; **167**: 160-166 [PMID: 24972364 DOI: 10.1016/j.jad.2014.06.003]

58 **Chibanda D**, Verhey R, Gibson LJ, Munetsi E, Machando D, Rusakaniko S, Munjoma R, Araya R, Weiss HA, Abas M. Validation of screening tools for depression and anxiety disorders in a primary care population with high HIV prevalence in Zimbabwe. *J Affect Disord* 2016; **198**: 50-55 [PMID: 27011359 DOI: 10.1016/j.jad.2016.03.006]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 352-361

DOI: 10.5501/wjv.v11.i5.352

ISSN 2220-3249 (online)

SYSTEMATIC REVIEWS

Mortality rate of COVID-19 infection in end stage kidney disease patients on maintenance hemodialysis: A systematic review and meta-analysis

Ivan Cancarevic, Mahmoud Nassar, Ahmed Daoud, Hatem Ali, Nso Nso, Angelica Sanchez, Avish Parikh, Asma Ul Hosna, Bhavana Devanabanda, Nazakat Ahmed, Karim M Soliman

Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Badri M, Iran; Wang MK, China
A-Editor: Yao QG, China

Received: February 1, 2022
Peer-review started: February 1, 2022
First decision: April 8, 2022
Revised: May 20, 2022
Accepted: July 25, 2022
Article in press: July 25, 2022
Published online: September 25, 2022

Ivan Cancarevic, Mahmoud Nassar, Nso Nso, Avish Parikh, Asma Ul Hosna, Bhavana Devanabanda, Nazakat Ahmed, Department of Medicine, Icahn School of Medicine at Mount Sinai (NYC Health and Hospitals: Queens), New York, NY 11432, United States

Ahmed Daoud, Department of Medicine, Kasr Alainy Medical School, Cairo University, Cairo 11562, Egypt

Hatem Ali, Department of Medicine, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, United Kingdom

Angelica Sanchez, Department of Medicine, Universidad Autonoma de Santo Domnigo, Santo Domingo 10105, Dominican Republic

Karim M Soliman, Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, United States

Corresponding author: Karim M Soliman, MD, MSc, Associate Professor, Department of Medicine, Medical University of South Carolina, 97 Jonathan Lucas St., Charleston, SC 29425, United States. drkarimsoliman@gmail.com

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has been the most talked-about disease of the past few years. Patients with significant comorbidities have been at particular risk of adverse outcomes. This study looked at the outcomes and risk factors for adverse outcomes among patients on chronic hemodialysis for end-stage renal disease, a group of patients known to be particularly susceptible to infectious complications.

AIM

To assess outcomes and risk factors for adverse outcomes of COVID-19 infection among patients on chronic hemodialysis.

METHODS

We searched PubMed/MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Web of Science databases for relevant

terms and imported the results into the Covidence platform. From there, studies were assessed in two stages for relevance and quality, and data from studies that satisfied all the requirements were extracted into a spreadsheet. The data was then analyzed descriptively and statistically.

RESULTS

Of the 920 studies identified through the initial database search, only 17 were included in the final analysis. The studies included in the analysis were mostly carried out during the first wave. We found that COVID-19 incidence among patients on hemodialysis was significant, over 10% in some studies. Those who developed COVID-19 infection were most likely going to be hospitalized, and over 1 in 5 died from the infection. Intensive care unit admission rate was lower than the infection lethality rate. Biochemical abnormalities and dyspnea were generally reported to be associated with adverse outcomes.

CONCLUSION

This systematic review confirms that patients on chronic hemodialysis are very high-risk individuals for COVID-19 infections, and a significant proportion was infected during the first wave. Their prognosis is overall much worse than in the general population, and every effort needs to be made to decrease their exposure.

Key Words: COVID-19; End stage kidney disease; Mortality; Maintenance hemodialysis; Infection; Systematic review

Core tip: This is a systematic review to find out the mortality of coronavirus disease 2019 (COVID-19) infection in end stage kidney disease patients that are on regular maintenance hemodialysis. We found that COVID-19 incidence among patients on hemodialysis was significant, over 10% in some studies. Those who developed COVID-19 infection were most likely going to be hospitalized, and over 1 in 5 died from the infection. Intensive care unit admission rate was lower than the infection lethality rate. Biochemical abnormalities and dyspnea were generally reported to be associated with adverse outcomes.

Citation: Cancarevic I, Nassar M, Daoud A, Ali H, Nso N, Sanchez A, Parikh A, Ul Hosna A, Devanabanda B, Ahmed N, Soliman KM. Mortality rate of COVID-19 infection in end stage kidney disease patients on maintenance hemodialysis: A systematic review and meta-analysis. *World J Virol* 2022; 11(5): 352-361
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/352.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.352

INTRODUCTION

Since early 2020, the coronavirus disease 2019 (COVID-19) pandemic has caused hundreds of thousands of deaths in the United States and millions worldwide, alongside unprecedented disruptions in everyday life. Elderly and patients with significant comorbidities are known to be more susceptible to severe forms of both viral and bacterial respiratory infections, and the same has been shown to be true with COVID-19[1-3]. Chronic kidney disease (CKD) is one of the most prevalent chronic conditions in the United States[4]. The high prevalence of diseases that frequently lead to CKD, such as cardiac disease, hypertension, and diabetes, likely means that the prevalence of CKD will remain high in years to come.

Patients with end-stage renal disease (ESRD) requiring hemodialysis are likely to be especially susceptible to infections. Infection-related complications in those patients exceed 40 in 100 patients per year[5]. Patients with ESRD often undergo in-center hemodialysis, making it more difficult to physically separate for infection control purposes. Also, frequent visits to healthcare facilities for routine check-ups may contribute to infection spread. Additionally, this group's comorbidities make them immunodeficient, increasing their risk of infection[6].

Furthermore, evidence suggests a high frequency of acute kidney injury (AKI) development among patients hospitalized with COVID-19, which is associated with significant mortality[7,8]. AKI is also a known risk factor for CKD development and progression[9].

All these factors make it plausible that COVID-19 would be an especially severe disease in patients with end-stage renal disease on hemodialysis. Due to the high prevalence of ESRD requiring HD and the number of COVID-19 infections worldwide, determining the actual impact COVID-19 has on this

population could enable clinicians to target the factors associated with increased mortality and, subsequently, improve the care they provide are delivering.

This systematic review will attempt to determine the prognosis of end-stage renal disease patients on hemodialysis who test positive for COVID-19 and any clinical or laboratory findings associated with adverse outcomes.

MATERIALS AND METHODS

Data sources and literature search

The databases used for our systematic review were PubMed/MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Web of Science, up to date as of April 10, 2022. The review aims to follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy for the PubMed database was: ("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "COVID-19" OR "COVID19" OR "novel coronavirus" OR "coronavirus 2019" OR "COVID" OR "SARS-CoV-2") AND ("Kidney Failure, Chronic"[Mesh] OR "CKD" OR "chronic kidney disease" OR "end-stage renal disease" OR "ESRD" OR " end stage kidney disease (ESKD) " OR "end-stage kidney disease" OR "end-stage renal disease" OR "end-stage kidney disease") AND ("Renal Dialysis"[Mesh] OR "renal dialysis" OR "hemodialysis" OR "dialysis") AND ("Prognosis"[Mesh] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "prognosis" OR "lethality" OR "mortality" OR "survival"). The search strategy for Web of Science and Embase was: ("COVID-19" OR "COVID 19" OR "novel coronavirus" OR "coronavirus 2019" OR "COVID" OR "SARS-CoV-2") AND ("CKD" OR "chronic kidney disease" OR "end-stage renal disease" OR "ESRD" OR "ESKD" OR "end-stage kidney disease" OR "end-stage renal disease" OR "end-stage kidney disease") AND ("renal dialysis" OR "hemodialysis" OR "dialysis") AND ("prognosis" OR "lethality" OR "mortality" OR "survival").

Articles were then imported into the Covidence platform, which automatically removed duplicates. Two reviewers then independently screened titles and abstracts for relevance. Conflicts were resolved through direct communication between the two reviewers. Where consensus could not be reached, the third reviewer made the decision.

Afterward, full texts were obtained and screened for relevance. Those that were deemed relevant were assessed for quality using the National Institute of Health scoring systems according to the type of study in question, and only those studies that scored no less than three points below the maximum were included in the final review.

Eligibility criteria

We included prospective and retrospective observational studies as well as clinical trials if they involved at least 100 adult patients with end-stage renal disease on chronic hemodialysis who developed COVID-19 infection. We excluded case reports, case series, all review articles, conference abstracts, letters, communications, and editorials. We also excluded studies that were written in languages other than English and those that could not be retrieved. Equally, we excluded studies that pertained to pediatric patients and those that involved patients on peritoneal dialysis.

Data extraction and quality assessment

A spreadsheet was created and used as a data extraction tool. The following data were extracted for all the studies: authors, title, quality assessment score, number of patients who were studied, the incidence of COVID-19 among patients on hemodialysis, number of patients who required intensive care unit (ICU) level of care, number of deaths, as well as any findings that were found to be associated with increased risk of death or severe disease.

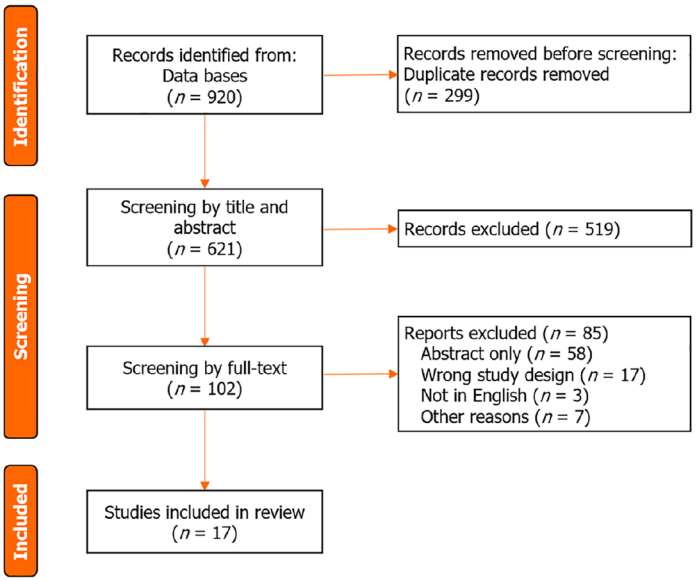
Statistical analysis

Data were entered into the spreadsheet and analyzed descriptively. Afterward, statistical analysis was done using SPSS software, and the results were presented in the form of a forest plot.

RESULTS

We found 920 articles through databases search. The 299 duplicate articles were automatically removed by the Covidence platform. The authors screened the titles and abstracts of 621 articles for relevance. The 519 articles were excluded at that stage. A total of 102 full texts were assessed for quality and relevance, and 85 of them were excluded. A total of 17 articles were included in our analysis, comprising a total of 37280 patients (Figure 1).

The number of ICU admissions was reported in 9 studies. The pooled analysis showed incidence of ICU admission of 17.4% (95%CI: 0.114-0.235) with high heterogeneity (I^2 = 95.59%, P < 0.001) (Figure 2A).



DOI: 10.5501/wjv.v11.i5.352

Figure 1 PRISMA image.

The number of hospital admissions was reported in 5 studies. The incidence of hospitalization after COVID-19 infection among patients included in those studies is 64.4% (95%CI: 0.521-0.767) with high heterogeneity (I^2 = 97.18%, P < 0.001) (Figure 2B).

All 17 studies reported mortality. The pooled estimate showed the incidence of mortality to be 23.3% (95%CI: 0.205-0.261) with significant heterogenicity I^2 = 88.52%, P < 0.001) (Figure 2C).

DISCUSSION

COVID -19 incidence

Not all the studies that were included in this review analyzed both the incidence and prognosis of COVID-19 patients on chronic hemodialysis. The incidence of COVID-19 is very difficult to analyze, considering that different studies looked at very different patient populations and different periods. However, several studies looked at the incidence in 2020, before vaccines were available. Lugon *et al*[10] reported that 741 out of 9877 Brazilian patients developed COVID-19 in 2020. Savino *et al*[11] reported the incidence of 4408 out of 22415 in England, Wales, and Northern Ireland; however, their study included the month of January 2021, when the United Kingdom was averaging tens of thousands of cases per day, the highest recorded up to that point in time[11,12]. De Meester *et al*[13] and Keller *et al*[14] reported a lower incidence, but their study period ended in May 2020, only including the infections that occurred during the first wave. Marino *et al*[15], however, reported a relatively low incidence of only 256 out of 4942 with their study period extending to November 2020 but still not taking into account the spike in winter 2020/2021, unlike Savino *et al*[11]. Ozturk *et al*[16] reported the incidence of 148 out of 746 until 05/11/2020 only in a single center in London, which is notably higher than in other studies covering the same study period.

The reported incidence of COVID-19 in patients on chronic hemodialysis is higher than in the general population, where the overall incidence in the first wave was relatively low despite the havoc it caused [12,17]. Cases started rising significantly in the winter of 2020/2021, but only Savino *et al*[11] covered the majority of that wave[12,17]. It needs to be said, however, that part of the explanation for the low incidence of COVID-19 during the first wave can be explained by the scarcity of testing for the general public, while patients on chronic hemodialysis would likely have been among the first ones to get tested, skewing the incidence numbers. It is also true that patients on chronic hemodialysis clearly have been in a very precarious and vulnerable position early in the pandemic. They were required to spend significant amounts of time in health care facilities when both tests and personal protective equipment were not widely available. Overall, while it is likely that the results were skewed by a difference in the availability of tests between hemodialysis patients and the general public, it is still likely that the incidence of COVID-19 infections among them was higher.

COVID-19 prognosis

There are multiple ways to look at the COVID-19 prognosis. In terms of the risk of hospitalization, it is significant among patients with end-stage renal disease. However, it is important to note that hospital-

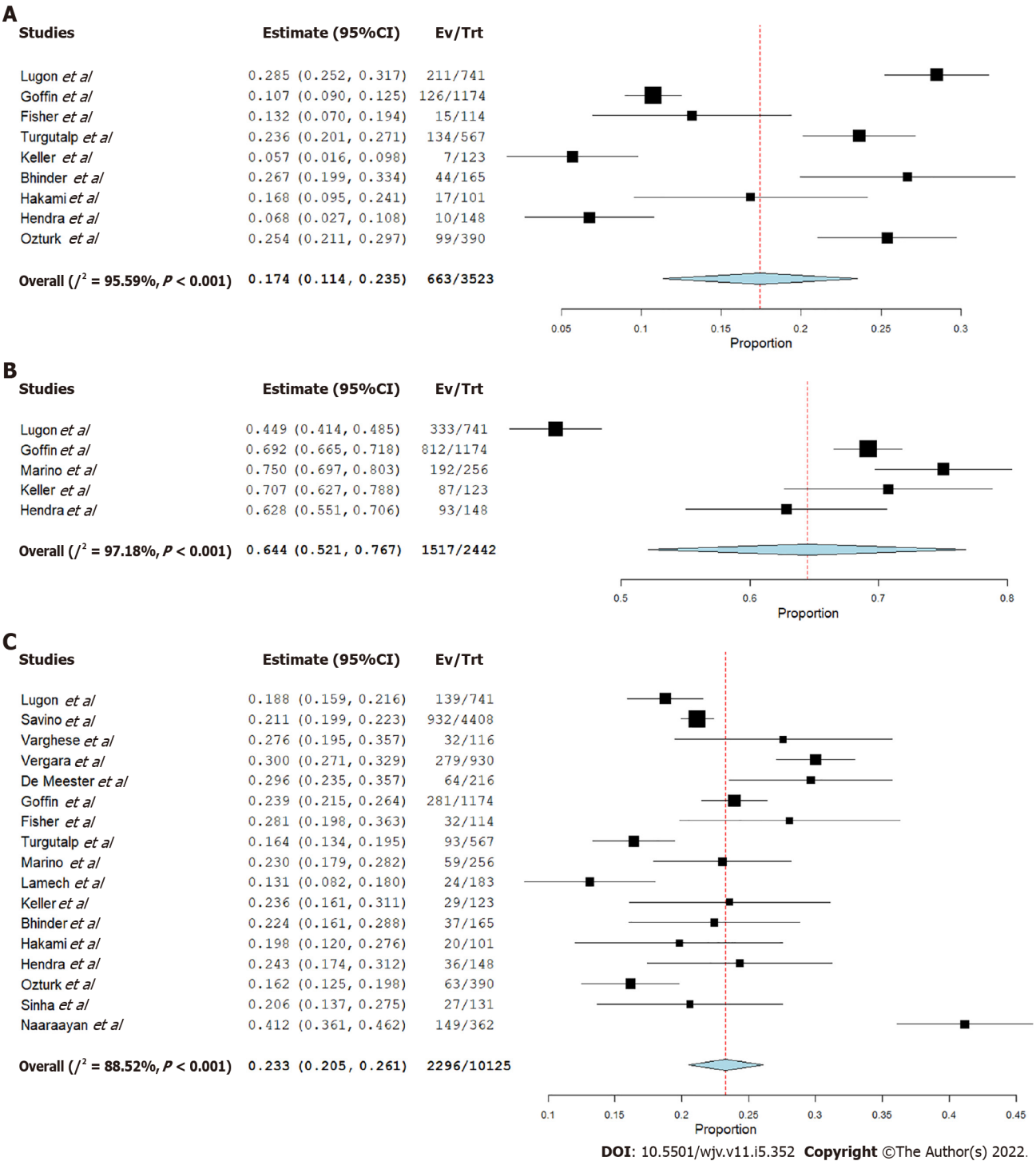


Figure 2 Forest plot. A: Incidence of intensive care unit admission; B: Incidence of hospital admission; C: Incidence of death.

ization criteria vary between institutions, and if, for example, desaturation is required to admit a patient without significant comorbidities, a far lower threshold may be employed for patients with ESRD. Furthermore, some of the studies only looked at hospitalized patients, possibly skewing numbers. In addition, most of the studies were done early in the course of the pandemic when the criteria were less clear, and there was a significant scarcity of ICU beds. That probably explains why in some of the studies, the incidence of death was higher than the incidence of ICU admission. While determining the exact COVID-19 Lethality is difficult due to the unknown number of cases that are undetected, what is undoubtedly true is that prognosis of COVID-19 infection is significantly worse in ESRD patients compared to the general public. In the studies involved in this systematic review, almost two-thirds of all the patients infected by COVID-19 were hospitalized, with 17.4% (95%CI: 0.114-0.235) $P < 0.001$ requiring ICU admission and 23.3% (95%CI: 0.205-0.261) $P < 0.001$ ultimately succumbing to the infection. There are no major outliers in terms of mortality, but it should be noted that studies such as Ozturk *et al*[16], Fisher *et al*[18], Turgutalp *et al*[19], Bhinder *et al*[20], Hakami *et al*[21], Sinha *et al*[22],

and Naaraayan *et al*[23] only reported cases that led to hospitalization so the mortality rates in those articles may be less representative unless a way to adjust them for hospitalization rate was found. A possibly relevant study to point to is Lamech *et al* which reported that close to one-third of all patients who tested positive for COVID-19 required mechanical ventilation[24]. HD itself may be an independent risk factor for mortality because, despite the required immunosuppressive treatment, Goffin *et al*[25] found mortality significantly lower among kidney transplant recipients than patients with HD. At the same time, De Meester *et al*[13] found that overall mortality among HD patients did not increase compared to pre-pandemic levels. That finding is surprising given that both Lugon *et al*[10] and Savino *et al*[11] found that a very significant proportion of HD patients developed COVID-19, and almost all the studies showed that those who do get infected are at significant risk of mortality. That would ordinarily raise the question about a possible selection bias in De Meester *et al*[13]; however, the study included the entire hemodialysis population of a region in Belgium, so barring a significant environmental confounder in that particular region, the study should be generalizable.

Risk factors for mortality

We looked at a number of risk factors that may be associated with mortality among hemodialysis patients who got infected by COVID-19. A number of prior studies suggest that diabetes worsens the prognosis of COVID-19[26]. Lugon *et al*[10] found a statistically significant association between diabetes and COVID-19 mortality among HD patients with an HR of 1.52 (1.05–2.19) $P = 0.026$. Hakami *et al*[21], Sinha *et al*[22], and Varghese *et al*[27] similarly found diabetes to be associated with COVID-19 mortality. Savino *et al*[11], Fisher *et al*[18], Turgutalp *et al*[19], Marino *et al*[15], Lamech *et al*[24], and Hendra *et al*[28] found no statistically significant difference in mortality among those with diabetes. While it can be assumed that this can be explained by sample sizes alone, that is not the case since the Savino *et al*[11] study included 4408 patients. Overall, those findings are difficult to interpret. Diabetes is a common cause of end-stage renal disease that also seems to worsen COVID-19 outcomes in the general population; however, it needs to be noted that all ESRD patients have significant comorbidity at baseline, and it remains unclear whether diabetes is uniquely associated with COVID-19 mortality compared to other conditions which also lead to ESRD.

Several studies looked at the association between common laboratory values and COVID-19 mortality. White blood cell (WBC) count and C-reactive peptide (CRP) were commonly reported as they normally correlate with the severity of infections. Varghese *et al*[27] and Hendra *et al*[28] found both to be associated with mortality, with CRP difference between those who died and those who survived being reported as 78.82 ± 89.16 *vs* 40.49 ± 43.16 ($P = 0.002$) by Varghese *et al*[27] and 128.0 (75.0-261.8) *vs* 40.5 (23.0-108.8) $P < 0.0001$ by Hendra *et al*[28] and WBC count difference 14.14 ± 8.88 *vs* 6.03 ± 2.37 ($P = 0.001$) reported by Varghese *et al*[27] and 7.45 (5.6-9.8) *vs* 5.40 (4-7) $P = 0.0007$ by Hendra *et al*[28]. In the study done by Keller *et al*[14], CRP was found to be associated with mortality [14.2 (10.2-27) *vs* 9.3 (3.8-18.9) $P = 0.005$], while WBC count was not [6.7 (4.7-9.5) *vs* 5.5 (3.9-7.6) $P = 0.6$]. Hakami *et al*[21] and Sinha *et al*[22] only reported the WBC difference as follows: 9.1 ± 1.3 *vs* 6.3 ± 0.4 $P = 0.04$ reported by Hakami *et al*[21] and 11.059 ± 5929 *vs* 7022 ± 2935 $P < 0.001$ reported by Sinha *et al*[22]. Keller *et al*[14] only reported the CRP difference and found it to be statistically significant: 95 (49-192) *vs* 44.5 (19-92) $P = 0.0003$.

Overall, it does appear that elevations in both CRP and WBC count are associated with worse outcomes. A meta-analysis by Malik *et al*[29] also reported that CRP elevation is associated with adverse outcomes in COVID-19 in the general population. It is worth noting that a number of conditions and treatments other than COVID-19 can be associated with CRP and WBC elevations. For example, corticosteroids can lead to elevated WBC counts, and corticosteroids are a common treatment for both severe COVID-19 and a number of conditions that may ultimately lead to ESRD. Further subgroup analysis would be required to evaluate further whether a significant confounder exists.

Varghese *et al*[27] also found hyponatremia and hyperkalemia to be associated with poor outcomes, while studies by Hakami *et al*[21] and Sinha *et al*[22] found no significant difference in outcomes based on sodium or potassium levels. Electrolyte abnormalities would, in general, be expected among patients on hemodialysis, especially on days when dialysis sessions are not scheduled. However, other studies have found that both sodium and potassium abnormalities are associated with worse COVID-19 outcomes in the general population[30,31]. It is almost undeniably true that every effort should be made to keep electrolytes within reference ranges, whether hyponatremia and hyperkalemia at presentation are associated with increased COVID-19 severity or simply a consequence of the dialysis schedule.

Ferritin is both an inflammatory marker and a relevant marker of iron stores in the body. Five of the studies included in this analysis looked at the significance of ferritin in determining the prognosis of COVID-19, and all found ferritin to be significantly higher among hemodialysis patients who succumb to COVID-19 in comparison to those who survive[18,19,21,27,28]. It is notable, however, that average ferritin levels varied widely between studies, and while in each study, patients with higher ferritin were more likely to die, in some studies, even the levels among those who survived were notably higher than those of those who died in a different study. Moreover, it needs to be remembered that patients with ESRD are likely to be anemic at baseline. Therefore, even though all the studies point towards an association between higher ferritin and mortality, it is difficult to interpret clinically.

Finally, dyspnea is one of the most common symptoms of severe respiratory infection, and decreased oxygen saturation is a marker of worsening respiratory status. The same has generally held true for COVID-19 throughout the pandemic, and oxygen saturation level is frequently used as one of the main criteria for the hospital admission. As would be expected, both dyspnea and oxygen saturation were associated with mortality. Of the five studies that analyzed the association between dyspnea and COVID-19 mortality in HD patients, all 5 showed statistical significance, with a *P* value never reaching 0.03[15,19,21,22,27]. Studies by Varghese *et al*[27] and Fisher *et al*[18] found a significant association between lower SpO_2 and mortality. Keller *et al*[14] and Hendra *et al*[28] failed to find a significant association. It should be noted that all 4 of the aforementioned studies had relatively small sample sizes, and oxygen saturation generally falls within a narrow range, likely impacting some of the findings. Moreover, patients tend to desaturate later in the course of the disease, and if HD patients were admitted to the hospital early due to their pre-existing comorbidities, it is possible that this could make SpO_2 at presentation less reliable as an indicator of COVID-19 severity in those patients.

Limitations

The study has several notable limitations. Firstly, most of the studies only looked at COVID-19 prognosis in the early phases of the pandemic when treatment options were also more limited, and no vaccines were available. Secondly, we excluded three as they were written in languages other than English. The way data was reported varied across studies, limiting the number of studies that reported each variable. Finally, hospital and ICU admission criteria vary between institutions, so they may not be a perfect indicator of disease severity.

CONCLUSION

Patients on chronic hemodialysis due to end-stage renal disease are among the most vulnerable members of society at increased risk of both catching and succumbing to COVID-19 infection. We found that the incidence of COVID-19 in hemodialysis patients was significant, and in some studies, more than one-tenth caught COVID-19 during the first wave. The prognosis was overall much poorer than in the general population, with the majority requiring hospitalization and more than one in five deaths. Generally, biochemical abnormalities and early dyspnea were associated with a higher degree of mortality. It would be interesting to see how much the numbers would change if the same studies were done during subsequent COVID-19 waves.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) has been the most talked-about disease of the past few years. Patients with significant comorbidities have been at particular risk of adverse outcomes. We looked at the outcomes and risk factors for adverse outcomes among patients on chronic hemodialysis.

Research motivation

The authors assess outcomes and risk factors for adverse outcomes of COVID-19 infection among patients on chronic hemodialysis.

Research objectives

The objective of this study is to assess outcomes and risk factors for adverse outcomes of COVID-19 infection among patients on chronic hemodialysis.

Research methods

The authors searched PubMed/MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Web of Science databases for relevant terms and imported the results into the Covidence platform. From there, studies were assessed in two stages for relevance and quality, and data from studies that satisfied all the requirements were extracted into a spreadsheet. The data was then analyzed descriptively and statistically.

Research results

Of the 920 studies identified through the initial database search, only 17 were included in the final analysis. The studies included in the analysis were mostly carried out during the first wave. The authors found that COVID-19 incidence among patients on hemodialysis was significant, over 10% in some studies. Those who developed COVID-19 infection were most likely going to be hospitalized, and over 1 in 5 died from the infection. ICU admission rate was lower than the infection lethality rate. Biochemical

abnormalities and dyspnea were generally reported to be associated with adverse outcomes.

Research conclusions

This systematic review confirms that patients on chronic hemodialysis are very high-risk individuals for COVID-19 infections, and a significant proportion was infected during the first wave. Their prognosis is overall much worse than in the general population, and every effort needs to be made to decrease their exposure.

Research perspectives

Further research can be done to assess the efficacy of protective measures and vaccines against COVID-19 among dialysis patients.

FOOTNOTES

Author contributions: All authors shared in preparing, writing and reviewing the manuscript.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: United States

ORCID number: Ivan Cancarevic 0000-0002-7455-6381; Mahmoud Nassar 0000-0002-5401-9562; Ahmed Daoud 0000-0001-6311-3887; Hatem Ali 0000-0002-3141-7015; Angelica Sanchez 0000-0002-7335-2002; Avish Parikh 0000-0002-2008-9861; Asma Ul Hosna 0000-0002-4780-2858; Bhavana Devanabanda 0000-0002-2749-0228; Nazakat Ahmed 0000-0002-6892-0319; Karim M Soliman 0000-0002-0960-2644.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Li X

REFERENCES

1 **Kim L**, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, Armistead I, Bennett NM, Billing L, Como-Sabetti K, Hill M, Kim S, Monroe ML, Muse A, Reingold AL, Schaffner W, Sutton M, Talbot HK, Torres SM, Yousey-Hindes K, Holstein R, Cummings C, Brammer L, Hall AJ, Fry AM, Langley GE. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis* 2021; **72**: e206-e214 [PMID: 32674114 DOI: 10.1093/cid/ciaa1012]

2 **Nassar M**, Nso N, Alfishawy M, Novikov A, Yaghi S, Medina L, Toz B, Lakhdar S, Idrees Z, Kim Y, Gurung DO, Siddiqui RS, Zheng D, Agladze M, Sumbly V, Sandhu J, Castillo FC, Chowdhury N, Kondaveeti R, Bhuiyan S, Perez LG, Ranat R, Gonzalez C, Bhangoo H, Williams J, Osman AE, Kong J, Ariyaratnam J, Mohamed M, Omran I, Lopez M, Nyabera A, Landry I, Iqbal S, Gondal AZ, Hassan S, Daoud A, Baraka B, Trandafirescu T, Rizzo V. Current systematic reviews and meta-analyses of COVID-19. *World J Virol* 2021; **10**: 182-208 [PMID: 34367933 DOI: 10.5501/wjv.v10.i4.182]

3 **Nassar M**, Nso N, Ariyaratnam J, Sandhu J, Mohamed M, Baraka B, Ibrahim A, Alfishawy M, Zheng D, Bhangoo H, Soliman KM, Li M, Rizzo V, Daoud A. Coronavirus disease 2019 and renal transplantation. *World J Clin Cases* 2021; **9**: 7986-7997 [PMID: 34621855 DOI: 10.12998/wjcc.v9.i27.7986]

4 **Murphy D**, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, Hsu CY; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in Prevalence of Chronic Kidney Disease in the United States. *Ann Intern Med* 2016; **165**: 473-481 [PMID: 27479614 DOI: 10.7326/M16-0273]

5 **Dalrymple LS**, Mu Y, Nguyen DV, Romano PS, Chertow GM, Grimes B, Kaysen GA, Johansen KL. Risk Factors for Infection-Related Hospitalization in In-Center Hemodialysis. *Clin J Am Soc Nephrol* 2015; **10**: 2170-2180 [PMID: 26567370 DOI: 10.2215/CJN.03050315]

6 **Hsu CM**, Weiner DE, Aweh G, Miskulin DC, Manley HJ, Stewart C, Ladik V, Hosford J, Lacson EC, Johnson DS, Lacson E Jr. COVID-19 Among US Dialysis Patients: Risk Factors and Outcomes From a National Dialysis Provider. *Am J Kidney*

Dis 2021; **77**: 748-756.e1 [PMID: 33465417 DOI: 10.1053/j.ajkd.2021.01.003]

7 **Chan L**, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I, Somani S, Richter F, Miotto R, Lala A, Kia A, Timsina P, Li L, Freeman R, Chen R, Narula J, Just AC, Horowitz C, Fayad Z, Cordon-Cardo C, Schadt E, Levin MA, Reich DL, Fuster V, Murphy B, He JC, Charney AW, Böttinger EP, Glicksberg BS, Coca SG, Nadkarni GN; Mount Sinai COVID Informatics Center (MSCIC). AKI in Hospitalized Patients with COVID-19. *J Am Soc Nephrol* 2021; **32**: 151-160 [PMID: 32883700 DOI: 10.1681/ASN.2020050615]

8 **Gabarre P**, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. *Intensive Care Med* 2020; **46**: 1339-1348 [PMID: 32533197 DOI: 10.1007/s00134-020-06153-9]

9 **Kurzhagen JT**, Dellepiane S, Cantaluppi V, Rabb H. AKI: an increasingly recognized risk factor for CKD development and progression. *J Nephrol* 2020; **33**: 1171-1187 [PMID: 32651850 DOI: 10.1007/s40620-020-00793-2]

10 **Lugon JR**, Neves PDMM, Pio-Abreu A, do Nascimento MM, Sesso R; COVID-19 HD-Brazil Investigators. Evaluation of central venous catheter and other risk factors for mortality in chronic hemodialysis patients with COVID-19 in Brazil. *Int Urol Nephrol* 2022; **54**: 193-199 [PMID: 34132971 DOI: 10.1007/s11255-021-02920-9]

11 **Savino M**, Santhakumaran S, Currie CSM, Onggo BSS, Evans KM, Medcalf JF, Nitsch D, Steenkamp R. Comparison of Outcomes of In-Centre Haemodialysis Patients between the 1st and 2nd COVID-19 Outbreak in England, Wales, and Northern Ireland: A UK Renal Registry Analysis. *Nephron* 2022; 1-12 [PMID: 35354143 DOI: 10.1159/000523731]

12 **UK Cit**. Cases in the UK Coronavirus in the UK 2022 [cited May 5, 2022]. Available from: https://coronavirus.data.gov.uk/details/cases

13 **De Meester J**, De Bacquer D, Naesens M, Meijers B, Couttenye MM, De Vriese AS; NBVN Kidney Registry Group. Incidence, Characteristics, and Outcome of COVID-19 in Adults on Kidney Replacement Therapy: A Regionwide Registry Study. *J Am Soc Nephrol* 2021; **32**: 385-396 [PMID: 33154174 DOI: 10.1681/ASN.2020060875]

14 **Keller N**, Chantrel F, Krummel T, Bazin-Kara D, Faller AL, Muller C, Nussbaumer T, Ismer M, Benmoussa A, Brahim-Bouna M, Beier S, Perrin P, Hannedouche T. Impact of first-wave COronaVIrus disease 2019 infection in patients on haemoDIALysis in Alsace: the observational COVIDIAL study. *Nephrol Dial Transplant* 2020; **35**: 1338-1411 [PMID: 32871594 DOI: 10.1093/ndt/gfaa170]

15 **Marino C**, Angelici L, Pistolesi V, Morabito S, Di Napoli A, Calandrini E, Cascini S, Bargagli AM, Petrosillo N, Agabiti N, Davoli M, On Behalf Of The Regional Registry Dialysis And Transplant Lazio Region. SARS-CoV-2 Infection in Patients on Dialysis: Incidence and Outcomes in the Lazio Region, Italy. *J Clin Med* 2021; **10** [PMID: 34945114 DOI: 10.3390/jcm10245818]

16 **Ozturk S**, Turgutalp K, Arici M, Odabas AR, Altiparmak MR, Aydin Z, Cebeci E, Basturk T, Soypacaci Z, Sahin G, Elif Ozler T, Kara E, Dheir H, Eren N, Suleymanlar G, Islam M, Ogutmen MB, Sengul E, Ayar Y, Dolarslan ME, Bakirdogen S, Safak S, Gungor O, Sahin I, Mentese IB, Merhametsiz O, Oguz EG, Genek DG, Alpay N, Aktas N, Duranay M, Alagoz S, Colak H, Adibelli Z, Pembegul I, Hur E, Azak A, Taymez DG, Tatar E, Kazancioglu R, Oruc A, Yuksel E, Onan E, Turkmen K, Hasbal NB, Gurel A, Yelken B, Sahutoglu T, Gok M, Seyahi N, Sevinc M, Ozkurt S, Sipahi S, Bek SG, Bora F, Demirelli B, Oto OA, Altunoren O, Tuglular SZ, Demir ME, Ayli MD, Huddam B, Tanrisev M, Bozaci I, Gursu M, Bakar B, Tokgoz B, Tonbul HZ, Yildiz A, Sezer S, Ates K. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. *Nephrol Dial Transplant* 2020; **35**: 2083-2095 [PMID: 33275763 DOI: 10.1093/ndt/gfaa271]

17 **Times NY**. Covid in the US: Latest Maps, Case and Death Counts: The New York Times; 2022 [cited May 5, 2022]. Available from: https://www.nytimes.com/interactive/2021/us/covid-cases.html

18 **Fisher M**, Yunes M, Mokrzycki MH, Golestaneh L, Alahiri E, Coco M. Chronic Hemodialysis Patients Hospitalized with COVID-19: Short-term Outcomes in the Bronx, New York. *Kidney360* 2020; **1**: 755-762 [PMID: 35372963 DOI: 10.34067/KID.0003672020]

19 **Turgutalp K**, Ozturk S, Arici M, Eren N, Gorgulu N, Islam M, Uzun S, Sakaci T, Aydin Z, Sengul E, Demirelli B, Ayar Y, Altiparmak MR, Sipahi S, Mentes IB, Ozler TE, Oguz EG, Huddam B, Hur E, Kazancioglu R, Gungor O, Tokgoz B, Tonbul HZ, Yildiz A, Sezer S, Odabas AR, Ates K. Determinants of mortality in a large group of hemodialysis patients hospitalized for COVID-19. *BMC Nephrol* 2021; **22**: 29 [PMID: 33446135 DOI: 10.1186/s12882-021-02233-0]

20 **Bhinder OS**, Swarnim S, Mantan M, Dabas A, Ahlawat RS. Chronic Kidney Disease and COVID-19: Outcomes of hospitalised adults from a tertiary care centre in North India. *Med J Armed Forces India* 2022 [PMID: 35169379 DOI: 10.1016/j.mjafi.2021.12.004]

21 **Hakami A**, Badedi M, Elsiddig M, Nadeem M, Altherwi N, Rayani R, Alhazmi A. Clinical Characteristics and Early Outcomes of Hospitalized COVID-19 Patients with End-Stage Kidney Disease in Saudi Arabia. *Int J Gen Med* 2021; **14**: 4837-4845 [PMID: 34475777 DOI: 10.2147/IJGM.S327186]

22 **Sinha S**, Swami R, Shakir A, Salman Ali S, Bansode J, Mehta K. Clinical Profile and Outcome of Hemodialysis Patients with SARS COV2 Infection in a Tertiary Care Centre in Mumbai, India. *Indian J Nephrol* 2021; **31**: 442-448 [PMID: 34880553 DOI: 10.4103/ijn.IJN_377_20]

23 **Naaraayan A**, Nimkar A, Hasan A, Pant S, Durdevic M, Elenius H, Nava Suarez C, Basak P, Lakshmi K, Mandel M, Jesmajian S. End-Stage Renal Disease Patients on Chronic Hemodialysis Fare Better With COVID-19: A Retrospective Cohort Study From the New York Metropolitan Region. *Cureus* 2020; **12**: e10373 [PMID: 33062496 DOI: 10.7759/cureus.10373]

24 **Lamech TM**, Nithya G, Aiswarya D, Gopalakrishnan N, Vathsalyan P, Sajmi S, Goutham K, Krishna R, Dineshkumar T, Sakthirajan R, Dhanapriya J, Padmaraj R. Clinical Profile and Outcomes of Coronavirus Disease 2019 (COVID-19) in Patients Undergoing Hemodialysis. *Indian J Nephrol* 2022; **32**: 16-21 [PMID: 35283577 DOI: 10.4103/ijn.IJN_511_20]

25 **Goffin E**, Candellier A, Vart P, Noordzij M, Arnol M, Covic A, Lentini P, Malik S, Reichert LJ, Sever MS, Watschinger B, Jager KJ, Gansevoort RT; ERACODA Collaborators. COVID-19-related mortality in kidney transplant and haemodialysis patients: a comparative, prospective registry-based study. *Nephrol Dial Transplant* 2021; **36**: 2094-2105 [PMID: 34132811 DOI: 10.1093/ndt/gfab200]

26 **Singh AK**, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr* 2020; **14**: 303-310 [PMID: 32298981 DOI: 10.1016/j.dsx.2020.04.004]

27 **Varghese B**, Raja N, Rajagopalan A, Arunachalam J, Durai R, Prasath A, Kumar S, Velu S. Clinical Characteristics and Short-Term Outcomes of ESKD Patients Undergoing Hemodialysis with COVID-19 Infection in Madurai, South India. *Turkish J Nephrol* 2022; **31** [DOI: 10.5152/turkjnephrol.2022.21020]

28 **Hendra H**, Vajgel G, Antonelou M, Neradova A, Manson B, Clark SG, Kostakis ID, Caplin B, Salama AD. Identifying prognostic risk factors for poor outcome following COVID-19 disease among in-centre haemodialysis patients: role of inflammation and frailty. *J Nephrol* 2021; **34**: 315-323 [PMID: 33515380 DOI: 10.1007/s40620-020-00960-5]

29 **Malik P**, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, Gabrilove JL, Sacks H. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med* 2021; **26**: 107-108 [PMID: 32934000 DOI: 10.1136/bmjebm-2020-111536]

30 **Ruiz-Sánchez JG**, Núñez-Gil IJ, Cuesta M, Rubio MA, Maroun-Eid C, Arroyo-Espliguero R, Romero R, Becerra-Muñoz VM, Uribarri A, Feltes G, Trabattoni D, Molina M, García Aguado M, Pepe M, Cerrato E, Alfonso E, Castro Mejía AF, Roubin SR, Buzón L, Bondia E, Marin F, López Pais J, Abumayyaleh M, D'Ascenzo F, Rondano E, Huang J, Fernandez-Perez C, Macaya C, de Miguel Novoa P, Calle-Pascual AL, Estrada Perez V, Runkle I; HOPE COVID-19 investigators. Prognostic Impact of Hyponatremia and Hypernatremia in COVID-19 Pneumonia. A HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry Analysis. *Front Endocrinol (Lausanne)* 2020; **11**: 599255 [PMID: 33329400 DOI: 10.3389/fendo.2020.599255]

31 **Amin A**, Moon R, Agiro A, Rosenthal N, Brown H, Legg R, Pottorf W. In-hospital mortality, length of stay, and hospitalization cost of COVID-19 patients with and without hyperkalemia. *Am J Med Sci* 2022 [PMID: 35490703 DOI: 10.1016/j.amjms.2022.04.029]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 362-374

DOI: 10.5501/wjv.v11.i5.362

ISSN 2220-3249 (online)

SYSTEMATIC REVIEWS

Anatomophysiological relationships and clinical considerations of taste and smell loss in patients with COVID-19

Maria Fernanda Rossi Vigliar, Karina Torres Pomini, Daniela Vieira Buchaim, Rogerio Leone Buchaim

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Liu D, China; Yuan H, China

Received: April 13, 2022
Peer-review started: April 13, 2022
First decision: June 16, 2022
Revised: June 24, 2022
Accepted: August 12, 2022
Article in press: August 12, 2022
Published online: September 25, 2022

Maria Fernanda Rossi Vigliar, Karina Torres Pomini, Rogerio Leone Buchaim, Department of Biological Sciences, Bauru School of Dentistry, University of São Paulo, Bauru 17012901, São Paulo, Brazil

Karina Torres Pomini, Daniela Vieira Buchaim, University of Marilia, Marilia 17525902, São Paulo, Brazil

Daniela Vieira Buchaim, University Center of Adamantina, Adamantina 17800000, São Paulo, Brazil

Rogerio Leone Buchaim, Faculty of Veterinary Medicine and Animal Science, University of São Paulo, São Paulo 05508270, São Paulo, Brazil

Corresponding author: Rogerio Leone Buchaim, PhD, Associate Professor, Department of Biological Sciences, Bauru School of Dentistry, University of São Paulo, Alameda Dr. Octávio Pinheiro Brisolla 9-75, Bauru 17012901, São Paulo, Brazil. rogerio@fob.usp.br

Abstract

BACKGROUND

There are numerous conflicting discussions about the outbreak of the new coronavirus 2019 (COVID-19).

AIM

To present some anatomical and physiological considerations about two of the symptoms reported by patients: The loss or reduction of smell and taste.

METHODS

The loss or reduction of smell and taste is presented in a peculiar way, with some cases of persistence even after COVID-19. For this, it was searched in three databases, PubMed/MEDLINE, Web of Science, and Scopus, using the following keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID-19", with no publication time restriction, only in English with full text available, excluding also brief communications, letters to the editor, editorials, reviews, comments, and conference abstracts.

RESULTS

The search found 776 articles in the PubMed/MEDLINE database, 1018 in the Web of Science database, and 552 in the Scopus database, from which duplicates were removed (104 articles). Finally, 17 studies were selected for detailed analysis

within the eligibility criteria, with titles and abstracts related to central nervous system lesions responsible for smell and taste. This review suggests that viral mechanisms of action may be related to lesions both at the local level and at the level of the central nervous system, lasting up to 3 to 4 wk. It is considered persistent if it exceeds this period, as reported in one case in this review. There are still few studies about the treatment, and among those addressed in this review, only two studies reported possible treatments and emphasized the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy

CONCLUSION

Given the scarcity of data, this review emphasizes the importance of prevention, through the correct use of personal protective equipment by health professionals and respect for local behavioral indications. It is also emphasized, through five studies, that there is a predominance of such symptoms in patients with COVID-19, which can be a tool to control dissemination, through the early isolation of patients until the results are ready.

Key Words: SARS-CoV-2; COVID-19; Coronavirus; Olfactory nerve; Smell; Taste

Core Tip: We discuss the anatomical and physiological considerations about two of the symptoms reported by patients: The loss or reduction of smell and taste. There are still few studies about the treatment, and among those addressed in this review, only two studies reported possible treatments and emphasized the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy. Given the scarcity of data, this review emphasizes the importance of prevention, through the correct use of personal protective equipment by health professionals and respect for local behavioral indications. It is also emphasized, through five studies, that there is a predominance of such symptoms in patients with coronavirus disease 2019, which can be a tool to control dissemination, through the early isolation of patients until the results are ready.

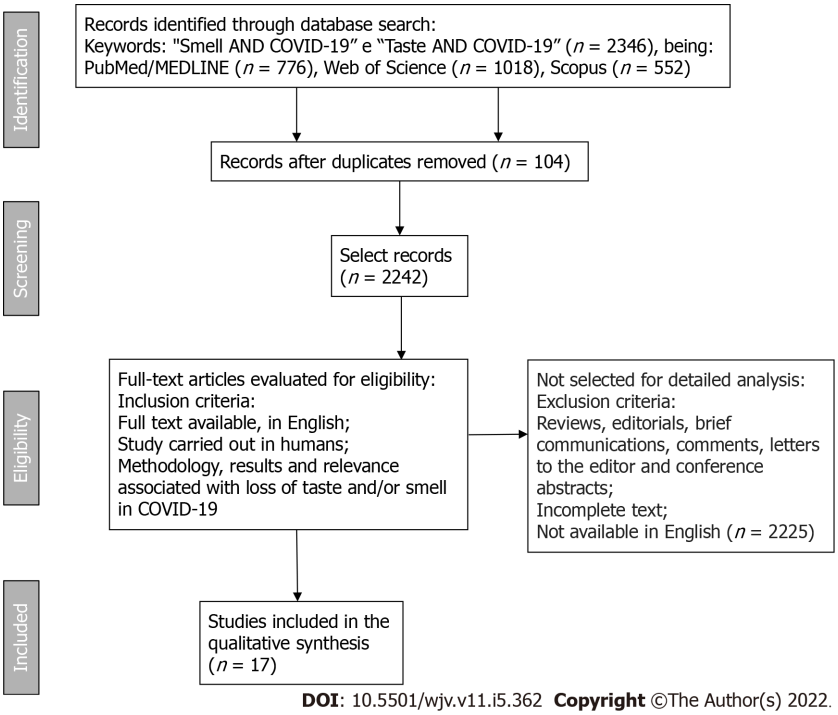
Citation: Vigliar MFR, Pomini KT, Buchaim DV, Buchaim RL. Anatomophysiological relationships and clinical considerations of taste and smell loss in patients with COVID-19. *World J Virol* 2022; 11(5): 362-374
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/362.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.362

INTRODUCTION

In December 2019 in Wuhan (China), the emergence of an acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 CoV (SARS-CoV-2), with a peculiar and highly contagious behavior, was reported[1]. Thus, the World Health Organization decreed on March 11, 2020 a state of pandemic, considering the condition of community transmission of human infection by the virus[2]. In the current world scenario, there are already approximately 493 million infected and 6.1 million dead people. In Brazil, there are approximately 30.1 million infected and 661 thousand dead ones[2]. Such global and national data are alarming and may be related to the high speed of dissemination, high mortality rate in people with comorbidity, and the coping strategies of each country, as well as socioeconomic and health conditions[3,4].

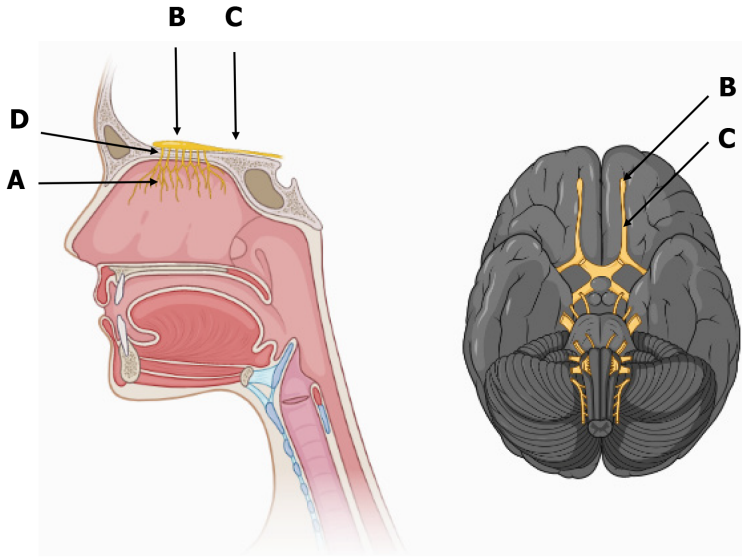
The clinical manifestations of the new coronavirus (COVID-19) are very varied, with the most common symptoms being fever (74%), cough (79%), fatigue (75%), headache (78%), gastrointestinal disorders (57%), and loss of smell (63%) and taste (65%). These symptoms, when present, lead to the diagnostic suspicion of COVID-19, until confirmed by examinations[5,6]. The sensory pathway of smell is initially given by the nerve endings of the olfactory nerve, the primary olfactory neuron, located in the upper third of the nasal cavity and nasal septum, stimulated by chemical substances from the air that are transformed into action potential[7-9]. This stimulus travels through the primary neuron crossing the cribriform plate of the ethmoid bone through its foramina[8]. Upon accessing the anterior cavity of the skull, they synapse with the secondary neuron. The olfactory nerve impulses terminate in the primary cortical projection area and travel to the thalamus, which proceeds to the orbitofrontal and rectus olfactory gyrus (Figure 1). There is also an association of some odors with the limbic system, causing reactions of pleasure or aversion[8-11] (Figures 2 and 3).

Taste is provided by the specialized sensitivity of the tongue, *via* the glossopharyngeal nerve (IX cranial nerve) in the posterior third, vagus nerve (X cranial nerve) with few branches at the base of the



DOI: 10.5501/wjv.v11.i5.362

Figure 1 Flow diagram showing the selection of articles in the PubMed/MEDLINE, Web of Science, and Scopus databases. COVID-19: The new coronavirus 2019.

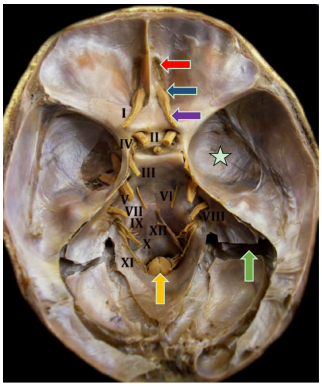


DOI: 10.5501/wjv.v11.i5.362

Figure 2 Olfactory pathway and its components. A: Fillets of the olfactory nerves, the first pair of cranial nerves, inside the nasal cavity in the upper third of the nasal septum; B: Olfactory bulb; C: Olfactory tract; D: Cribriform plate of the ethmoid bone, which communicates the nasal cavity with the anterior cranial fossa.

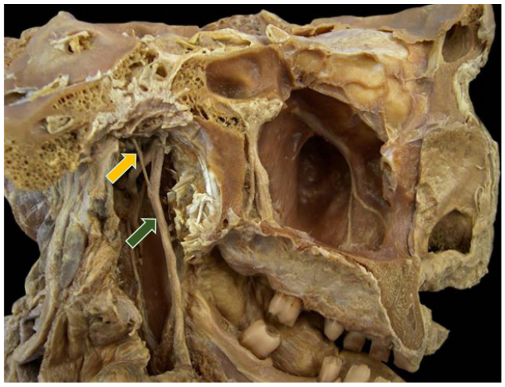
tongue and epiglottis, and chorda tympani nerve (branch of the VII cranial nerve, the facial-intermediate nerve) in the anterior two thirds of the tongue[7,8]. They receive the stimulus through taste buds that are made up of epithelial cells that have different receptors for each type of flavor, distributed throughout the tongue[12]. From there, the stimuli travel through the primary afferent fibers of the respective gustatory sensory nerves to the solitary tract in the medulla, then to the thalamus, passing to the cortex[8] (Figures 4 and 5).

Given this context, research has sought strategies in order to clarify the sensory alterations of loss of smell and taste, the possible mechanism of action of the virus in these nerves, and its treatment. Thus, the present study aimed to review the anatomy and physiology of the olfactory and gustatory pathways, and their relationship with symptomatology in patients with COVID-19.



DOI: 10.5501/wjv.v11.i5.362

Figure 3 Endocranial view of the 12 pairs of cranial nerves in a natural anatomical piece. I: Olfactory nerve; II: Optic nerve; III: Oculomotor nerve; IV: Trochlear nerve; V: Trigeminal nerve; VI: Abducens nerve; VII: Facial and intermediate nerve; VIII: Vestibulocochlear nerve; IX: Glossopharyngeal nerve; X: Vagus nerve; XI: Accessory nerve; XII: Hypoglossal nerve. Red arrow indicates the cribriform plate of the ethmoid bone; blue arrow indicates the olfactory bulb; purple arrow indicates the olfactory tract; yellow arrow indicates the beginning of the spinal cord at the level of the foramen magnum; green arrow indicates the sigmoid sinus; white star indicates the cranial dura mater.



DOI: 10.5501/wjv.v11.i5.362

Figure 4 Natural anatomical piece in midsagittal section (medial view). Yellow arrow represents the chorda tympani nerve, a branch of the intermediate nerve; green arrow represents the lingual nerve, a branch of the mandibular division of the trigeminal nerve.

MATERIALS AND METHODS

For this study, PubMed/MEDLINE, Web of Science, and Scopus databases were searched, using the following terms as keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID -19", without publication time restriction and only in the English language. Works that present titles and abstracts related to the topic of the initial research were verified, using the variables taste and/or smell and COVID-19. Subsequently, the text was evaluated of the articles previously selected by the abstract. The methodology, results, and relevance were considered to list the choice of articles. For inclusion in the research, the articles must necessarily be accessed in their full content (Figure 1).

The inclusion criteria were: Description of changes in smell and taste due to COVID-19; Human studies; Publications in English only; Publications that allow full access to the text. The exclusion criteria were: Articles that have been duplicated; Animal studies; The title was not related to the objective; There was no loss of taste; There was no loss of smell; Other languages (except English); Access to the full text has not been obtained; Brief communications, letters to the editor, editorials, reviews, comments, and conference abstracts.

RESULTS

The search found 776 articles in the PubMed/MEDLINE database, 1018 in the Web of Science database, and 552 in the Scopus database, from which duplicates were removed (104 articles), then editorials, review articles, brief communications, letters to the editor, comments, conference abstracts, and articles without full text available or not produced in English were excluded, as they are outside the eligibility criteria. Seventeen studies that met the eligibility criteria were selected (Table 1).

Table 1 Seventeen studies that meet the eligibility criteria

Database	Title	Ref.	Sample/study type	Conclusion	Anatomophysiological relationship
PubMed/MEDLINE and Web of Science	A structural equation model to examine the clinical features of mild to moderate coronavirus disease 2019 (COVID-19): An Italian multicenter study	Barillari *et al* [15], 2021	294 patients/multicenter study	It has been reported that anosmia should be considered as a specific symptom for COVID-19, especially when the patient is "suspected" or untested	Inflammation in the olfactory epithelium or damage to olfactory receptor neurons, since the cells that make up this tissue have high expression of ACE2 and TMPRSS2, which have a strong capacity to bind the virus, being particularly susceptible to infection
PubMed/MEDLINE and Web of Science	Acute loss of smell and taste among patients with symptoms compatible with COVID-19	Bodnia and Katzeinstein [20], 2020	95 patients/cross-sectional study	There was persistence of mild olfactory and/or taste changes even after the other symptoms of COVID-19 had disappeared. In addition, loss of smell and taste was reported in 50% of patients with COVID-19, especially in adults	Human angiotensin-converting enzyme 2 is the main receptor of the SARS-CoV-2 host cell, present in nasal and olfactory respiratory epithelial cells. In addition, ACE2 is expressed in the oral cavity
PubMed/MEDLINE	Anosmia in COVID-19 associated with olfactory bulb lesion evidenced on MRI	Aragão *et al* [19], 2020	5 patients/retrospective study	This study documented for the first time, through neuroimaging, a type of lesion of the olfactory bulb in patients with COVID-19, demonstrating that the possible mechanism of action that causes olfactory dysfunction, either through the olfactory bulbs or intracranially, by a microvascular phenomenon	Intracranial olfactory bulb lesion, studied and documented by magnetic resonance imaging
PubMed/MEDLINE	COVID-19 viral load in the severity and recovery of olfactory and gustatory dysfunction	Cho *et al* [21], 2020	143 patients/Prospective cross-sectional cohort study	Symptom severity is not correlated with SARS-CoV-2 viral load, and there is a high prevalence of olfactory and gustatory dysfunction in COVID-19	The virus has affinity for ACE2 receptors that are found in the nasal and olfactory epithelium, causing peripheral neuropathy, which affects the functions of smell and taste. The virus is also able to invade the central nervous system through the olfactory bulb
PubMed/MEDLINE and Scopus	Evolution of olfactory disorders in patients with COVID-19	Gorzkowski *et al*[14], 2020	229 patients/Cross-sectional study	Olfactory and taste disturbances can be an isolated symptom of COVID-19, being reported in two-thirds of COVID-19 patients. Knowledge of these symptoms and their evolution can be useful in creating therapeutic strategies for cases of persistence even after the resolution of other symptoms of COVID-19	Mechanisms of olfactory disorders related to SARS-CoV-2 infection are still unknown, but it is likely to be associated with the outcomes of various patterns, such as nasal mucosa edema, olfactory epithelial damage (including neural and non-neural epithelium), and even involvement of olfactory pathways
PubMed/MEDLINE and Web of Science	Frequency and outcome of olfactory impairment and sinonasal involvement in hospitalized patients with COVID-19	Jalessi *et al* [22], 2020	100 patients/prospective descriptive study	In patients with COVID-19, there is a high prevalence of sudden temporary olfactory loss and upper airway infection symptoms. However, among all these symptoms, there was a predominance of olfactory loss, showing that this symptom is not associated with the generalized mucosal edema that occurs during an upper respiratory infection with common coronaviruses	Binding between ACE2 receptors and SARS-CoV-2 spike protein on target cells. In addition, infected cells secrete pro-inflammatory cytokines and chemokines, which can generate localized edema
PubMed/MEDLINE	Importance of anosmia in SARS-CoV-2: from phenomenology for neurobiology	Pallanti[13], 2020	2 patients/descriptive study	Anosmia and hypogeusia among respiratory symptoms can be considered a symptom of COVID-19 infection, if confirmed; these symptoms	The neuroinvasive potential of SARS-CoV-2 was highlighted: When penetrated transnasally, it may access the brain, possibly *via* the olfactory torsion nerves, and

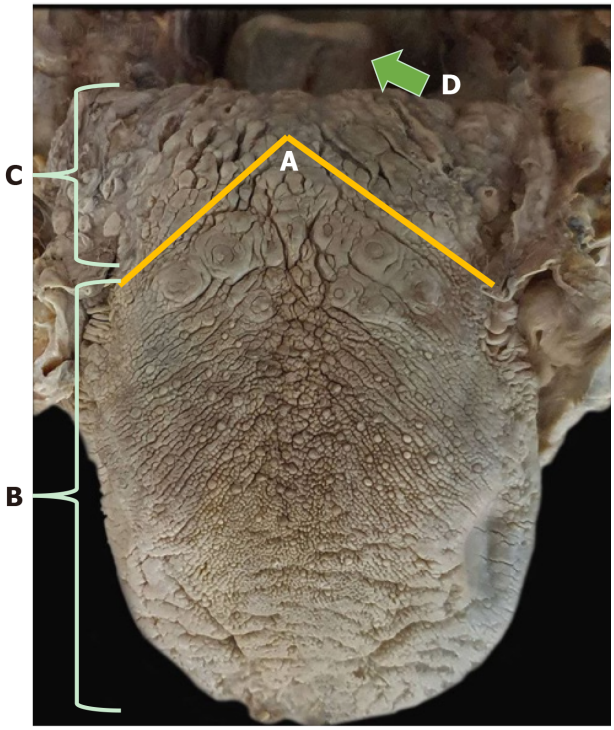
				could represent early markers or signs of SARS-CoV-2 infection to trigger quarantine. These symptoms go beyond sensory aspects, involving extensive neural circuits	from there rapidly spread to some specific brain areas, including the thalamus and brainstem
PubMed/MEDLINE and Web of Science	Loss of smell in COVID-19 patients: MRI data reveal transient swelling of the olfactory clefts	Eliezer *et al* [16], 2020	20 patients/prospective, mono-centric, case-controlled study	Olfactory clefts were evaluated, as well as olfactory function in a cohort study of patients with SARS-CoV-2 infection with loss of olfactory function, which was present in the initial phase of the disease, with improvement at 1-mo follow-up, supporting the hypothesis that this loss, in patients infected with SARS-CoV-2, is caused, at least in part, by reversible inflammatory changes in the olfactory epithelium	SARS-CoV-2 infects cells through interactions between its S protein and ACE2 protein on target cells. Furthermore, it is suggested that SARS-CoV-2 could invade the brain through the cribriform plate near the medulla and olfactory epithelium, causing some structural changes in the olfactory bulb
PubMed/MEDLINE and Web of Science	Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, time and associated characteristics	Speth *et al* [17], 2020	103 patients/prospective, cross-sectional	Olfactory dysfunction is very prevalent during COVID-19, often in conjunction with loss of taste. This dysfunction is negatively associated with advanced age and positively associated with female sex	SARS-CoV-2 has great affinity with the host cell surface receptor, ACE2, located in the nasal mucosa, in particular in the ciliated epithelium and goblet cells. In addition, the virus appears to have neurotropism in which olfactory neurons are susceptible to infection
PubMed/MEDLINE	Histopathological findings of the olfactory epithelium reported anosmia due to long-term coronavirus disease 2019	Vaira *et al* [18], 2020	1 patient/case report	3 mo after the onset of COVID-19 anosmia, a biopsy was performed, which showed massive rupture of the olfactory epithelium, changing the focus of invasion of the olfactory bulb, encouraging further studies of treatments aimed at the superficial epithelium	The epithelium showed thinning with loss of the characteristic three-layer structure, and reduction in the number of olfactory receptor cells, while those that were present had no cilia. There was also an irregular regeneration of the olfactory epithelium interspersed with the respiratory epithelium and, in some cases, the olfactory epithelium was replaced by metaplastic squamous epithelium
PubMed/MEDLINE, Web of Science and Scopus	Psychophysical assessment of chemosensory functions after 5 weeks of olfactory loss due to COVID-19: a prospective cohort study in 72 patients	Le Bon *et al* [23], 2021	72 patients/prospective cohort study	Possibly, SARS-CoV-2 mainly affected odor thresholds, suggesting that the main cause of the loss of smell is at the level of the olfactory neuroepithelium rather than the central nervous system	The loss of taste may be related to a direct injury to the taste organ, and ACE2 receptors have been identified in the mouth and, in particular, on the tongue. ACE-2 receptors are also found in olfactory tissue, inducing olfactory loss at the peripheral rather than the more central nervous level. There is thickening of the olfactory cleft mucosa during COVID-19, reporting olfactory neuritis during COVID-19. There may also be viral spread to the central nervous system that started in the olfactory neuroepithelium
PubMed/MEDLINE	Head and neck symptomatology in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2	Freni *et al* [24], 2020	50 patients/ prospective descriptive study	The authors tried to confirm the theories about the neuroinvasiveness of the virus, from a clinical point of view, so the coronaviruses are neurotropic since the neural cells express the ACE2 entry protein, being able to enter the CNS by several routes, mainly by intranasal inoculation and by peripheral nerve pathway using trans-synaptic pathways. In addition, anosmia, dysgeusia, and xerostomia are the first symptoms of COVID-19, which can be exploited for early quarantine and a	SARS-CoV-2 has neuroinvasive and neurotropic properties. First, there is infection of the neuronal olfactory receptor in the olfactory mucosa, then the virus is transported antegrade to the olfactory bulb, and then there is diffusion through channels formed by cells of the olfactory envelope, which form an open connection with the central nervous system

				limitation of viral contagion	
PubMed/MEDLINE	Trends in olfactory and gustatory dysfunction in quarantined COVID-19 patients	Seo *et al*[25], 2020	62 patients/prospective surveillance study	The prevalence of olfactory and gustatory dysfunction was 24.2% in patients with mild COVID-19, which may be characteristic indicators in these cases. All patients had hyposmia due to sensorineural olfactory dysfunction, confirmed by validated methods of olfactory and gustatory assessment and endoscopic examinations	It may involve olfactory neurons related to the central nervous system or non-neuronal olfactory epithelial cells. When viral infection occurs in olfactory neurons, permanent olfactory dysfunction may occur, and even if there is recovery, it may take a long time. Therefore, the location of olfactory neurons with sensorineural olfactory dysfunction can be inferred from the clinical course
Web of Science	Taste and smell disorders in COVID-19 patients: role of interleukin-6	Cazzolla *et al*[26], 2020	125 patients/observational study	This study based on clinical evidence and laboratory data highlighted the importance of IL-6 in the pathogenesis of chemosensitive disorders	Action of local inflammatory phenomena on the receptors of olfactory and gustatory cells, rather than permanent cell damage linked to the action of the virus. The dysfunctions may be linked to the peripheral action of IL-6 at the level of cell receptors infected by the virus and to the central action of IL-6 at the level of intermediate taste stations and olfactory pathways, especially in the thalamus
Scopus	Brain metabolic correlates with persistent olfactory dysfunction after SARS-Cov-2 infection	Donegani *et al*[27], 2021	22 patients/cross-sectional study	The study provided a group analysis on brain metabolism of patients with persistent olfactory dysfunction after infection with SARS-CoV-2 for the first time proven by olfactory test. It highlighted the confusion of the subtle sequelae of SARS-COV-2 infection and its reflection on PET and other biomarkers	The virus can enter the central nervous system through the first neurons of the olfactory pathway located in the olfactory mucosa. Post-infectious olfactory dysfunction is thought to be caused by damage to the olfactory epithelium or central olfactory processing pathways, with current evidence that hypometabolism in two symmetrical and similar regions within the limbic cortex may support the occurrence of distal olfactory pathway involvement
Scopus	Olfactory function and chest CT findings in COVID-19: is there any correlation?	Mangia *et al* [28], 2021	57 patients/cohort-nested cross-sectional study	Olfactory dysfunction does not correlate with radiological lung involvement in hospitalized patients with COVID-19	The nasal mucosa is an important entry site for SARS-COV-2, as it has a predilection for this neuroepithelium, in addition to having neurotrophic properties. The smell disorder in COVID-19 would not arise from local edema and nasal secretion, preventing odor molecules from reaching the olfactory neuroepithelium
Scopus	Structural and metabolic brain abnormalities in patients with sudden loss of smell with COVID-19	Niesen *et al* [29], 2021	12 patients/prospective descriptive study	This PET-MR study suggests that the sudden loss of smell in COVID-19 is not related to central involvement due to SARS-CoV-2 neuroinvasiveness. Loss of smell is associated with subtle brain metabolic changes in high-order central and cortical olfactory areas, likely related to combined processes of deaeration and active functional reorganization secondary to lack of olfactory stimulation	Considering that the metabolic abnormalities were not associated with any MRI signal abnormalities, they likely do not represent neuroimaging evidence supporting the neuroinvasive potential of SARS-CoV-2, but rather functional brain markers of olfactory deficit

ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MRI: Magnetic resonance imaging; PET: Positron emission tomography; CT: Computed tomography.

DISCUSSION

The present study aimed to select and evaluate articles that elucidate the anatomophysiological relationships of the olfactory and gustatory pathways with the loss of smell and taste as the main symptoms in patients with COVID-19[13,14]. This knowledge can help in the therapeutic approach



DOI: 10.5501/wjv.v11.i5.362

Figure 5 Dorsal region of the tongue. A-C: Yellow line indicates the terminal sulcus, which separates the tongue into body or two anterior thirds and root or posterior third; D: Green arrow indicates the epiglottis cartilage of the larynx, where taste is made by the vagus nerve.

during infection and in persistent post-infection cases. In addition, by giving due relevance to this symptomatology, which has a high incidence in patients with COVID-19, isolation is possible of patients with this symptomatology, even before the test results, thus decreasing the transmissibility of SARS-CoV-2[13,14].

Among all the articles selected, through the methodology used, the presence of a very variable number of patient samples was found, in addition, there was a variability in the anatomical structure placed as the focus of the discussion, which were studied and evaluated by different parameters. Six articles[15,18,20,22,23,28] focused on the olfactory and gustatory epithelium as the main responsible for the loss of smell and taste, due to the fact that they have angiotensin-converting enzyme 2 (ACE2) receptors, which at the time of the entry of SARS-CoV-2 alter and damage this mucosa, making it unable to act as local chemoreceptors. Eleven articles[13,14,16,17,19,21,24-27,29] in addition to highlighting ACE2 receptors as a gateway, indicate the olfactory pathways as the access pathways to the central nervous system by SARS-CoV-2, due to its neurotropic properties, which intracranially, are capable of injuring regions responsible for these senses.

Some studies concluded that there is a high prevalence of loss of smell and taste in patients with COVID-19, there was a variation in the ages studied and the degree of severity of the patient's disease [13-17], but due to the strong correlation of the symptomatology with the COVID-19 is considered a specific symptom of the disease[13,14]. These symptoms usually resolve in approximately 1 mo[17]; however, there are cases of persistent loss of smell and taste[18], which was observed by Vaira *et al*[18]. After biopsy of the nasal mucosa, there was alteration of the olfactory epithelium, which in some places, instead of forming normal tissues, formed metaplastic tissue, which is a possible explanation for the persistence in some cases.

Most articles[13,14,16,17,19,21,24-27,29] highlighted the neurotropic activity of SARS-CoV-2, allowing access and changes in the central nervous system. In the study carried out by Aragão *et al*[19], a microvascular lesion in the olfactory bulb in a patient with COVID-19 and loss of smell and taste were documented through magnetic resonance imaging (MRI), demonstrating a possible mechanism of action of the virus in addition to its action on the olfactory epithelium.

The study by Izquierdo-Dominguez *et al*[30], not included in this study because it is a systematic review, confirms the change in smell and taste due to the presence of ACE2 receptors in the respective mucosa and the fact that SARS-CoV-2 has affinity for these receptors. In addition to these sites, ACE2 can be found in various types of tissues, such as those of the central nervous system, which may also represent one of the causes of loss of smell and taste, if damaged. Studies that performed the autopsy of patients with COVID-19 and found hyperemic, swollen brain tissue and some sites with degenerated neurons were also discussed in this article, and also detected the presence of SARS-CoV-2 nucleic acid in the cerebrospinal fluid[30].

Among the main questions on the subject, in addition to the cause of the loss of smell and taste, as well as its anatomophysiological relationships, there are also discussions on whether there are possible preventions and what therapeutic measures can be carried out in the treatment in cases of persistent losses. Among the selected articles, there are no reports of possible preventive measures for loss of smell and taste, but Xu *et al*[31] raised the hypothesis that the use of vitamin D, as it has several independent neuroprotective mechanisms, can generate protection of central and peripheral nervous tissues, through neurotrophins. The authors hypothesized that the neuroprotective potential could prevent the neurological complications of COVID-19[31].

Regarding therapeutic measures, we selected the study by Vaira *et al*[18] who cited the existence of evidence of the use of steroid rinses and a pilot study with submucosal injection of platelet-rich plasma into the epithelium, obtaining relevant improvement, but they need more studies to reach significant conclusions and be indicated as clinical treatments for lesions[18]. The study by Kanjanaumpor *et al*[32], not addressed in our study because it is a systematic review, argued that there is still no significant evidence to recommend any type of pharmacological treatment; however, olfactory training, without contraindications but with low cost and evidence of improvement, is an interesting therapy in patients with persistent loss of smell and taste with COVID-19[32].

About prognosis, Kanjanaumpor *et al*[32] revealed that in about 32-66% of patients, there is spontaneous recovery and that a US study reported improvement in the loss of smell and taste in 74% of infected patients correlating with the overall resolution of clinical symptoms. Jalessi *et al*[22] mentioned recovery of smell in 44.0% of patients in the short term (2 wk) and Vaira *et al*[18] reported that about 66% of patients achieved complete recovery in an average of 19.3 d from the onset of symptoms.

Regarding preventive measures against COVID-19 and its symptoms, such as loss of smell and taste, the importance of using personal protective equipment (PPE) is found in the literature, as in the study by Kim *et al*[34]. Limited access to this equipment (mask, lab coat, new gloves, and face shield) was significantly associated with a higher risk of developing symptoms of COVID-19, in addition to being associated with more severe disease, with moderate or severe symptoms[34].

Adequate access to PPE by health professionals, especially those on the front line, is associated with a lower chance of contracting the disease, and even if PPE fails, there is an association with less severe and shorter forms[34].

There are numerous studies in progress, including a study by da Fonseca Orcina *et al*[36], who proposed the therapeutic use of a phthalocyanine-derived mouthwash, which is able to reduce the severity of the disease locally, the viral load in the oral cavity, and consequently the clinical symptoms, such as sore throat, cough, and mouth ulcers. It can thus also reduce the severity of the general disease by reducing the viral load and dissemination, since the oral cavity and oropharynx are an important means of dissemination of SARS-CoV-2[35,36]. The authors emphasized the need for more randomized clinical trials for further conclusions[36].

Regarding therapeutic measures in the loss of smell and taste, there are ongoing research testing several drugs; among them, the therapy with sprays and topical rinses based on corticosteroids has obtained good results, in addition to presenting a high safety profile, being appropriate for post-infection patients with persistent loss of these senses[37]. However, smell and taste training is the only specific therapy with proven efficacy. Although the exact mechanism of action is not known, it is believed that through repeated stimulation, there is an increase in the neuroplastic and regenerative capacity of the brain. Thus, it is an important therapy indicated at first in patients with a persistent condition[37-39].

There are difficulties in quantifying the prevalence and incidence of gustatory and olfactory dysfunction in the general population, due to causes such as analysis and evaluation methods, sample size and area, and the correct definitions of dysfunctions[40]. Multicentric research from Europe, in the year 2020, showed interesting data: 85.6% of patients with COVID-19 reported olfactory loss. It was also one of the pioneering studies in the identification of taste loss, which at the time was 88.0% in patients with COVID-19. In addition, that study described that infected patients could experience this loss in the absence of other significant symptoms[40].

With the emergence of coronavirus variants, infections caused by Omicron can currently be highlighted, which resulted in mild disease, mainly due to the discovery and use of vaccines. Compared to other strains such as Delta, Omicron infections were more often associated with symptomatology and upper respiratory tract infections, and have lower viral loads, less dysregulated immune cell profiles, and lower levels of pro-inflammatory cytokines[41].

A study, through questionnaires, evaluated the clinical profile of patients who developed COVID-19 after full vaccination, in symptomatic patients. The most frequent symptoms were asthenia (82.4%), chemosensory dysfunction (63.4%), headache (59.5%), coryza (58.2%), muscle pain (54.9%), loss of appetite (54.3%), and nasal obstruction (51.6%). However, 62.3% and 53.6% of survey participants reported olfactory and gustatory dysfunction, respectively. Symptom severity was mild or moderate in almost all cases. Chemosensory dysfunction is still a frequent symptom, even in people who contracted the infection after full vaccination. In this way, the sudden loss of smell and taste may continue to represent a useful and specific diagnostic aid in suspected COVID-19, even in vaccinated individuals [42].

As limitations of this study, one can consider the rapid change in the literature on COVID-19, as well as the emergence of new variants, with different symptoms from the initial versions.

CONCLUSION

Most of the articles studied reported that possible anatomophysiological mechanisms related to the loss of smell and taste, are local lesions in the olfactory and gustatory tissue due to having ACE-2 receptors, with the SARS-CoV-2 gateway being the oral and nasal cavity. In addition to local lesions, there are central changes in the tissues of the nervous system related to taste and smell, which are also damaged by the neurotropic capacity of SARS-CoV-2. The duration, in most cases, can extend from 3 to 4 wk, and it is considered persistent after 1 mo.

Therapeutic conducts in persistent cases with better initial results, which could be indicated by the doctor, are the use of steroid-based sprays and rinses and, mainly, the training of the senses of smell and taste. Likewise, the best measure to be taken is prevention, with the correct use of PPE by health professionals, and respect for local health recommendations determined in order to reduce viral spread.

ARTICLE HIGHLIGHTS

Research background

There are numerous conflicting discussions about the outbreak of the new coronavirus (COVID-19).

Research motivation

Describe the anatomy and physiology relationships of taste and smell losses due to COVID-19

Research objectives

To present some anatomical and physiological considerations about two of the symptoms reported by patients: the loss or reduction of smell and taste.

Research methods

Since, these symptoms are presented in a peculiar way, with some cases of persistence even after COVID-19. For this, it was searched in three databases, PubMed/MEDLINE, Web of Science and Scopus, using the following keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID-19", no publication time restriction, only in English with full text available, excluding also brief communications, letters to the editor, editorials, reviews, comments and conference abstracts.

Research results

The search found 776 articles in the database PubMed/MEDLINE, 1018 in the Web of Science database, and 552 in the Scopus database, from which duplicates were removed (104 articles). Finally, 17 studies were selected for detailed analysis within the eligibility criteria, with titles and abstracts related to central nervous system lesions responsible for smell and taste. This review suggests that viral mechanisms of action may be related to lesions both at the local level and at the level of the central nervous system, lasting up to 3 to 4 wk. It is considered persistent if it exceeds this period, as reported in one case in this review. There are still few studies about the treatment, and among those addressed in this review, only two studies reported possible treatments and emphasized the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy

Research conclusions

Most of the articles studied reported that possible anatomophysiological mechanisms related to the loss of smell and taste, are local lesions in the olfactory and gustatory tissue due to having ACE-2 receptors, with the SARS-CoV-2 gateway being the oral and nasal cavity. In addition to local lesions, there are central changes in the tissues of the nervous system related to taste and smell, which are also damaged by the neurotropic capacity of SARS-CoV-2. The duration, in most cases, can extend from 3 to 4 wk, and it is considered persistent after 1 mo. Therapeutic conducts in persistent cases with better initial results, which could be indicated by the doctor, are the use of steroid-based sprays and rinses and, mainly, the training of the senses of smell and taste. Likewise, the best measure to be taken is prevention, with the correct use of PPE by health professionals, and respect for local health recommendations determined in order to reduce viral spread.

Research perspectives

Future studies should further describe the relationships between the anatomy and physiology of taste and smell losses due to COVID-19.

ACKNOWLEDGEMENTS

The authors thank Mr. Junqueira JAG from the Faculty of Dentistry of Araçatuba for providing the anatomical images.

FOOTNOTES

Author contributions: Vigliar MFR and Buchaim RL conceptualized, designed, and contributed to the outline of the review article; Pomini KT and Buchaim DV contributed to drafting, editing, and formatting of the manuscript; all authors wrote, read, and approved the final manuscript.

Conflict-of-interest statement: All authors declare no conflicts of interest for this article.

PRISMA 2009 Checklist statement: All authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Brazil

ORCID number: Maria Fernanda Rossi Vigliar 0000-0001-9151-6990; Karina Torres Pomini 0000-0003-2858-4717; Daniela Vieira Buchaim 0000-0002-9914-1262; Rogerio Leone Buchaim 0000-0002-5881-2218.

S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

REFERENCES

1 **Li YC**, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020; **92**: 552-555 [PMID: 32104915 DOI: 10.1002/jmv.25728]
2 **Pan American Health Organization (PAHO)**. [cited 20 April 2022]. Available from: https://www.paho.org/pt/covid19
3 **Shenoy R**, D'Souza V, Roma M. The safety of dental care for older adults during COVID-19 pandemic era. *Patient Saf Surg* 2021; **15**: 32 [PMID: 34602070 DOI: 10.1186/s13037-021-00300-x]
4 **Lima DLF**, Dias AA, Rabelo RS, Cruz IDD, Costa SC, Nigri FMN, Neri JR. Covid-19 in the State of Ceará: behaviors and beliefs in the arrival of the pandemic. *Cien Saude Colet* 2020; **25**: 1575-1586 [PMID: 32402018 DOI: 10.1590/1413-81232020255.07192020]
5 **Zayet S**, Klopfenstein T, Mercier J, Kadiane-Oussou NJ, Lan Cheong Wah L, Royer PY, Toko L, Gendrin V. Contribution of anosmia and dysgeusia for diagnostic of COVID-19 in outpatients. *Infection* 2021; **49**: 361-365 [PMID: 32410112 DOI: 10.1007/s15010-020-01442-3]
6 **Mullol J**, Alobid I, Mariño-Sánchez F, Izquierdo-Domínguez A, Marin C, Klimek L, Wang DY, Liu Z. The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. *Curr Allergy Asthma Rep* 2020; **20**: 61 [PMID: 32748211 DOI: 10.1007/s11882-020-00961-1]
7 **Doty RL**, Cometto-Muñiz JE, Jalowayski AA, Dalton P, Kendal-Reed M, Hodgson M. Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans. *Crit Rev Toxicol* 2004; **34**: 85-142 [PMID: 15112751 DOI: 10.1080/10408440490269586]
8 **Buchaim RL**, Issa JPM. Manual de Anatomia Odontologica (Book). 1o edição ed. São Paulo: Ed. Manole, 2018
9 **Martin JH**. Neuroanatomia Texto e Atlas (Book). 4o edição ed. Porto Alegre: Ed. Artmed, 2013
10 **Williams PL et al Gray Anatomia (Book)**. 37o ed. Ed. Rio de Janeiro: Guanabara Koogan, 1995
11 **Machado A**, Haertel LM. Neuroanatomia Funcional (Book). 3° ed. São Paulo: Ed. Atheneu, 2013
12 **Negri R**, Di Feola M, Di Domenico S, Scala MG, Artesi G, Valente S, Smarrazzo A, Turco F, Morini G, Greco L. Taste perception and food choices. *J Pediatr Gastroenterol Nutr* 2012; **54**: 624-629 [PMID: 22197939 DOI: 10.1097/MPG.0b013e3182473308]
13 **Pallanti S**. Importance of SARs-Cov-2 anosmia: From phenomenology to neurobiology. *Compr Psychiatry* 2020; **100**: 152184 [PMID: 32422426 DOI: 10.1016/j.comppsych.2020.152184]
14 **Gorzkowski V**, Bevilacqua S, Charmillon A, Jankowski R, Gallet P, Rumeau C, Nguyen DT. Evolution of Olfactory Disorders in COVID-19 Patients. *Laryngoscope* 2020; **130**: 2667-2673 [PMID: 32617990 DOI: 10.1002/lary.28957]
15 **Barillari MR**, Bastiani L, Lechien JR, Mannelli G, Molteni G, Cantarella G, Coppola N, Costa G, Trecca EMC, Grillo C, La Mantia I, Chiesa-Estomba CM, Vicini C, Saussez S, Nacci A, Cammaroto G. A structural equation model to examine the clinical features of mild-to-moderate COVID-19: A multicenter Italian study. *J Med Virol* 2021; **93**: 983-994 [PMID:

32710639 DOI: 10.1002/jmv.26354]

16 **Eliezer M**, Hamel AL, Houdart E, Herman P, Housset J, Jourdaine C, Eloit C, Verillaud B, Hautefort C. Loss of smell in patients with COVID-19: MRI data reveal a transient edema of the olfactory clefts. *Neurology* 2020; **95**: e3145-e3152 [PMID: 32917809 DOI: 10.1212/WNL.0000000000010806]

17 **Speth MM**, Singer-Cornelius T, Oberle M, Gengler I, Brockmeier SJ, Sedaghat AR. Olfactory Dysfunction and Sinonasal Symptomatology in COVID-19: Prevalence, Severity, Timing, and Associated Characteristics. *Otolaryngol Head Neck Surg* 2020; **163**: 114-120 [PMID: 32423357 DOI: 10.1177/0194599820929185]

18 **Vaira LA**, Hopkins C, Sandison A, Manca A, Machouchas N, Turilli D, Lechien JR, Barillari MR, Salzano G, Cossu A, Saussez S, De Riu G. Olfactory epithelium histopathological findings in long-term coronavirus disease 2019 related anosmia. *J Laryngol Otol* 2020; **134**: 1123-1127 [PMID: 33190655 DOI: 10.1017/S0022215120002455]

19 **Aragão MFVV**, Leal MC, Cartaxo Filho OQ, Fonseca TM, Valença MM. Anosmia in COVID-19 Associated with Injury to the Olfactory Bulbs Evident on MRI. *AJNR Am J Neuroradiol* 2020; **41**: 1703-1706 [PMID: 32586960 DOI: 10.3174/ajnr.A6675]

20 **Bodnia NC**, Katzenstein TL. Acute loss of smell and taste among patients with symptoms compatible with COVID-19. *Dan Med J* 2020; **67**: A05200370 [PMID: 32800063]

21 **Cho RHW**, To ZWH, Yeung ZWC, Tso EYK, Fung KSC, Chau SKY, Leung EYL, Hui TSC, Tsang SWC, Kung KN, Chow EYD, Abdullah V, van Hasselt A, Tong MCF, Ku PKM. COVID-19 Viral Load in the Severity of and Recovery From Olfactory and Gustatory Dysfunction. *Laryngoscope* 2020; **130**: 2680-2685 [PMID: 32794209 DOI: 10.1002/lary.29056]

22 **Jalessi M**, Barati M, Rohani M, Amini E, Ourang A, Azad Z, Hosseinzadeh F, Cavallieri F, Ghadirpour R, Valzania F, Iaccarino C, Ahmadzadeh A, Farhadi M. Frequency and outcome of olfactory impairment and sinonasal involvement in hospitalized patients with COVID-19. *Neurol Sci* 2020; **41**: 2331-2338 [PMID: 32656713 DOI: 10.1007/s10072-020-04590-4]

23 **Le Bon SD**, Pisarski N, Verbeke J, Prunier L, Cavelier G, Thill MP, Rodriguez A, Dequanter D, Lechien JR, Le Bon O, Hummel T, Horoi M. Psychophysical evaluation of chemosensory functions 5 weeks after olfactory loss due to COVID-19: a prospective cohort study on 72 patients. *Eur Arch Otorhinolaryngol* 2021; **278**: 101-108 [PMID: 32754871 DOI: 10.1007/s00405-020-06267-2]

24 **Freni F**, Meduri A, Gazia F, Nicastro V, Galletti C, Aragona P, Galletti B, Galletti F. Symptomatology in head and neck district in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2. *Am J Otolaryngol* 2020; **41**: 102612 [PMID: 32574896 DOI: 10.1016/j.amjoto.2020.102612]

25 **Seo MY**, Seok H, Hwang SJ, Choi HK, Jeon JH, Sohn JW, Park DW, Lee SH, Choi WS. Trend of Olfactory and Gustatory Dysfunction in COVID-19 Patients in a Quarantine Facility. *J Korean Med Sci* 2020; **35**: e375 [PMID: 33107232 DOI: 10.3346/jkms.2020.35.e375]

26 **Cazzolla AP**, Lovero R, Lo Muzio L, Testa NF, Schirinzi A, Palmieri G, Pozzessere P, Procacci V, Di Comite M, Ciavarella D, Pepe M, De Ruvo C, Crincoli V, Di Serio F, Santacroce L. Taste and Smell Disorders in COVID-19 Patients: Role of Interleukin-6. *ACS Chem Neurosci* 2020; **11**: 2774-2781 [PMID: 32786309 DOI: 10.1021/acschemneuro.0c00447]

27 **Donegani MI**, Miceli A, Pardini M, Bauckneht M, Chiola S, Pennone M, Marini C, Massa F, Raffa S, Ferrarazzo G, Arnaldi D, Sambuceti G, Nobili F, Morbelli S. Brain Metabolic Correlates of Persistent Olfactory Dysfunction after SARS-Cov2 Infection. *Biomedicines* 2021; **9** [PMID: 33808956 DOI: 10.3390/biomedicines9030287]

28 **Mangia LRL**, Soares MB, de Souza TSC, Scarabotto PC, De Masi RDJ, Salvador GLO, Hamerschmidt R. Olfactory function and findings on chest computed tomography in COVID-19: is there any correlation? *Acta Otolaryngol* 2021; **141**: 293-298 [PMID: 33346687 DOI: 10.1080/00016489.2020.1854852]

29 **Niesen M**, Trotta N, Noel A, Coolen T, Fayad G, Leurkin-Sterk G, Delpierre I, Henrard S, Sadeghi N, Goffard JC, Goldman S, De Tiège X. Structural and metabolic brain abnormalities in COVID-19 patients with sudden loss of smell. *Eur J Nucl Med Mol Imaging* 2021; **48**: 1890-1901 [PMID: 33398411 DOI: 10.1007/s00259-020-05154-6]

30 **Izquierdo-Dominguez A**, Rojas-Lechuga MJ, Mullol J, Alobid I. Olfactory Dysfunction in the COVID-19 Outbreak. *J Investig Allergol Clin Immunol* 2020; **30**: 317-326 [PMID: 32406374 DOI: 10.18176/jiaci.0567]

31 **Xu Y**, Baylink DJ, Chen CS, Reeves ME, Xiao J, Lacy C, Lau E, Cao H. The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19. *J Transl Med* 2020; **18**: 322 [PMID: 32847594 DOI: 10.1186/s12967-020-02488-5]

32 **Kanjanaumporn J**, Aeumjaturapat S, Snidvongs K, Seresirikachorn K, Chusakul S. Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options. *Asian Pac J Allergy Immunol* 2020; **38**: 69-77 [PMID: 32563234 DOI: 10.12932/AP-030520-0826]

33 **Villani FA**, Aiuto R, Paglia L, Re D. COVID-19 and Dentistry: Prevention in Dental Practice, a Literature Review. *Int J Environ Res Public Health* 2020; **17** [PMID: 32604906 DOI: 10.3390/ijerph17124609]

34 **Kim H**, Hegde S, LaFiura C, Raghavan M, Sun N, Cheng S, Rebholz CM, Seidelmann SB. Access to personal protective equipment in exposed healthcare workers and COVID-19 illness, severity, symptoms and duration: a population-based case-control study in six countries. *BMJ Glob Health* 2021; **6** [PMID: 33509841 DOI: 10.1136/bmjgh-2020-004611]

35 **de Toledo Telles-Araujo G**, Caminha RDG, Kallás MS, Sipahi AM, da Silva Santos PS. Potential mouth rinses and nasal sprays that reduce SARS-CoV-2 viral load: What we know so far? *Clinics (Sao Paulo)* 2020; **75**: e2328 [PMID: 33263622 DOI: 10.6061/clinics/2020/e2328]

36 **da Fonseca Orcina B**, Vilhena FV, Cardoso de Oliveira R, Marques da Costa Alves L, Araki K, Toma SH, Ragghianti Zangrando MS, da Silva Santos PS. A Phthalocyanine Derivate Mouthwash to Gargling/Rinsing as an Option to Reduce Clinical Symptoms of COVID-19: Case Series. *Clin Cosmet Investig Dent* 2021; **13**: 47-50 [PMID: 33628060 DOI: 10.2147/CCIDE.S295423]

37 **Cavazzana A**, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: A retrospective study on 791 patients. *Laryngoscope* 2018; **128**: 10-15 [PMID: 28556265 DOI: 10.1002/lary.26606]

38 **Buchaim RL**, Barbalho SM, Hamzé AL, de Alvares Goulart R, Rocha KTP, Reis CHB. Loss of smell and COVID-19: Anatomical and physiological considerations. *Int J Adv Eng Res Sci* 2020; **7**: 278-280 [DOI: 10.22161/ijaers.75.34]

39 **Buchaim RL**. Bioengineering applied to Covid-19 pandemic: from bench to bedside. *AIMS Bioengineering* 2021; **8**: 14-15 [DOI: 10.3934/bioeng.2021002]

40 **Lechien JR**, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souchay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020; **277**: 2251-2261 [PMID: 32253535 DOI: 10.1007/s00405-020-05965-1]

41 **Young B**, Fong SW, Chang Z, Tan KS, Rouers A, Goh YS, Tay DJW, Ong SWX, Hao Y, Chua SL. Comparison of the Clinical Features, viral Shedding and Immune Response in Vaccine Breakthrough Infection by the Omicron and Delta Variants. *Research Square* 2022 [DOI: 10.21203/rs.3.rs-1281925/v1]

42 **Vaira LA**, De Vito A, Lechien JR, Chiesa-Estomba CM, Mayo-Yàñez M, Calvo-Henrìquez C, Saussez S, Madeddu G, Babudieri S, Boscolo-Rizzo P, Hopkins C, De Riu G. New Onset of Smell and Taste Loss Are Common Findings Also in Patients With Symptomatic COVID-19 After Complete Vaccination. *Laryngoscope* 2022; **132**: 419-421 [PMID: 34812498 DOI: 10.1002/lary.29964]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 375-390

DOI: 10.5501/wjv.v11.i5.375

ISSN 2220-3249 (online)

SYSTEMATIC REVIEWS

Utility of cardiac bioenzymes in predicting cardiovascular outcomes in SARS-CoV-2

Anjani Muthyala, Sandeep Sasidharan, Kevin John John, Amos Lal, Ajay K Mishra

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mukhopadhyay A, India; Munteanu C, Romania

Received: April 25, 2022
Peer-review started: April 25, 2022
First decision: May 31, 2022
Revised: June 12, 2022
Accepted: August 10, 2022
Article in press: August 10, 2022
Published online: September 25, 2022

Anjani Muthyala, Sandeep Sasidharan, Department of Internal Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Kevin John John, Department of Critical Care, Belivers Church Medical College Hospital, Thiruvalla 689103, Kerela, India

Amos Lal, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Ajay K Mishra, Department of Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Corresponding author: Ajay K Mishra, FACP, MBBS, MD, Academic Fellow, Assistant Professor, Department of Cardiology, Saint Vincent Hospital, 123 Summer Street, Worcester, MA 01608, United States. ajay.mishra@stvincenthospital.com

Abstract

BACKGROUND

Cardiovascular complications have been increasingly recognized in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19). Cardiac biomarkers are released because of this ongoing cardiovascular injury and can act as surrogate markers to assess the disease severity.

AIM

To review the variation and utility of these biomarkers in COVID-19 to ascertain their role in diagnosis, prognosis and clinical outcomes of the disease.

METHODS

We performed a literature search in PubMed, Medline and the Reference Citation Analysis (RCA), using the search terms "COVID-19" and "cardiac bioenzymes" or "cardiac biomarkers". Additionally, we also used the latest reference citation analysis tool to identify more articles.

RESULTS

Cardiac troponin has been consistently elevated in patients with COVID-19 associated myocarditis, and strongly correlated with adverse prognosis. Natriuretic peptides including brain natriuretic peptide (BNP) and pro-BNP is elevated in patients with COVID-19 associated cardiac injury, irrespective of their prior

heart failure status, and independently correlated with worst outcomes. Alongside these traditional biomarkers, novel cardiac bioenzymes including presepsin, soluble ST2 and copeptin, are also increasingly recognized as markers of cardiovascular injury in COVID-19 and can be associated with poor outcomes.

CONCLUSION

Assessment of cardiac bioenzymes at admission and their serial monitoring can help assess the severity of disease and predict mortality in patients with SARS-CoV-2 infection. Future studies are needed to elude the critical importance of novel biomarkers.

Key Words: SARS-CoV-2; Troponin; Brain natriuretic peptide; Prognosis; Outcomes; Heart failure

Core Tip: Cardiac bioenzymes act as surrogate markers for various cardiovascular complications associated with coronavirus disease 2019 (COVID-19). Cardiac bioenzymes at admission and their serial monitoring can help assess the disease severity and predict mortality in patients with COVID-19. This review summarizes the role of these bioenzymes in diagnosis, prognosis and clinical implications on outcomes of various cardiovascular complications associated with COVID-19.

Citation: Muthyala A, Sasidharan S, John KJ, Lal A, Mishra AK. Utility of cardiac bioenzymes in predicting cardiovascular outcomes in SARS-CoV-2. *World J Virol* 2022; 11(5): 375-390
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/375.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.375

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has since infected nearly 500 million people across 200 different countries and killed more than six million people worldwide. Lung injury is the most common presentation seen; however, cardiac injury is another dreaded consequence of this viral disease. Multiple mechanisms of injury have been hypothesized that culminate in widespread inflammation and cytokine storm causing significant cardiovascular dysfunction. A few authors have hypothesized that the inciting events for this injury include microvascular damage in the heart, causing perfusion defects, vessel hyperpermeability, and vasospasm[1-5]. Cardiac biomarkers are released because of this ongoing cardiovascular injury and can act as surrogate markers to assess the disease severity. These biomarkers can be elevated in many cardiac conditions, including acute Myocardial infarction (AMI), heart failure (HF), arrhythmias and cardiomyopathies. Among the available biomarkers, cardiac troponin (cTn) and natriuretic peptides including brain natriuretic peptide (BNP) and N terminal pro-BNP (NT-proBNP), have been extensively studied. Numerous reports from China have noted elevated cTn in COVID-19 patients[6,7]. A major review on cardiac biomarkers in HF emphasized the importance of negative NPs in ruling out HF[8]. In addition, novel biomarkers including soluble ST2 (sST2), Galectin-3 (Gal-3), and copeptin have also been studied. In this review, we aimed to study in detail the various cardiac biomarkers that have been reported in the literature in patients with COVID-19. We also aimed to identify the role of these cardiac biomarkers in diagnosing the impact of cardiac injury and their role in prognostication of morbidity and mortality among patients with COVID-19.

MATERIALS AND METHODS

We conducted an extensive review of the literature of all the studies on patients with COVID-19 associated cardiac injury and cardiac bioenzymes. We screened for articles on cardiac biomarkers in patients with COVID-19 in the MEDLINE/PubMed database. Published articles between November 2019 and March 2022 were reviewed. Keywords for the search criteria included "Coronavirus disease 2019", OR "COVID-19", OR "Severe Acute Respiratory Syndrome Coronavirus-2", OR "cardiac bioenzymes", OR 'biomarkers", OR "prognosis", OR "heart failure", OR "myocarditis" OR "outcome", OR "morbidity", and "mortality". We also used the related article search feature and manual search of references to identify further articles. Additionally, we used the latest reference citation analysis tool to screen for more articles. Two independent trained physician reviewers were involved in screening and

reviewing relevant articles. As of March 2022, a total of 560 papers were identified. Among them, only 61 papers were eligible to be included (Figure 1). All articles with details on COVID-19 patients with cardiac injury and measured cardiac biomarkers were eligible to be included in this review. We included all articles published in English from all over the world. Independent reviews, editorials, letters, abstracts, preprints, and opinions were excluded. Most studies reporting cardiac biomarkers in patients with COVID-19 were from China, North America, and Europe. The reporting of study design, methodology, data collection, biomarker levels, and measured outcomes were not consistent across all the studies. To simplify the role of each cardiac biomarker with regard to COVID-19 disease diagnosis, prognosis, and mortality, we subdivided this review into three principal sections. The three sections were (1) Studies on the role of cardiac troponin in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality; (2) Studies on the role of natriuretic peptides in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality; and (3) Studies on the role of other biomarkers and novel cardiac biomarkers in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality.

Cardiac troponin

Pathophysiology: cTn include troponin T (cTnT) and troponin I (cTnI), which are universally accepted markers of cardiac injury[9]. Cardiac troponin, a regulatory protein complex with three units, is located at the sarcomere thin filament. The inhibitory unit cTnI and a tropomyosin binding unit cTnT are responsible for maintaining a relaxed state when intracellular Ca2+ concentrations are low in diastole. In systole, the rise in intracellular Ca2+ leads to Ca2+ binding to cardiac troponin C (cTnC), releasing inhibition and promoting contraction and ejection[10].

Troponin as a diagnostic marker of cardiovascular injury in COVID-19: In the early phases of the pandemic caused by SARS-CoV-2, the emphasis was on lung damage and treatment of the same. Guidelines from AHA had recommended against the determination of cTnT and cTnI. However, this notion changed in 2020, when Chapman *et al*[11] published a statement strongly supporting the determination of serum cTnI and cTnT, emphasizing their role as biomarkers for cardiac injury in COVID-19 infected patients. Initially, the exact mechanism leading to serum elevations of these biomarkers was unclear, with several theories being proposed. Recent evidence showed direct infection of cardiac myocytes by SARS-CoV-2[12], leading to a decrease in Angiotensin-converting enzyme 2 (ACE2) and an increase in Angiotensin II (AngII). The dysfunctional signaling leads to necrosis or membrane instability, causing the leak of the bioenzymes[13]. Multiple additional studies[14-16] have reiterated the importance of cardiac troponin as a diagnostic tool and have been summarized in Table 1. Cardiac troponins have been reported to be elevated irrespective of the pattern of cardiac injury and clinical presentation. Levels have been reported to be higher among patients with an ischemic pattern of injury than in non-ischemic injury. The release of cTn has been seen in COVID-19 patients with acute coronary syndrome, tachyarrhythmias, cardiomyopathy, and myocarditis. In COVID-19, patients' cTn has been used as a marker of inflammation and myocardial injury. A large observational study from New York on patients hospitalized with SARS-CoV-2 showed a positive correlation between elevated cTnT and inflammatory markers[14].

Role of troponin as a prognostic indicator of cardiovascular outcomes in COVID-19: Sandoval *et al*[17] found higher levels of cTn in severe SARS-CoV-2 infection and opined that their serial measurement can aid in the risk stratification of COVID-19 patients. Based on the progression of the disease, they grouped COVID-19 patients in three phases; first - during admission where cTn elevation reflected the comorbidities; second - further rise in cTn with critical acute respiratory distress syndrome (ARDS) and; third - peak cTn with COVID-19 associated complications, including myocarditis and pulmonary embolism. Studies have shown that a high level of cTn and serial up-trending of cTn have been predictive of worse prognosis[18-20]. Troponin levels between 0.03 and 0.09 ng/mL were considered to be predictive of cardiac damage, with levels above 0.09 ng/mL conferring an even higher risk. A few studies utilising high sensitivity troponin have shown that troponin levels above 4 ng/L, 13 ng/L and 37 ng/L to be predictive of mild, severe and critical illness respectively[19]. Similarly, lower levels of cTn at presentation and a downward trend have been consistently reported among the survivors. Importantly COVID-19 patients with prior cardiovascular comorbidities have been at risk of further cardiovascular injury. Among these patients with cardiovascular comorbidities, cTn has been associated with further adverse prognosis.

Role of troponin on outcomes and mortality in COVID-19: Among patients with COVID-19, cTn was higher in deceased patients compared to survivors. Multiple studies have shown a significant correlation between cTn and in-hospital adverse events and mortality even in patients without comorbidities[14,21-28] (Table 1). Multiple studies show that cTnT and cTnI are independent predictors of mortality even after adjusting for confounding factors[29,30]. Scarl *et al*[21] reported that, in hospitalized patients with pre-existing comorbidities and SARS-CoV-2, there was a significant correlation between serum cTnI level and mortality. Salvatici *et al*[27] in their study utilising high sensitivity troponin, showed that in hospital survival rates was about 90% when cTnI was normal. The survival rate decreased to 87% when cTnI was above normal but less than 40 ng/L, and further reduced to 59%

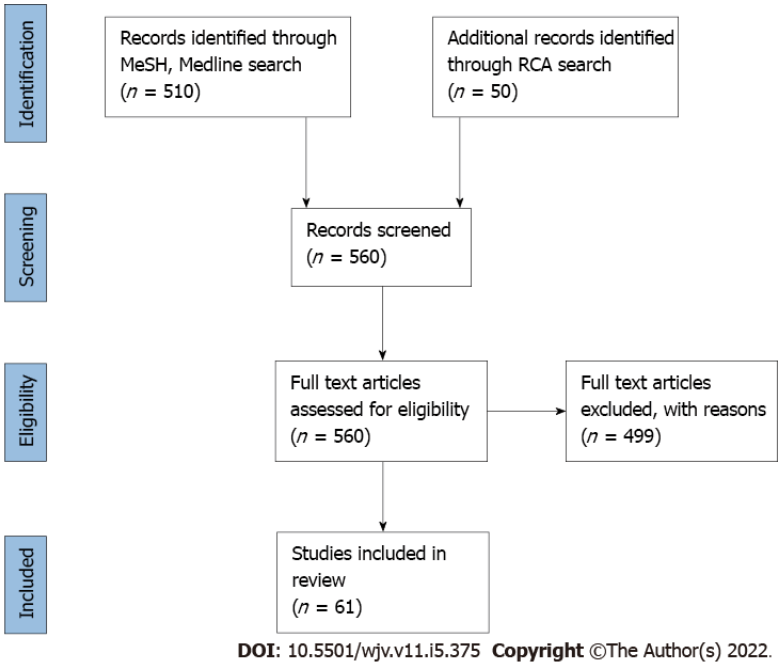
Table 1 Summary of studies characterizing the role of cardiac troponin

Study	Type of study	Location	Number of participants	Recommendation
Diagnostic and prognostic utility of troponin				
Lala *et al*[14], 2020	Single center, Observational	New York	2736	cTn elevated in patients with primary cardiac etiology including MI. Other etiologies included arrythmias, HF, myocarditis and Takotsubu cardiomyopathy
Khaloo *et al* [15], 2022	Multicenter, Retrospective	Massachusetts	2450	
Sandoval *et al* [17], 2020	Review			Serial cTn measurement aids in risk stratification
Almeida *et al* [18], 2020	Single center, Retrospective	Brazil	183	Elevated cTn measured within first 24 h is associated with worst prognosis. Increased need for MV
Maino *et al* [19], 2021	Single center, Retrospective	Italy	189	
Arcari *et al* [20], 2020	Multicenter, Observational	Italy	111	cTn elevation correlated with poor prognosis and need for MV
Role in outcome and mortality				
Scarl *et al*[21], 2021	Single center, Retrospective	Ohio	81	In patients with pre-existing comorbidities, CTnI elevation is associated with mortality
Lala *et al*[14], 2020	Single center, Observational	New York	2,736	Threefold increase in mortality in patients with cTnI three times the upper limit of normal
Mueller *et al* [22], 2021	Review			cTn elevation is associated with significant in hospital adverse events
Henein *et al* [23], 2021	Multicenter, Retrospective	International, mainly European	748	
Kermali *et al* [24], 2020	Systematic review	China	607	
Arcari *et al* [25], 2021	Multicenter, Retrospective	Italy	252	cTn significantly elevated in patients with pre-existing comorbidities, and is associated with increased mortality
Lombardi *et al*[26], 2020	Multicenter,Cross sectional	Italy	614	Elevation in cTn associated with mortality. 45.3% patients had elevated cTn and correlated with 71% increase in mortality, and a 2-fold increase in additional complications inlcuding sepsis, PE, AKI
Salvatici *et al* [27], 2020	Single center, Retrospective	Italy	523	cTnT and cTnI remain independent predictors of mortality even after adjusting for potential confounders
Al Abbasi *et al*[28], 2020	Single center, Retrospective	Florida	257	Elevated cTnI in the first 24 h of admission had a significantly higher in hospital mortality, with 89.7% negative predictive value

cTn: Cardiac troponin; cTnT: Troponin T; cTnI: Troponin I; HF: Heart failure; MV: Mechanical ventilation; PE: Pulmonary embolism; AKI: Acute kidney injury.

with cTnI above 40 ng/L. These studies have shown that cTn drawn at admission had a high positive predictive value for serious illness and a high negative predictive value for death. An up-trending cTn among COVID-19 patients is shown to correlate with a twofold increase in complications including sepsis, pulmonary embolism, and acute kidney injury and a threefold increase in mortality. The level of cTn has been shown to correlate with the outcome within 24 h of hospital admission. A study from Florida showed that COVID-19 patients with elevated cTnI levels in the first 24 h of admission had a significantly higher in-hospital mortality as compared to those with a normal cTnI level[28]. Patients with a normal cTnI level at admission had a low risk of worse outcome demonstrating an 89.7% negative predictive value. Similar results were reported by two other studies showing an increased need for invasive mechanical ventilation and risk of death among patients with elevated cTn levels within the first 24 h of admission[18,19]. Therefore, measurement of cTnI after hospitalization for COVID-19, followed by longitudinal monitoring, can help clinicians intercept dynamic changes in the levels of cTnI as a surrogate marker of myocardial injury.

Troponin as a surrogate marker of cardiovascular dysfunction post-discharge in COVID-19: Elevated cTn has been associated with impaired left ventricular relaxation and decline in right ventricular function resulting in long-term sequelae. As a component of Long COVID-19, the persistence of cardiac injury has been reported in young patients following an acute COVID-19 episode until six months. A



DOI: 10.5501/wjv.v11.i5.375

Figure 1 PRISMA diagram of literature search and selection.

cross-sectional study of 144 patients who were followed up for 85 d after their recovery from SARS-CoV-2 showed that patients with baseline elevations in cTn had a higher incidence of dyspnea after discharge. These patients also had impaired diastolic dysfunction and elevated pulmonary artery (PA) pressures, as noted by echocardiography. They also had persistence of cTn until mid-follow-up[31]. A rise in the incidence of HF has also been seen in COVID-19 patients with elevated cTn in two large multicenter studies[15,26]. These studies signify that cTn can be used as diagnostic and prognostic tools for long-term cardiac outcomes related to SARS-CoV-2 infection in select subgroup of patients. Despite these observations, clinical judgment should be used to avoid any unnecessary diagnostic and therapeutic interventions triggered by the isolated cTn elevation.

Natriuretic peptides

Pathophysiology: Natriuretic peptides (NPs), including BNP and NT-proBNP, are quantitative biomarkers of hemodynamic myocardial stress and heart failure[32]. Brain natriuretic peptide is a preprohormone which is split into a single peptide and a propeptide (pro-BNP). Natriuretic peptides mediate their biological effects through guanylyl cyclase receptors [natriuretic peptide receptor (NPR)] A, B and C. Stress of the ventricular wall due to volume or pressure overload is the primary inducer of BNP synthesis, which acts on the kidney to induce natriuresis and diuresis[33] Natriuretic peptides are considered one of the initial diagnostic tools in acute HF patients. Historically, studies like TOPCAT[34] have supported its value, and over the past years, NT-proBNP has had a growing role in the standardization of the definition of HF.

Natriuretic peptides as a diagnostic marker of cardiovascular injury in COVID-19: Prior to the advent of SARS-CoV-2, multiple viral infections have been reported to induce HF due to direct viral invasion and pro-inflammatory cytokines leading to sympathetic activation. In SARS-CoV-2, elevation in NPs is a result of inflammatory overdrive, specifically interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1), which can lead to fulminant myocarditis. The rise in NPs is believed to be secondary to hypoxia and cardiac injury. In addition, widespread inflammation and decreased nitric oxide levels result in endothelial dysfunction, which causes heart failure symptoms. This can be a combination of pre-existing cardiac disease and the acute hemodynamic and hypoxemic stress related to COVID-19[32,35]. The use of vasopressor therapy, hypoxia-induced pulmonary vasoconstriction, inflammatory involvement of the myocardium, oxidative stress, and fibrin microthrombi in the vasculature contributes to the release of NPs[36-38]. Across multiple studies, NPs level were high among COVID-19 patients with and without HF. Higher levels of NPs have not been consistently shown to correlate with severe COVID-19 disease. Still, they have been shown to correlate with developing or worsening of heart failure in these patients (Table 2).

Role of natriuretic peptides as a prognostic indicator of cardiovascular complications in HF and COVID-19: In patients with COVID-19 and myocardial injury, the elevation of NPs has been reported consistently[7,36]. Mehra *et al*[39] suggested that in patients with COVID-19 and cardiac comorbidities,

Table 2 Summary of studies characterizing the role of natriuretic peptides

Study	Type of study	Location	Number of participants	Recommendation
Diagnostic and prognostic utility of natriuretic peptides				
Arcari *et al*[20], 2020	Multicenter, Observational	Italy	111	Positive correlation between the rise in NPs and COVID-19 disease severity. Half of these patients had their NP level above the upper limit of normal
Caro-Codón *et al*[40], 2021	Population	Spain	396	In patients with history of HF, elevation in NT-proBNP above the cut-off for normal suggested development of acute HF
Gao *et al*[41], 2020	Multicenter, Prospective	China	402	This study proposed a triple cut point strategy of NT-proBNP (HF unlikely if NT-proBNP < 300pg/L, grey zone 300-900 pg/L and HF likely if > 900 pg/L) for its role in developing acute HF and in determining prognosis. Thirty day mortality in HF group was 40.8%.
Sorrentino *et al* [42], 2020	Meta-analysis of 13 observational studies		2248	Natriuretic peptides have significant prognostic importance in predicting severity of COVID-19
Yoo *et al*[43], 2021	Single center, Retrospective cohort	New York	679	In patients without a history of HF, elevated admission NT-proBNP correlated with fewer hospital free, ICU free and ventilator free days compared to those with low NT-proBNP levels
Alvarez-Garcia *et al*[44], 2020	Single center, Retrospective	New York	6439	No difference identified in the level of NP and COVID-19 disease severity
Dawson *et al* [45], 2020	Meta-analysis	China	12 studies included	
Abdeen *et al* [46], 2021	Single center, Retrospective	New Jersey	230	
Role in outcome and mortality				
Gao *et al*[48], 2020	Single center, Retrospective	China	102	Natriuretic peptides independently associated with in-hospital mortality in severe COVID-19 patients. The cut off value predicting in hospital death was 88.64 pg/mL with a 100% sensitivity and 66.7% specificity.
Caro-Codón *et al*[40], 2021	Population	Spain	396	Elevations in NP correlated with in-hospital mortality, even after adjusting for relevant confounders
Calvo-Fernández A *et al*[49], 2021	Single center, Retrospective	Spain	872	Natriuretic peptide elevation is independently related to death or mechanical ventilation in COVID-19 patients
Selcuk *et al*[50], 2021	Single center, Retrospective	Istanbul	137	Among patients who did not have a baseline diagnosis of HF, NPs were independent predictors of mortality. This study used a cut off threshold of 260pg/ml predicting an in-hospital mortality with 82% sensitivity and 93% specificity
Iorio *et al*[51], 2022	Multicenter, Retrospective observational	Italy	341	The level of NP elevation correlated with mortality. Cut off threshold used in this study is 2598 pg/L predicting a 30-d mortality with 91.7% sensitivity and an 80% specificity
Belarte-Tornero *et al*[52], 2021	Single center, Retrospective	Spain	129	
Dalia *et al*[53], 2021	Systematic review	India	5967	Patients with fulminant COVID-19 and elevated NPs had an eight-fold increased risk of acute cardiac injury and death when compared to their counterparts
Pranata *et al* [54], 2020	Meta analysis		967	In patients with HF, natriuretic peptide elevation is associated with disease progression and mortality. This effect was seen even after adjustment for troponin and CKMB
Iorio *et al*[51], 2022	Multicenter, Retrospective observational	Italy	341	The combined effect of cTn and NT-proBNP was studied in COVID-19 patients. Irrespective of prior HF history, increased mortality was seen in patients with both biomarker elevation. In patients with only one biomarker elevation, case fatality higher in patients with NP elevation
Stefanini *et al* [55], 2020	Single center, Retrospective	Italy	397	

NP: Natriuretic peptide; NT-proBNP: N terminal pro-brain natriuretic peptide; HF: Heart failure; cTn: Cardiac troponin; COVID-19: Corona virus disease 2019.

the earliest manifestation of cardiac decompensation is due to diastolic dysfunction. This is secondary to hemodynamic instability and pulmonary complications in the early course of the disease. Subsequently, because of cytokine storm, systolic dysfunction ensues. A large multicenter study from Italy showed a

positive correlation between the rise in NPs and associated SARS-CoV-2 severity[20]. Half of the patients in this study had their NP level above the upper limit of normal. Similar results were reported from a large meta-analysis of 13 observational studies, including 2248 patients. The average NT-proBNP among COVID-19 patients with severe disease was 791 pg/mL, *vs* 160 pg/mL in non severe patients [42]. In patients with pre-existing HF and COVID-19, an elevation of NT-proBNP above the cut-off for normal[32] suggested an acute decompensation of HF, leading to a prolonged hospital stay[40]. Interestingly, in a different study from New York that included 679 patients without a history of HF, elevations in NT-proBNP correlated with longer ICU stay, hospital stay, and the increased need for mechanical ventilation[43]. Negative results were also seen in a few studies which did not identify any difference in the NP levels and COVID-19 severity[44-46]. These were however small studies, and given the lack of a diverse population, the results cannot be generalized.

Role of natriuretic peptide on outcomes and mortality in COVID-19: Heart failure per se is a significant risk factor for developing severe COVID-19[1,2,12]. In a series of 113 patients who died from SARS-CoV-2, HF was the most frequent cause of death after ARDS and sepsis[47]. In a large population study from Spain that enrolled patients with HF, elevation in NT-proBNP above the cut-off for normal was independently associated with mortality, even after adjusting for confounders[40]. Gao *et al*[48] reported an increased mortality in COVID-19 patients who had an elevated BNP above 88.64 pg/mL, with a 100% sensitivity and a 66.7% specificity. The significance of NPs in predicting mortality among SARS-CoV-2 patients is independent of their HF status. A single-center study with 137 patients without a prior diagnosis of HF showed that elevation of NPs is an independent predictor of mortality[50]. This study used a cut-off value of 260 pg/mL, predicting in-hospital mortality with 82% sensitivity and 93% specificity. It must be noted that the threshold used for NT-pro BNP in this study is lower than the cut-off used in the clinic and clinical trials for the diagnosis of HF. This implies that elevated NT-pro BNP levels even within the upper limit of the normal reference range could indicate an occult cardiac injury in COVID-19 patients. In patients with chronic HF, an elevated pro-BNP above suggested cut off of 2598 pg/mL was associated with an increased odds of 30 d mortality[52]. An extensive systematic review from India, including 5967 patients, found that non-survivors and patients with fulminant SARS-CoV-2 with elevated NPs, had an 8-fold increased risk of acute cardiac injury and death compared to their counterparts[53]. The average NT-proBNP across patients with severe COVID-19 was 1142 pg/mL. Two large center studies from Italy studied the combined role of troponins and NPs in COVID-19 associated disease progression and mortality. They found that patients with dual biomarker elevation had increased mortality, irrespective of their prior HF status[51,55].

Natriuretic peptides as a surrogate marker for new-onset heart failure post-discharge: Elevated NT-proBNP in COVID-19 patients without cardiac comorbidities indicates SARS-CoV-2 mediated cardiac complications. New-onset HF was seen in 23% of hospitalized patients with COVID-19 and was the most frequent cause of death after sepsis and ARDS[47]. A large prospective study in COVID-19 patients[56] used HFA-PEFF score (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology) with a specificity of 93% and a positive predictive value of 98% to rule in HFpEF. These patients had higher NT-proBNP levels when compared to their counterparts. Cardiac biomarkers are known to decline after the resolution of acute infection, as seen in ECHOVID-19 study[57]. On the contrary, persistent biomarker elevation despite infection resolution has been noted in two different studies[58,59]. They also had echocardiographic parameters of ventricular dysfunction. The exact cause of reduced ventricular myocardial function is unknown; however, it is presumed to be secondary to systemic inflammation and ventricular remodeling[60-62]. If the recovery is good, the prognosis is better, else, it predisposes them to the development of HF[63].

Additional biomarkers

Other biomarkers have also been implicated in determining prognosis and predicting mortality in patients with SARS-CoV-2. Significant elevations in creatine kinase MB (CK-MB) and NT-proBNP above the upper limit of normal are seen in critically ill patients with COVID-19, helping in risk stratification [64,65]. An increase in the level of myoglobin (MYO), NT-proBNP, and cTnI correlated with disease severity in patients with SARS-CoV-2[66]. Similar results were seen in two other studies identifying the prognostic significance of myoglobin, procalcitonin, and d-dimer in COVID-19[67,68]. Alongside troponin and natriuretic peptides, elevations in CK-MB and LDH (lactate dehydrogenase) have been shown to predict in-hospital mortality in patients with COVID-19[69]. Similarly, a rise in IL-6 and INR predicted an increased odds of 7-d mortality in patients admitted with SARS-CoV-2[64]. In addition, there is now data on novel emerging biomarkers and their role in predicting the disease severity in COVID-19. Among them, presepsin, growth differentiation factor 15 (GDF-15), soluble ST2, galectin 3, and copeptin have been studied.

Presepsin

Presepsin is a CD14 biomarker released into circulation by pro-inflammatory signals during infection. Through its interaction with T and B cells, it acts as an immunomodulator and has diagnostic and

prognostic significance in sepsis[70]. Its role has been implicated alongside natriuretic peptides in the diagnosis of HF. A single-center study with 506 patients showed that presepsin was elevated in patients with acute HF decompensation and correlated with their 6-month mortality[71]. Similar results were seen in another study, with higher presepsin levels correlating with longer ICU stay and increased mortality[72].

Role of presepsin in prognosis and outcomes in COVID-19: Presepsin elevation has been noted in patients with COVID-19, thus serving as a reliable biomarker[73]. Studies have shown a four-to-five-fold increase in serum presepsin, which correlates with disease severity when compared to their counterparts[74-76]. Fukada *et al*[77] in a small series of patients with COVID-19-related respiratory failure, found that presepsin is more expressed in severe cases than in mild cases. Similar results have been seen in other studies identifying the prognostic importance of presepsin with COVID-19 related disease severity[73,78]. Patients with presepsin values higher than 250 ng/L had a longer ICU stay when compared to the patients with lower values[78]. Park *et al*[74] suggested that an elevated presepsin level at 717 pg/mL is a significant predictor of 30-d mortality. A threefold rise in presepsin has been identified as a very specific indicator of 30-d mortality[75,79]. Thus, routine assessment of presepsin in COVID-19 may provide valuable clinical information for predicting adverse outcomes, as well as for guiding the clinical and therapeutic decision-making.

Soluble ST2

Soluble ST2 (sST2) is among the most important novel biomarkers for prognosis in HF. Upregulated in states of mechanical strain, it plays an essential role in myocardial hypertrophy and fibrosis. Studies have shown an increase in sST2 gene expression in the presence of cardiac injury. High circulating levels of sST2 are involved in the aberrant inflammatory process of ARDS and have also been linked to acute and chronic HF, myocardial infarction, sepsis, and fibrosis[80]. Among patients with ARDS, sST2 elevations up to ten times the normal expected for HF has been seen, and this correlated with an increase in their mortality[81,82]. As evident in PRIDE study, among the 593 patients admitted with acute dyspnea, sST2 concentrations were higher among those with acute HF[79]. NT-proBNP however outperformed sST2 for acute HF diagnosis (AUC = 0.94 *vs* 0.80; $P < 0.001$). In patients with HFpEF, Manzano-Fernández *et al*[83] showed sST2 to be superior to NT-proBNP for prognosis. In addition, it also strongly correlated to the 30-d, one-year, and four-year mortality. Rehman *et al*[84] found that values of sST2 correlated with the severity of HF, making it a powerful predictor of mortality. Lassus *et al*[85] showed that in patients with pre-existing HF, sST2, relative to other biomarkers, is a powerful variable for one-year mortality. Similarly, Breidthardt *et al*[86] reported that a dynamic change in sST2 value from admission to discharge was a stronger predictor of mortality than baseline values alone.

Role of sST2 in prognosis and outcomes in COVID-19: Soluble ST2 is linked to SARS-CoV-2 viremia and indicators of inflammation, cardiovascular disease, and thrombosis. Omland *et al*[87] found an association between sST2 and disease severity among patients hospitalized for COVID-19 and was independent of established risk factors. Elevated ST2 concentrations above 37.9 ng/mL correlated with severe disease, with non-survivors having concentration as high as 107 ng/mL. Similar results were seen by Huang *et al*[88] and Ragusa *et al*[89], who concluded that sST2 is an important COVID-19 prognostic marker and correlated with disease severity. This association was deemed secondary to pulmonary fibrosis, seen as a complication in COVID-19. Elevations in sST2 Levels strongly correlated with mortality in ICU patients with sepsis secondary to COVID-19[87,90]. Omland *et al*[87] also noted that elevations in sST2 correlated with poor outcomes on days 3 and 9 of hospitalization among patients with COVID-19.

Galectin-3

Galectin-3 (GAL-3) is a mineralocorticoid receptor-regulated pro-inflammatory molecule. It exhibits a pleiotropic role in mediating infection and inflammation. Gal-3 is a biomarker of fibrosis and inflammation and has been implicated in the development and progression of HF[91]. ARDS is chiefly mediated by releasing IL-1, IL-6, and TNF-α from macrophages, monocytes, and dendritic cells[92]. Gal-3 inhibition has been shown to reduce the release of these cytokines from immune cells[93]. The PRIDE study showed that higher galectin-3 concentration was a strong independent predictor of 60-d mortality and recurrent HF admissions[94]. Shah *et al*[95] showed that galectin-3 above a median value of 15.0 had a strong prognostic significance in HF and was a significant predictor of 4-year mortality.

Role of galectin-3 in prognosis and outcomes in COVID-19: Multiple studies have shown Gal-3 to be upregulated in patients suffering from severe COVID-19. Among patients with COVID-19, Gal-3 was shown to be considerably higher in bronchoalveolar immune cells in patients with severe disease when compared to those with mild disease[96]. Higher galectin-3 levels were found to be a major predictor of 60-d mortality and recurrent HF hospitalizations. In a study of SARS-CoV-2 associated ARDS patients, high Gal-3 above 35.3 ng/mL was linked to worse outcomes and shorter survival[97].

Copeptin

Copeptin is a surrogate marker for vasopressin release. Copeptin is an arginine-vasopressin (AVP) glycopeptide composed of 39 amino acids. It is released from the neurohypophysis by osmotic or hemodynamic stimulation with AVP, and its plasma levels correlate well. AVP is an antidiuretic and vasoconstrictive hormone. It shows the endogenous stress response and is released by stimuli including hypotension, hypoxia, and infections. However, its circadian rhythm, short half-life, and unstable molecule make it impossible to use it as a biomarker[98]. Copeptin is a more stable peptide, and its level in the blood can be easily detected. The role of copeptin has been implicated in chronic HF. Elevated copeptin levels, especially in HF patients with hyponatremia, has been linked to poor outcomes. Maisel *et al*[99] noted that patients with elevated copeptin levels had a greater risk of 90-d mortality and HF readmission.

Role of copeptin in prognosis and outcomes in COVID-19: The importance of copeptin as a biomarker in COVID-19 patients has not been very well studied. Gregoriano *et al*[100] found that the rise in copeptin levels correlated with the disease severity in COVID-19 patients. Copeptin level of 20 pmol/L had an 88.2% sensitivity and a 64.9% specificity for identifying severe disease. Similar results were seen by Hammad *et al*[101] by using a cut off level of 18.5 pmol/L, yielding a sensitivity of 93.3% and a specificity of 100% for severe COVID-19 disease. In these studies, patients with severe COVID-19 disease were also noted to have increased mortality.

Growth differentiation factor 15

Growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine (MIC-1), is a member of the transforming growth factor-beta (TGF-β) superfamily that helps tissues survive inflammatory stress. GDF-15 expression outside the reproductive organs is low to absent; it is upregulated in pathological conditions that involve inflammation or oxidative stress, including cancer, cardiovascular, pulmonary, and renal disease[102].

Role of GDF-15 in prognosis and outcomes in COVID-19: In a study of 84 patients with COVID-19, Apfel *et al*[103] determined that higher circulating levels of GDF-15 correlated with the disease severity. Patients with COVID-19 had an average GDF-15 level of 2051 pg/mL when compared to 582 pg/mL in non COVID patients. GDF-15 levels were higher in patients requiring mechanical ventilation and correlated with increasing oxygen requirements. In a different study by Verhamme *et al*[102], higher GDF-15 Levels were associated with increased mortality risk. Figure 2 illustrates the variation of different cardiac bioenzymes across different etiologies for cardiovascular dysfunction.

RESULTS

A total of 560 papers were identified after extensive literature review, as depicted in the PRISMA diagram (Figure 1). Among them, 61 papers were eligible to be included in the review. Cardiac troponin and natriuretic peptides were the most extensively studied of the bioenzymes. The evidence of cardiac troponin as a diagnostic marker for cardiovascular injury in COVID-19 is robust and has been shown on thousands (n = 11290) of patients worldwide, in both prospective and retrospective studies (Table 1). A consistently elevated level of cTn has been reported in COVID-19 patients with mild myocarditis to severe cardiogenic shock. Multiple studies have shown that troponin levels above the 99th percentile of upper limit of normal, to be associated with worse prognosis. Elevated cTn has been shown to correlate with severe disease, higher oxygen requirement, ARDS, the need for respiratory support including noninvasive and invasive mechanical ventilation, the requirement of intensive care unit admission, acute kidney injury, multiorgan failure, sepsis, pulmonary embolism, major bleeding and in-hospital mortality (Table 1). Troponin levels elevated five times the upper limit of normal have shown a 2.5% increase in in-hospital mortality. NPs are the second most studied cardiac biomarker in studies reporting cardiac injury in patients with COVID-19. Multiple studies have echoed a significant positive correlation between the rise in natriuretic peptides and disease severity in SARS-CoV-2[20,40-43] (summary in Table 2). Many of these studies have utilised the cutoff points for NT-proBNP based off the triple cut point strategy from European society guidelines[32] . In patients with pre-existing HF, natriuretic peptides have been independently associated with increased odds of the need for mechanical ventilation and death across studies[40,48-55] (Table 2). Novel biomarkers including presepsin, copeptin, soluble ST2 and galectin have also been implicated as prognostic markers in COVID-19, as detailed in Table 3.

DISCUSSION

SARS-CoV-2 associated COVID-19 infection is a global disease with multiple clinical manifestations. Cardiovascular complications are a dreaded outcome, and assessment of cardiac bio enzymes is crucial

Table 3 Summary of studies characterizing the role of novel biomarkers in prognosis and outcomes in COVID-19

Biomarker in COVID	Study	Recommendation
Presepsin	Favaloro *et al*[73]	Presepsin elevation is a reliable biomarker in COVID-19
	Park *et al*[74]	A four-to-five-fold increase in presepsin correlates with disease severity in COVID-19
	Lippi *et al*[75]	
	Koyjit *et al*[73]	
	Fukada *et al*[77]	Presepsin is elevated in severe cases of SARS-CoV-2 associated respiratory complications
	Park *et al*[74]	Presepsin level at 717pg/ml is a significant predictor of 30-day mortality
	Dell'Aquila *et al*[79]	A threefold rise in presepsin has been identified as a very specific indicator of 30-day mortality
	Lippi *et al*[75]	
Soluble ST2 (sST2)	Omland *et al*[87]	Robust association between baseline sST2 level and disease severity along with poor outcome
	Huang *et al*[88]	Baseline sST2 is associated with a worse prognosis
	Ragusa *et al*[89]	Circulating level of sST2 can be used as a discharge prognosticator
Galectin-3	Caniglia *et al*[96]	Gal-3 is considerably higher in bronchoalveolar immune cells in patients with severe COVID-19 disease
	Portacci *et al*[97]	Higher galectin-3 is associated with worse outcomes and shorter survival
Copeptin	Gregoriano *et al* [100]	Serum copeptin level above 20 Pmol/L had sensitivity of > 88% to predict severe COVID-19
	Hammad *et al*[101]	Serum copeptin level above 18.5 Pmol/L had sensitivity of > 93% and specificity of 100% to predict severe COVID-19
GDF 15	Apfel *et al*[103]	Higher levels of GDF-15 correlated with severity of COVID-19

Gal-3: Galectin-3; GDF-15: Growth differentiation factor 15; sST2: Soluble ST2.

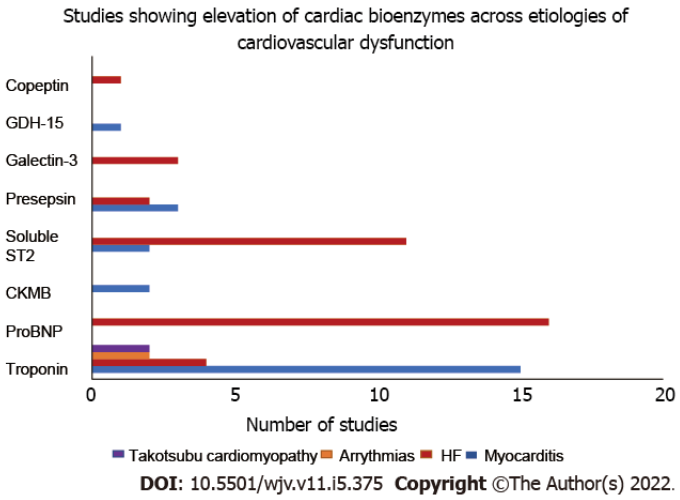


Figure 2 Studies showing elevation of cardiac bioenzymes across different etiologies of cardiovascular dysfunction.

in gauging the disease severity. Our review aims at highlighting the variation in these bio enzymes through the disease process and their role in predicting outcomes.

Troponin has been seen as a robust indicator of cardiovascular injury across aetiologies including myocarditis, coronary syndromes, and cardiomyopathy. Serum cTn above 0.09 ng/mL have been shown to confer a higher risk of cardiovascular injury. Generally, studies have shown that troponin levels above the 99th percentile of upper limit of normal are associated with a worse prognosis. Elevated levels on admission, and serial up-trending carry a high positive predictive value for worse prognosis. Furthermore, long term sequelae with impaired ventricular function and subsequent development of heart failure is seen in a select subset of patients with cTn elevation[103]. Alongside cTn, natriuretic peptides help in prognostication mainly in patients with HF. Elevations in levels above cut off for

normal[32] have been associated with worse outcomes. Multiple different studies citing the utility of NPs have been included in this review, and each of them had a unique cut off for HF. Irrespective of the cut-off used, elevated NT-proBNP was independently associated with poor outcomes regardless of the HF status[104]. This finding was common across studies.

The role of a few of these cardiac biomarkers has been studied before. However, our review is unique in its discussion about the role of novel biomarkers including presepsin, soluble ST2, galectin-3 which have not been studied extensively yet. Prior studies have highlighted their importance in HF, but not so much in COVID-19. Our review has consolidated these studies, to mention that these biomarkers, similar to troponin and NPs are elevated in patients with severe COVID-19 and can aid in prognosis [105,106].

Our study has a few limitations too. Majority of the studies that have been included are from China and European countries. This is partly because many studies were originally from Wuhan China, where the pandemic began, opening a possibility that many patients would have been repeated across studies. Another limitation is the nature of these studies, majority were retrospective or observational in nature. The trend of these bio enzymes could not be followed in patients who recovered from the illness. Small sample size of a few of these studies also precludes the generalisability. Hence future large prospective studies with follow up will be beneficial, especially for novel biomarkers.

CONCLUSION

SARS-CoV-2 associated COVID-19 infection undeniably has respiratory complications, however, extensive cardiovascular implications are also seen. Multiple cardiac biomarkers can help predict the severity of the disease and serve as prognostic indicators for outcomes and mortality. Assessment of cardiac bioenzymes at admission and their serial monitoring can help assess the severity of disease and predict mortality in patients with SARS-CoV-2 infection. A more liberal determination of cardiac biomarkers may improve early diagnosis and management of AHF, and other cardiovascular complications. COVID-19 associated myocarditis and HF have sequential effects even after the resolution of primary illness, and hence long-term correlation needs to be studied. In addition, there is emerging data on novel biomarkers, including growth GDF-15, soluble ST2, galectin 3, presepsin, and copeptin, which can aid in evaluation alongside natriuretic peptides and troponins. Further studies are needed to elude the critical importance of these novel markers.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is prevalent worldwide. Though lung injury is the most common presentation, cardiovascular dysfunction is seen on account of the widespread inflammation.

Research motivation

Cardiac biomarkers are released secondary to cardiovascular injury, and can be used as surrogate markers to gauge the disease severity.

Research objectives

To identify the role of individual biomarkers in diagnosing cardiac injury, and implications in determining prognosis and mortality.

Research methods

An extensive literature search was conducted for all studies on patients with COVID-19 associated cardiovascular injury and cardiac bioenzymes. Articles were screened using PubMed/Medline database, additionally reference citation analysis tool was also used. Eligible articles were then included in the study.

Research results

Cardiac troponin was seen as a robust diagnostic marker of cardiovascular injury across studies. Elevated troponin levels correlated with the level of disease severity. Similar results were seen alongside elevations in natriuretic peptides, irrespective of their prior diagnosis of heart failure.

Research conclusions

Multiple cardiac biomarkers can help predict the severity of disease and serve for prognostication purposes. Assessment of bioenzymes at admission and their serial monitoring can help predict

mortality in patients with COVID-19.

Research perspectives

New data is emerging on novel biomarkers including soluble ST2, galectin-3, presepsin and copeptin which can further aid in diagnostic evaluation alongside troponins and natriuretic peptides.

FOOTNOTES

Author contributions: Mishra AK and Muthyala A contributed to the conceptual design of the study; Muthyala A and Sasidharan S independently screened the articles and extracted the data; Muthyala A, Sasidharan S, Mishra AK contributed to write-up and submission of the study; Mishra AK, John KJ and Lal A reviewed the final manuscript; all authors reviewed and agreed with the final content of the article.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: United States

ORCID number: Anjani Muthyala 0000-0002-2287-9285; Sandeep Sasidharan 0000-0002-9513-2713; Kevin John John 0000-0003-3382-0294; Amos Lal 0000-0002-0021-2033; Ajay K Mishra 0000-0003-4862-5053.

S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

REFERENCES

1 **Inciardi RM**, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac Involvement in a Patient with Coronavirus Disease 2019 (COVID-19). *JAMA Cardio* 2020; **5**: 819-824
2 **Zeng JH**, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection* 2020; **48**: 773-777
3 **Hu H**, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. *Eur Heart J* 2021; **42**: 206 [PMID: 32176300 DOI: 10.1093/eurheartj/ehaa190]
4 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422
5 **Zheng YY**, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020; **17**: 259-260 [PMID: 32139904 DOI: 10.1038/s41569-020-0360-5]
6 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506
7 **Guo T**, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 811-818 [PMID: 32219356 DOI: 10.1001/jamacardio.2020.1017]
8 **Aleksova A**, Sinagra G, Beltrami AP, Pierri A, Ferro F, Janjusevic M, et al. Biomarkers in the management of acute heart failure: state of the art and role in COVID-19 era. *ESC Heart Fail* 2021; **8**: 4465-4483
9 **Solaro CR**, Solaro RJ. Implications of the complex biology and micro-environment of cardiac sarcomeres in the use of high affinity troponin antibodies as serum biomarkers for cardiac disorders. *J Mol Cell Cardiol* 2020; **143**: 145-158 [PMID: 32442660 DOI: 10.1016/j.yjmcc.2020.05.010]
10 **Kobayashi T**, Solaro RJ. Calcium, thin filaments, and the integrative biology of cardiac contractility. *Annu Rev Physiol* 2005; **67**: 39-67 [PMID: 15709952 DOI: 10.1146/annurev.physiol.67.040403.114025]
11 **Chapman AR**, Bularga A, Mills NL. High-Sensitivity Cardiac Troponin Can Be an Ally in the Fight Against COVID-19. *Circulation* 2020; **141**: 1733-1735 [PMID: 32251612 DOI: 10.1161/CIRCULATIONAHA.120.047008]
12 **Tavazzi G**, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020; **22**: 911-915
13 **Solaro RJ**, Rosas PC, Langa P, Warren CM, Wolska BM, Goldspink PH. Mechanisms of troponin release into serum in cardiac injury associated with COVID-19 patients. *Int J Cardiol Cardiovasc Dis* 2021; **1**: 41-47 [PMID: 34734211 DOI: 10.46439/cardiology.1.006]

14 **Lala A**, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* 2020; **76**: 533-546

15 **Khaloo P**, Shaqdan A, Ledesma PA, Uzomah UA, Galvin J, Ptaszek LM, et al. Distinct etiologies of high-sensitivity troponin T elevation predict different mortality risks for patients hospitalized with COVID-19. *Int J Cardiol* 2022; **351**: 118-125

16 **Rezabakhsh A**, Sadat-Ebrahimi SR, Ala A, Nabavi SM, Banach M, Ghaffari S. A close-up view of dynamic biomarkers in the setting of COVID-19: Striking focus on cardiovascular system. *J Cell Mol Med* 2022; **26**: 274-286 [PMID: 34894069 DOI: 10.1111/jcmm.17122]

17 **Sandoval Y**, Januzzi JL Jr, Jaffe AS. Cardiac Troponin for Assessment of Myocardial Injury in COVID-19: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020; **76**: 1244-1258 [PMID: 32652195 DOI: 10.1016/j.jacc.2020.06.068]

18 **Almeida Junior GLG**, Braga F, Jorge JK, Nobre GF, Kalichsztein M, Faria PMP, Bussade B, Penna GL, Alves VO, Pereira MA, Gorgulho PC, Faria MRDSE, Drumond LE, Carpinete FBS, Neno ACLB, Neno ACA. Prognostic Value of Troponin-T and B-Type Natriuretic Peptide in Patients Hospitalized for COVID-19. *Arq Bras Cardiol* 2020; **115**: 660-666 [PMID: 33111866 DOI: 10.36660/abc.20200385]

19 **Maino A**, Di Stasio E, Grimaldi MC, Cappannoli L, Rocco E, Vergallo R, et al. Prevalence and characteristics of myocardial injury during COVID-19 pandemic: A new role for high-sensitive troponin. *Int J Cardiol* 2021; **338**: 278-285

20 **Arcari L**, Luciani M, Cacciotti L, Musumeci MB, Spuntarelli V, Pistella E, et al. Incidence and determinants of high-sensitivity troponin and natriuretic peptides elevation at admission in hospitalized COVID-19 pneumonia patients. *Intern Emerg Med* 2020; **15**: 1467-1476

21 **Scarl RT**, Balada-LIasat JM, Nowacki N, Solaro RJ, Williams J, Li J. Myocardial Injury, Inflam-mation and Prothrombotic Response Are Associated with Outcomes of COVID-19 Patients. *Ann Cardiol Vasc Med* 2021; **4**: 1041 [DOI: 10.26502/fccm.92920125]

22 **Mueller C**, Giannitsis E, Jaffe AS, Huber K, Mair J, Cullen L. Cardiovascular biomarkers in patients with COVID-19. *Eur Heart J Acute Cardiovasc Care* 2021; **10**: 310-319 [DOI: 10.1093/ehjacc/zuab009]

23 **Henein MY**, Mandoli GE, Pastore MC, Ghionzoli N, Hasson F, Nisar MK. Biomarkers Predict In-Hospital Major Adverse Cardiac Events in COVID-19 Patients: A Multicenter International Study. *J Clin Med* 2021; **10**: 5863

24 **Kermali M**, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci* 2020; **254**: 117788 [PMID: 32475810 DOI: 10.1016/j.lfs.2020.117788]

25 **Arcari L**, Luciani M, Cacciotti L, Pucci M, Musumeci MB, Pietropaolo L. Coronavirus disease 2019 in patients with cardiovascular disease: clinical features and implications on cardiac biomarkers assessment. *J Cardio Med* 2021; **22** Available from: https://journals.lww.com/jcardiovascularmedicine/Fulltext/2021/11000/Coronavirus_disease_2019_in_patients_with.6.aspx

26 **Lombardi CM**, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia LA, Giovinazzo S, Maccagni G, Mapelli M, Margonato D, Monzo L, Nuzzi V, Oriecuia C, Peveri G, Pozzi A, Provenzale G, Sarullo F, Tomasoni D, Ameri P, Gnecchi M, Leonardi S, Merlo M, Agostoni P, Carugo S, Danzi GB, Guazzi M, La Rovere MT, Mortara A, Piepoli M, Porto I, Sinagra G, Volterrani M, Specchia C, Metra M, Senni M. Association of Troponin Levels With Mortality in Italian Patients Hospitalized With Coronavirus Disease 2019: Results of a Multicenter Study. *JAMA Cardiol* 2020; **5**: 1274-1280 [PMID: 32845276 DOI: 10.1001/jamacardio.2020.3538]

27 **Salvatici M**, Barbieri B, Cioffi SMG, Morenghi E, Leone FP, Maura F. Association between cardiac troponin I and mortality in patients with COVID-19. *Biomarkers* 2020; **25**: 634-640

28 **Al Abbasi B**, Torres P, Ramos-Tuarez F, Dewaswala N, Abdallah A, Chen K. Cardiac Troponin-I and COVID-19: A Prognostic Tool for In-Hospital Mortality. *Cardiol Res* 2020; **11**: 398-404

29 **Ghossein MA**, Driessen RGH, van Rosmalen F, Sels JWEM, Delnoij T, Geyik Z. Serial Assessment of Myocardial Injury Markers in Mechanically Ventilated Patients With SARS-CoV-2 (from the Prospective MaastrICCht Cohort). *Am J Cardiol* 2022; **170**: 118-127

30 **Laouan Brem F**, Chaymae M, Rasras H, Merbouh M, Bouazzaoui MA, Bkiyar H, Abda N, Zakaria B, Ismaili N, Housni B, El Ouafi N. Acute Myocardial Injury Assessed by High-Sensitive Cardiac Troponin Predicting Severe Outcomes and Death in Hospitalized Patients with COVID-19 Infection. *Clin Appl Thromb Hemost* 2022; **28**: 10760296221090227 [PMID: 35360970 DOI: 10.1177/10760296221090227]

31 **Italia L**, Ingallina G, Napolano A, Boccellino A, Belli M, Cannata F. Subclinical myocardial dysfunction in patients recovered from COVID-19. *Echocardiography* 2021; **38**: 1778-1786

32 **Mueller C**, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019; **21**: 715-731

33 **Schlueter N**, de Sterke A, Willmes DM, Spranger J, Jordan J, Birkenfeld AL. Metabolic actions of natriuretic peptides and therapeutic potential in the metabolic syndrome. *Pharmacol Ther* 2014; **144**: 12-27 [PMID: 24780848 DOI: 10.1016/j.pharmthera.2014.04.007]

34 **Myhre PL**, Vaduganathan M, Claggett BL, Anand IS, Sweitzer NK, Fang JC, O'Meara E, Shah SJ, Desai AS, Lewis EF, Rouleau J, Pitt B, Pfeffer MA, Solomon SD. Association of Natriuretic Peptides With Cardiovascular Prognosis in Heart Failure With Preserved Ejection Fraction: Secondary Analysis of the TOPCAT Randomized Clinical Trial. *JAMA Cardiol* 2018; **3**: 1000-1005 [PMID: 30140899 DOI: 10.1001/jamacardio.2018.2568]

35 **Mueller C**, Laule-Kilian K, Frana B, Rodriguez D, Scholer A, Schindler C, Perruchoud AP. Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. *Am Heart J* 2006; **151**: 471-477 [PMID: 16442916 DOI: 10.1016/j.ahj.2005.03.036]

36 **Shi S**, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802-810 [PMID: 32211816 DOI: 10.1001/jamacardio.2020.0950]

37 **Thomas-Rüddel D**, Winning J, Dickmann P, Ouart D, Kortgen A, Janssens U, Bauer M. Coronavirus disease 2019

(COVID-19): update for anesthesiologists and intensivists March 2020. *Anaesthesist* 2021; **70**: 1-10 [PMID: 32211920 DOI: 10.1007/s00101-020-00760-3]

38 **Bois MC**, Boire NA, Layman AJ, Aubry MC, Alexander MP, Roden AC. COVID-19-Associated Nonocclusive Fibrin Microthrombi in the Heart. *Circulation* 2021; **143**: 230-243

39 **Mehra Mandeep R**, Ruschitzka Frank. COVID-19 Illness and Heart Failure. *JACC: Heart Failure* 2020; **8**: 512-514

40 **Caro-Codón J**, Rey JR, Buño A, Iniesta AM, Rosillo SO, Castrejon-Castrejon S. Characterization of NT-proBNP in a large cohort of COVID-19 patients. *Eur J Heart Fail* 2021; **23**: 456-464

41 **Gao W**, Fan J, Sun D, Yang M, Guo W, Tao L, Zheng J, Zhu J, Wang T, Ren J. Heart Failure Probability and Early Outcomes of Critically Ill Patients With COVID-19: A Prospective, Multicenter Study. *Front Cardiovasc Med* 2021; **8**: 738814 [PMID: 34901205 DOI: 10.3389/fcvm.2021.738814]

42 **Sorrentino S**, Cacia M, Leo I, Polimeni A, Sabatino J, Spaccarotella CAM. B-Type Natriuretic Peptide as Biomarker of COVID-19 Disease Severity-A Meta-Analysis. *J Clin Med* 2020; **9**: 2957

43 **Yoo J**, Grewal PK, Hotelling J, Papamanoli A, Cao K, Dhaliwal S. Admission Nt_proBNP and outcomes in patients without history of heart failure hospitalized with COVId_19. *ESC Heart Fail* 2021; **8**: 4278-4287

44 **Alvarez-Garcia J**, Lee S, Gupta A, Cagliostro M, Joshi AA, Rivas-Lasarte M. Prognostic Impact of Prior Heart Failure in Patients Hospitalized With COVID-19. *J Am Coll Cardiol* 2020; **76**: 2334-2348

45 **Dawson D**, Dominic P, Sheth A, Modi M. Prognostic value of Cardiac Biomarkers in COVID-19 Infection: A Meta-analysis. *Res Sq* 2020 [PMID: 32702736 DOI: 10.21203/rs.3.rs-34729/v1]

46 **Abdeen Y**, Kaako A, Alnabulsi M, Okeh A, Meng W, Miller R. The prognostic effect of brain natriuretic peptide levels on outcomes of hospitalized patients with COVID-19. *Avicenna J Med* 2021; **11**: 20-26 [PMID: 33520785 DOI: 10.4103/ajm.ajm_169_20]

47 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: 32217556 DOI: 10.1136/bmj.m1091]

48 **Gao L**, Jiang D, Wen XS, Cheng XC, Sun M, He B. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res* 2020; **21**: 83-83

49 **Calvo-Fernández A**, Izquierdo A, Subirana I, Farré N, Vila J, Durán X, García-Guimaraes M, Valdivielso S, Cabero P, Soler C, García-Ribas C, Rodríguez C, Llagostera M, Mojón D, Vicente M, Solé-González E, Sánchez-Carpintero A, Tevar C, Marrugat J, Vaquerizo B. Markers of myocardial injury in the prediction of short-term COVID-19 prognosis. *Rev Esp Cardiol (Engl Ed)* 2021; **74**: 576-583 [PMID: 33153955 DOI: 10.1016/j.rec.2020.09.011]

50 **Selcuk M**, Keskin M, Cinar T, Gunay N, Dogan S, Cicek V, et al. Prognostic significance of N-Terminal Pro-BNP in patients with COVID-19 pneumonia without previous history of heart failure. *Eur Heart J* 2021; **42**: ehab724.0866

51 **Iorio A**, Lombardi CM, Specchia C, Merlo M, Nuzzi V, Ferraro I, Peveri G, Oriecuia C, Pozzi A, Inciardi RM, Carubelli V, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia L, Giovinazzo S, Maccagni G, Mapelli M, Margonato D, Monzo L, Provenzale G, Sarullo F, Tomasoni D, Ameri P, Gnecchi M, Leonardi S, Agostoni P, Carugo S, Danzi GB, Guazzi M, La Rovere MT, Mortara A, Piepoli M, Porto I, Volterrani M, Sinagra G, Senni M, Metra M. Combined Role of Troponin and Natriuretic Peptides Measurements in Patients With Covid-19 (from the Cardio-COVID-Italy Multicenter Study). *Am J Cardiol* 2022; **167**: 125-132 [PMID: 35063263 DOI: 10.1016/j.amjcard.2021.11.054]

52 **Belarte-Tornero LC**, Valdivielso-Moré S, Vicente Elcano M, Solé-González E, Ruíz-Bustillo S, Calvo-Fernández A. Prognostic Implications of Chronic Heart Failure and Utility of NT-proBNP Levels in Heart Failure Patients with SARS-CoV-2 Infection. *J Clin Med* 2021; **10**: 323

53 **Dalia T**, Lahan S, Ranka S, Acharya P, Gautam A, Goyal A, et al. Impact of congestive heart failure and role of cardiac biomarkers in COVID-19 patients: A systematic review and meta-analysis. *Indian Heart J* 2021; **73**: 91-98

54 **Pranata R**, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. *Postgrad Med J* 2020; **96**: 387-391 [PMID: 32434874 DOI: 10.1136/postgradmedj-2020-137884]

55 **Stefanini GG**, Chiarito M, Ferrante G, Cannata F, Azzolini E, Viggiani G, De Marco A, Briani M, Bocciolone M, Bragato R, Corrada E, Gasparini GL, Marconi M, Monti L, Pagnotta PA, Panico C, Pini D, Regazzoli D, My I, Kallikourdis M, Ciccarelli M, Badalamenti S, Aghemo A, Reimers B, Condorelli G; Humanitas COVID-19 Task Force. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. *Heart* 2020; **106**: 1512-1518 [PMID: 32817312 DOI: 10.1136/heartjnl-2020-317322]

56 **Pieske B**, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40**: 3297

57 **Lassen MCH**, Skaarup KG, Lind JN, Alhakak AS, Sengeløv M, Nielsen AB. Recovery of cardiac function following COVID-19 - ECHOVID-19: a prospective longitudinal cohort study. *Eur J Heart Fail* 2021; **23**: 1903-1912

58 **Skaarup KG**, Lassen MCH, Lind JN, Alhakak AS, Sengeløv M, Nielsen AB, Espersen C, Hauser R, Schöps LB, Holt E, Johansen ND, Modin D, Sharma S, Graff C, Bundgaard H, Hassager C, Jabbari R, Lebech AM, Kirk O, Bødtger U, Lindholm MG, Joseph G, Wiese L, Schiødt FV, Kristiansen OP, Walsted ES, Nielsen OW, Madsen BL, Tønder N, Benfield TL, Jeschke KN, Ulrik CS, Knop FK, Pallisgaard J, Lamberts M, Sivapalan P, Gislason G, Solomon SD, Iversen K, Jensen JUS, Schou M, Biering-Sørensen T. Myocardial Impairment and Acute Respiratory Distress Syndrome in Hospitalized Patients With COVID-19: The ECHOVID-19 Study. *JACC Cardiovasc Imaging* 2020; **13**: 2474-2476 [PMID: 32994145 DOI: 10.1016/j.jcmg.2020.08.005]

59 **Lassen MCH**, Skaarup KG, Lind JN, Alhakak AS, Sengeløv M, Nielsen AB, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. *ESC Heart Fail* 2020; **7**: 4189-4197

60 **Puntmann VO**, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265-1273 [PMID: 32730619 DOI: 10.1001/jamacardio.2020.3557]

61 **Huang L**, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020; **13**: 2330-2339 [PMID: 32763118 DOI: 10.1016/j.jcmg.2020.05.004]

62 **Moody WE**, Liu B, Mahmoud-Elsayed HM, Senior J, Lalla SS, Khan-Kheil AM, Brown S, Saif A, Moss A, Bradlow WM, Khoo J, Ahamed M, McAloon C, Hothi SS, Steeds RP. Persisting Adverse Ventricular Remodeling in COVID-19 Survivors: A Longitudinal Echocardiographic Study. *J Am Soc Echocardiogr* 2021; **34**: 562-566 [PMID: 33539950 DOI: 10.1016/j.echo.2021.01.020]

63 **Escher F**, Westermann D, Gaub R, Pronk J, Bock T, Al-Saadi N. Development of diastolic heart failure in a 6-year follow-up study in patients after acute myocarditis. *Heart* 2011; **97**: 709

64 **Li C**, Jiang J, Wang F, Zhou N, Veronese G, Moslehi JJ, Ammirati E, Wang DW. Longitudinal correlation of biomarkers of cardiac injury, inflammation, and coagulation to outcome in hospitalized COVID-19 patients. *J Mol Cell Cardiol* 2020; **147**: 74-87 [PMID: 32827510 DOI: 10.1016/j.yjmcc.2020.08.008]

65 **Saleh A**, Matsumori A, Abdelrazek S, Eltaweel S, Salous A, Neumann FJ. Myocardial involvement in coronavirus disease 19. *Herz* 2020; **45**: 719-725

66 **Han H**, Xie L, Liu R, Yang J, Liu F, Wu K. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. *J Med Virol* 2020; **92**: 819-823

67 **Qin JJ**, Cheng X, Zhou F, Lei F, Akolkar G, Cai J, Zhang XJ, Blet A, Xie J, Zhang P, Liu YM, Huang Z, Zhao LP, Lin L, Xia M, Chen MM, Song X, Bai L, Chen Z, Zhang X, Xiang D, Chen J, Xu Q, Ma X, Touyz RM, Gao C, Wang H, Liu L, Mao W, Luo P, Yan Y, Ye P, Chen M, Chen G, Zhu L, She ZG, Huang X, Yuan Y, Zhang BH, Wang Y, Liu PP, Li H. Redefining Cardiac Biomarkers in Predicting Mortality of Inpatients With COVID-19. *Hypertension* 2020; **76**: 1104-1112 [PMID: 32673499 DOI: 10.1161/HYPERTENSIONAHA.120.15528]

68 **Wungu CDK**, Khaerunnisa S, Putri EAC, Hidayati HB, Qurnianingsih E, Lukitasari L. Meta-analysis of cardiac markers for predictive factors on severity and mortality of COVID-19. *Int J Infect Dis* 2021; **105**: 551-559

69 **Shoar S**, Hosseini F, Naderan M, Mehta JL. Meta-analysis of Cardiovascular Events and Related Biomarkers Comparing Survivors Versus Non-survivors in Patients With COVID-19. *Am J Cardiol* 2020; **135**: 50-61 [PMID: 32916148 DOI: 10.1016/j.amjcard.2020.08.044]

70 **Yang HS**, Hur M, Yi A, Kim H, Lee S, Kim SN. Prognostic value of presepsin in adult patients with sepsis: Systematic review and meta-analysis. *PLoS One* 2018; **13**: e0191486 [PMID: 29364941 DOI: 10.1371/journal.pone.0191486]

71 **Nishimura H**, Ishii J, Muramatsu T, Harada M, Motoyama S, Matsui S, et al. Presepsin, Soluble CD14 Subtype, Is a Novel Marker of Short-term Mortality in Patients Hospitalized for Worsening Heart Failure. *J Cardiac Failure* 2017; **23**: S61

72 **Zhou W**, Rao H, Ding Q, Lou X, Shen J, Ye B. Soluble CD14 Subtype in Peripheral Blood is a Biomarker for Early Diagnosis of Sepsis. *Lab Med* 2020; **51**: 614-619

73 **Favaloro EJ**, Lippi G. Recommendations for Minimal Laboratory Testing Panels in Patients with COVID-19: Potential for Prognostic Monitoring. *Semin Thromb Hemost* 2020; **46**: 379-382 [PMID: 32279286 DOI: 10.1055/s-0040-1709498]

74 **Park M**, Hur M, Kim H, Lee CH, Lee JH, Kim HW. Prognostic Utility of Procalcitonin, Presepsin, and the VACO Index for Predicting 30-day Mortality in Hospitalized COVID-19 Patients. *Ann Lab Med* 2022; **42**: 406-414

75 **Lippi G**, Sanchis-Gomar F, Henry BM. Presepsin value predicts the risk of developing severe/critical COVID-19 illness: results of a pooled analysis. *Clin Chem Lab Med* 2022; **60**: e1-e3 [PMID: 34472764 DOI: 10.1515/cclm-2021-0848]

76 **Koyjit A**, Sogut O, Durmus E, Kao1mdan E, Guler EM, Kaplan O. Circulating furin, IL-6, and presepsin levels and disease severity in SARS-CoV-2_infected patients. *Science Progress* 2021; 104

77 **Fukada A**, Kitagawa Y, Matsuoka M, Sakai J, Imai K, Tarumoto N. Presepsin as a predictive biomarker of severity in COVID-19: A case series. *J Med Virol* 2021; **93**: 99-101

78 **Zaninotto M**, Mion MM, Cosma C, Rinaldi D, Plebani M. Presepsin in risk stratification of SARS-CoV-2 patients. *Clin Chim Acta* 2020; **507**: 161-163 [PMID: 32333860 DOI: 10.1016/j.cca.2020.04.020]

79 **Dell'Aquila P**, Raimondo P, Racanelli V, De Luca P, De Matteis S, Pistone A, Melodia R, Crudele L, Lomazzo D, Solimando AG, Moschetta A, Vacca A, Grasso S, Procacci V, Orso D, Vetrugno L. Integrated lung ultrasound score for early clinical decision-making in patients with COVID-19: results and implications. *Ultrasound J* 2022; **14**: 21 [PMID: 35648278 DOI: 10.1186/s13089-022-00264-8]

80 **Homsak E**, Gruson D. Soluble ST2: A complex and diverse role in several diseases. *Clin Chim Acta* 2020; **507**: 75-87 [PMID: 32305537 DOI: 10.1016/j.cca.2020.04.011]

81 **Bajwa EK**, Volk JA, Christiani DC, Harris RS, Matthay MA, Thompson BT, Januzzi JL; National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome Network. Prognostic and diagnostic value of plasma soluble suppression of tumorigenicity-2 concentrations in acute respiratory distress syndrome. *Crit Care Med* 2013; **41**: 2521-2531 [PMID: 23939353 DOI: 10.1097/CCM.0b013e3182978f91]

82 **Bajwa EK**, Mebazaa A, Januzzi JL. ST2 in Pulmonary Disease. *Am J Cardiol* 2015; **115**: 44B-47B

83 **Manzano-Fernández S**, Mueller T, Pascual-Figal D, Truong QA, Januzzi JL. Usefulness of soluble concentrations of interleukin family member ST2 as predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. *Am J Cardiol* 2011; **107**: 259-267 [PMID: 21211603 DOI: 10.1016/j.amjcard.2010.09.011]

84 **Rehman SU**, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. *J Am Coll Cardiol* 2008; **52**: 1458-1465 [PMID: 19017513 DOI: 10.1016/j.jacc.2008.07.042]

85 **Lassus J**, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J Cardiol* 2013; **168**: 2186-2194

86 **Breidthardt T**, Balmelli C, Twerenbold R, Mosimann T, Espinola J, Haaf P, Thalmann G, Moehring B, Mueller M, Meller B, Reichlin T, Murray K, Ziller R, Benkert P, Osswald S, Mueller C. Heart failure therapy-induced early ST2 changes may offer long-term therapy guidance. *J Card Fail* 2013; **19**: 821-828 [PMID: 24239955 DOI: 10.1016/j.cardfail.2013.11.003]

87 **Omland T**, Prebensen C, Jonassen C, Svensson M, Berdal JE, Seljeflot I, Myhre PL. Soluble ST2 concentrations associate with in-hospital mortality and need for mechanical ventilation in unselected patients with COVID-19. *Open Heart* 2021; **8** [PMID: 34933965 DOI: 10.1136/openhrt-2021-001884]

88 **Huang J**. Comparing biomarkers for COVID-19 disease with commonly associated preexisting conditions and complications. medRxiv. 2020; 2020.10.02.20205609.

89 **Ragusa R**, Basta G, Del Turco S, Caselli C. A possible role for ST2 as prognostic biomarker for COVID-19. *Vascul Pharmacol* 2021; **138**: 106857 [PMID: 33746068 DOI: 10.1016/j.vph.2021.106857]

90 **Hoogerwerf JJ**, Tanck MW, van Zoelen MA, Wittebole X, Laterre PF, van der Poll T. Soluble ST2 plasma concentrations predict mortality in severe sepsis. *Intensive Care Med* 2010; **36**: 630-637 [PMID: 20151106 DOI: 10.1007/s00134-010-1773-0]

91 **Martínez-Martínez E**, Calvier L, Fernández-Celis A, Rousseau E, Jurado-López R, Rossoni LV, Jaisser F, Zannad F, Rossignol P, Cachofeiro V, López-Andrés N. Galectin-3 blockade inhibits cardiac inflammation and fibrosis in experimental hyperaldosteronism and hypertension. *Hypertension* 2015; **66**: 767-775 [PMID: 26238446 DOI: 10.1161/HYPERTENSIONAHA.115.05876]

92 **Zhang C**, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents* 2020; **55**: 105954 [PMID: 32234467 DOI: 10.1016/j.ijantimicag.2020.105954]

93 **Chen SS**, Sun LW, Brickner H, Sun PQ. Downregulating galectin-3 inhibits proinflammatory cytokine production by human monocyte-derived dendritic cells *via* RNA interference. *Cell Immunol* 2015; **294**: 44-53 [PMID: 25684095 DOI: 10.1016/j.cellimm.2015.01.017]

94 **Januzzi JL Jr**, Peacock WF, Maisel AS, Chae CU, Jesse RL, Baggish AL, O'Donoghue M, Sakhuja R, Chen AA, van Kimmenade RR, Lewandrowski KB, Lloyd-Jones DM, Wu AH. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *J Am Coll Cardiol* 2007; **50**: 607-613 [PMID: 17692745 DOI: 10.1016/j.jacc.2007.05.014]

95 **Shah RV**, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail* 2010; **12**: 826-832 [PMID: 20525986 DOI: 10.1093/eurjhf/hfq091]

96 **Caniglia JL**, Asuthkar S, Tsung AJ, Guda MR, Velpula KK. Immunopathology of galectin-3: an increasingly promising target in COVID-19. *F1000Res* 2020; **9**: 1078 [PMID: 33082935 DOI: 10.12688/f1000research.25979.2]

97 **Portacci A**, Diaferia F, Santomasi C, Dragonieri S, Boniello E, Di Serio F. Galectin-3 as prognostic biomarker in patients with COVID-19 acute respiratory failure. *Respir Med* 2021; **187**: 106556-106556

98 **Christ-Crain M**, Fenske W. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. *Nat Rev Endocrinol* 2016; **12**: 168-176 [PMID: 26794439 DOI: 10.1038/nrendo.2015.224]

99 **Maisel A**, Xue Y, Shah K, Mueller C, Nowak R, Peacock WF. Increased 90-Day Mortality in Patients With Acute Heart Failure With Elevated Copeptin. *Circulation: Heart Failure* 2011; **4**: 613-620

100 **Gregoriano C**, Molitor A, Haag E, Kutz A, Koch D, Haubitz S, Conen A, Bernasconi L, Hammerer-Lercher A, Fux CA, Mueller B, Schuetz P. Activation of Vasopressin System During COVID-19 is Associated With Adverse Clinical Outcomes: An Observational Study. *J Endocr Soc* 2021; **5**: bvab045 [PMID: 34056499 DOI: 10.1210/jendso/bvab045]

101 **Hammad R**, Elshafei A, Khidr EG, El-Husseiny AA, Gomaa MH, Kotb HG, Eltrawy HH, Farhoud H. Copeptin: a neuroendocrine biomarker of COVID-19 severity. *Biomark Med* 2022; **16**: 589-597 [PMID: 35350852 DOI: 10.2217/bmm-2021-1100]

102 **Verhamme FM**, Freeman CM, Brusselle GG, Bracke KR, Curtis JL. GDF-15 in Pulmonary and Critical Care Medicine. *Am J Respir Cell Mol Biol* 2019; **60**: 621-628 [PMID: 30633545 DOI: 10.1165/rcmb.2018-0379TR]

103 **Apfel T**, Riecher-Rössler A. [Do psychiatric patients receive disability pension before adequate diagnostics and treatment? *Psychiatr Prax* 2005; **32**: 172-176 [PMID: 15852209 DOI: 10.1055/s-2004-828496]

104 **John KJ**, Mishra AK, Ramasamy C, George AA, Selvaraj V, Lal A. Heart failure in COVID-19 patients: Critical care experience. *World J Virol* 2022; **11**: 1-19 [PMID: 35117968 DOI: 10.5501/wjv.v11.i1.1]

105 **Mishra AK**, Lal A, Sahu KK, Kranis M, Sargent J. Quantifying and reporting cardiac findings in imaging of COVID-19 patients. *Monaldi Arch Chest Dis* 2020; **90** [PMID: 33169595 DOI: 10.4081/monaldi.2020.1394]

106 **Philip AM**, George LJ, John KJ, George AA, Nayar J, Sahu KK, Selvaraj V, Lal A, Mishra AK. A review of the presentation and outcome of left ventricular thrombus in coronavirus disease 2019 infection. *J Clin Transl Res* 2021; **7**: 797-808 [PMID: 34988332]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 September 25; 11(5): 391-393

DOI: 10.5501/wjv.v11.i5.391

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Possible agent for COVID-19 treatment: Rifampicin

Ozlem Celik Aydin, Sonay Aydın, Sureyya Barun

Specialty type: Pharmacology and pharmacy

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Gupta S, United States; Varshney K, Australia

Received: April 20, 2022
Peer-review started: April 20, 2022
First decision: June 8, 2022
Revised: June 20, 2022
Accepted: August 25, 2022
Article in press: August 25, 2022
Published online: September 25, 2022

Ozlem Celik Aydin, Department of Medical Pharmacology, Erzincan University, Mengucek Gazi Education and Research Hospital, Erzincan 24100, Turkey

Sonay Aydın, Sureyya Barun, Department of Pharmacology, Gazi University, Ankara 06500, Turkey

Sonay Aydın, Department of Radiology, Erzincan University, Erzincan 24100, Turkey

Corresponding author: Ozlem Celik Aydin, MD, Doctor, Department of Medical Pharmacology, Erzincan University, Mengucek Gazi Education and Research Hospital, Başbağlar Mahallesi Hacı Ali Akın Caddesi No. 32 Erzincan/Merkez, Erzincan 24100, Turkey. ozlemclk_89@hotmail.com

Abstract

Rifampicin is a promising drug for the treatment of coronavirus disease 2019 based on its antiviral properties and recent *in silico* studies. *In silico* studies can serve as a foundation for further studies.

Key Words: Rifampicin; COVID-19; Treatment; *In silico*; Drug-drug interaction; Therapeutic potential

Core Tip: Rifampicin may be used as a treatment for coronavirus disease 2019 (COVID-19). Although it has a variety of drug-drug interactions, none of the important ones for the currently utilised COVID-19 medicines, favipiravir, enoxaparin, and aspirin, have been defined.

Citation: Aydin OC, Aydın S, Barun S. Possible agent for COVID-19 treatment: Rifampicin. *World J Virol* 2022; 11(5): 391-393
URL: https://www.wjgnet.com/2220-3249/full/v11/i5/391.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i5.391

TO THE EDITOR

We read the review written by Panayiotakopoulos and Papadimitriou[1] with interest.

The impacts of the coronavirus disease 2019 (COVID-19) pandemic are still being felt, and research into this topic continues due to the lack of a precise therapy. It is feasible to repurpose medications already used for other reasons for the treatment of COVID-19. The authors discussed rifampicin's antiviral capabilities, its potential effects in computer simulations, its safety, and its role in clinical practice. Rifampicin is an antibacterial drug that inhibits DNA-dependent RNA polymerase in *Mycobacterium tuberculosis*, and its antiviral effect has been shown on some viruses[2]. On this basis, the potential efficacy of rifampicin as a COVID-19 treatment drug has been demonstrated in *in silico* research[3]. We concur with the authors' suggestion for more research into the potential use of rifampicin for COVID-19.

In a study in which 20 United States Food and Drug Administration (FDA)-approved drugs were screened by molecular docking method in a possible drug design for COVID-19, rifampicin showed *in silico* binding to more than one target protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Other macrocyclic antibiotics showing binding are polymyxin B and bafilomycin A[4]. In another *in silico* study of FDA-approved drugs to treat COVID-19 infection, rifampicin has stronger binding affinity for the COVID-19 main protease Mpro[5]. However, additional studies are needed for validation.

Due to the properties of rifampicin, various drug-drug interactions (DDIs) may occur during its possible use. Rifampicin promotes the expression of cytochrome p450 3A4 (CYP3A4) in the small intestine and liver, as noted in the review. Additionally, according to the work by Panayiotakopoulos and Papadimitriou[1], an essential feature of rifampicin is that it activates proteins such as the P glycoprotein (P-gp) drug transporter and CYP2C-mediated metabolism[6]. There are possible DDIs with drugs used for the treatment of COVID-19 and for additional diseases. Favipiravir is one of the antiviral medications used for the treatment of COVID-19. It is metabolized mostly *via* aldehyde oxidase and xanthine oxidase[7], and the probability of a pharmacological interaction between rifampicin and favipiravir is low. Lopinavir and ritonavir are two additional widely used antivirals; coadministration of these drugs with rifampin may result in a decrease in the plasma concentrations of ritonavir and lopinavir due to rifampin's induction of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of ritonavir and lopinavir[8]. Remdesivir is widely used for COVID-19 treatment, which is metabolized through hydrolysis reaction to its triphosphate active form *via* by carboxylesterase 1 (80%), cathepsin A (10%), and CYP3A (10%). Since rifampicin is a potential inductor of CYP3A4, concomitant administration might increase the metabolism of remdesivir[9]. Dexamethasone has a strong anti-inflammatory impact and is typically used as an adjunctive treatment for COVID-19 pneumonia. Rifampin may increase corticosteroid hepatic metabolism, hence diminishing their therapeutic impact. Corticosteroids' half-life of elimination is shortened by up to 45% when co-administered with rifampin [10,11].

It has been suggested that prophylaxis of thrombosis in COVID-19 should include both anticoagulant and antiplatelet medications. Enoxaparin and aspirin are the two most often used anticoagulant and antiplatelet medications[12]. Fortunately, no significant medication interactions between these drugs and rifampicin have been identified. Apixaban and other direct oral anticoagulants can also be utilised. Rifampicin coadministration significantly increased apixaban plasma concentrations. When used orally, approximately 15% of apixaban is metabolised by CYP3A and roughly 6% by CYP1A2 and CYP2J2. The balance (50%) is eliminated unaltered in the form of faeces and urine. A single dose of rifampicin decreased apixaban clearance by 25%. Rifampicin largely influences apixaban absorption (and/or distribution), which could be attributed to an impairment of intestinal P-gp[13].

The authors said that rifampicin has been shown to be quite effective in treating COVID-19 in *in silico* tests. Additionally, multiple medication classes have been examined *in silico* for the treatment of COVID-19. Melatonin, ramelteon, and agomelatine, for example, have been demonstrated to significantly limit virus entry into cells in investigations. Ramelteon was proven to be the most effective antiviral against SARS-CoV-2[14].

FOOTNOTES

Author contributions: Aydın S, Aydin OC and Barun S conceived the study; Aydın S, Aydin OC and Barun S were responsible for designing, materials and supervision; Aydın S, Aydin OC and Barun S did the literature search, wrote the manuscript, and reviewed the manuscript critically; All authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: Turkey

ORCID number: Ozlem Celik Aydin 0000-0002-8287-7126; Sonay Aydın 0000-0002-3812-6333; Sureyya Barun 0000-0003-3726-8177.

S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM

REFERENCES

1 **Panayiotakopoulos GD**, Papadimitriou DT. Rifampicin for COVID-19. *World J Virol* 2022; **11**: 90-97 [PMID: 35433334 DOI: 10.5501/wjv.v11.i2.90]
2 **Abulfathi AA**, Decloedt EH, Svensson EM, Diacon AH, Donald P, Reuter H. Clinical Pharmacokinetics and Pharmacodynamics of Rifampicin in Human Tuberculosis. *Clin Pharmacokinet* 2019; **58**: 1103-1129 [PMID: 31049868 DOI: 10.1007/s40262-019-00764-2]
3 **Kumar A**, Mishra DC, Angadi UB, Yadav R, Rai A, Kumar D. Inhibition Potencies of Phytochemicals Derived from Sesame Against SARS-CoV-2 Main Protease: A Molecular Docking and Simulation Study. *Front Chem* 2021; **9**: 744376 [PMID: 34692642 DOI: 10.3389/fchem.2021.744376]
4 **Elmorsy MA**, El-Baz AM, Mohamed NH, Almeer R, Abdel-Daim MM, Yahya G. In silico screening of potent inhibitors against COVID-19 key targets from a library of FDA-approved drugs. *Environ Sci Pollut Res Int* 2022; 29: 12336-12346 [PMID: 34562220 DOI: 10.1007/s11356-021-16427-4]
5 **Pathak Y**, Mishra A, Tripathi V. Rifampicin may be repurposed for COVID-19 treatment: Insights from an in-silico study. *Research Square* 2020 [DOI: 10.21203/rs.3.rs-22546/v1]
6 **Niemi M**, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin : clinical relevance. *Clin Pharmacokinet* 2003; **42**: 819-850 [PMID: 12882588 DOI: 10.2165/00003088-200342090-00003]
7 **Du YX**, Chen XP. Favipiravir: Pharmacokinetics and Concerns About Clinical Trials for 2019-nCoV Infection. *Clin Pharmacol Ther* 2020; **108**: 242-247 [PMID: 32246834 DOI: 10.1002/cpt.1844]
8 **American Thoracic Society**; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR Recomm Rep* 2003; **52**: 1-77 [PMID: 12836625]
9 **Deb S**, Reeves AA, Hopefl R, Bejusca R. ADME and Pharmacokinetic Properties of Remdesivir: Its Drug Interaction Potential. *Pharmaceuticals (Basel)* 2021; **14** [PMID: 34358081 DOI: 10.3390/ph14070655]
10 **Lee KH**, Shin JG, Chong WS, Kim S, Lee JS, Jang IJ, Shin SG. Time course of the changes in prednisolone pharmacokinetics after co-administration or discontinuation of rifampin. *Eur J Clin Pharmacol* 1993; **45**: 287-289 [PMID: 8276057 DOI: 10.1007/BF00315399]
11 **Ahmed MH**, Hassan A. Dexamethasone for the Treatment of Coronavirus Disease (COVID-19): a Review. *SN Compr Clin Med* 2020; **2**: 2637-2646 [PMID: 33163859 DOI: 10.1007/s42399-020-00610-8]
12 **Aydin S**, Kantarci M, Karavas E, Unver E, Yalcin S, Aydin F. Lung perfusion changes in COVID-19 pneumonia: a dual energy computerized tomography study. *Br J Radiol* 2021; **94**: 20201380 [PMID: 34415201 DOI: 10.1259/bjr.20201380]
13 **Mikus G**, Foerster KI, Schaumaeker M, Lehmann ML, Burhenne J, Haefeli WE. Application of a microdosed cocktail of 3 oral factor Xa inhibitors to study drug-drug interactions with different perpetrator drugs. *Br J Clin Pharmacol* 2020; **86**: 1632-1641 [PMID: 32159869 DOI: 10.1111/bcp.14277]
14 **Yadalam PK**, Balaji TM, Varadarajan S, Alzahrani KJ, Al-Ghamdi MS, Baeshen HA, Alfarhan MFA, Khurshid Z, Bhandi S, Jagannathan R, Patil VR, Raj AT, Ratnayake J, Patil S. Assessing the therapeutic potential of agomelatine, ramelteon, and melatonin against SARS-CoV-2. *Saudi J Biol Sci* 2022; **29**: 3140-3150 [PMID: 35095308 DOI: 10.1016/j.sjbs.2022.01.049]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2022 November 25; 11(6): 394-504

Published by Baishideng Publishing Group Inc

World Journal of Virology

Contents

Bimonthly Volume 11 Number 6 November 25, 2022

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

SYSTEMATIC REVIEWS

World Journal of Virology

Bimonthly Volume 11 Number 6 November 25, 2022

Contents

LETTER TO THE EDITOR

World Journal of Virology

Bimonthly Volume 11 Number 6 November 25, 2022

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
November 25, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 394-398

DOI: 10.5501/wjv.v11.i6.394

ISSN 2220-3249 (online)

EDITORIAL

Intensive care unit adaptations in the COVID-19 pandemic: Lessons learned

Anwar Khedr, David Rokser, Jeanine Borge, Hannah Rushing, Greta Zoesch, Wade Johnson, Han-Yin Wang, April Lanz, Brian N Bartlett, Jessica Poehler, Salim Surani, Syed A Khan

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Freund O, Israel; Isac S, Romania

Received: August 1, 2022
Peer-review started: August 1, 2022
First decision: September 5, 2022
Revised: September 17, 2022
Accepted: October 19, 2022
Article in press: October 19, 2022
Published online: November 25, 2022

Anwar Khedr, Department of Medicine, BronxCare Health System, Bronx, NY 10457, United States

David Rokser, Department of Critical Care Medicine, Mayo Health System, Mankato, MN 56001, United States

Jeanine Borge, Hannah Rushing, Greta Zoesch, Jessica Poehler, Syed A Khan, Department of Critical Care Medicine, Mayo Clinic Health System, Mankato, MN 56001, United States

Wade Johnson, April Lanz, Department of Administration, Mayo Clinic Health System, Mankato, MN 56001, United States

Han-Yin Wang, Hospital Medicine, Mayo Clinic Health System, Mankato, MN 56001, United States

Brian N Bartlett, Department of Emergency Medicine, Mayo Clinic Health System, Mankato, MN 56001, United States

Salim Surani, Department of Medicine, Texas A&M University, Health Science Center, College Station, TX 77843, United States

Corresponding author: Salim Surani, FCCP, MD, MS, Professor, Department of Medicine, Texas A&M University, Health Science Center, 400 Bizzell Street, College Station, TX 77843, United States. srsurani@hotmail.com

Abstract

The coronavirus disease 2019 pandemic had deleterious effects on the healthcare systems around the world. To increase intensive care units (ICUs) bed capacities, multiple adaptations had to be made to increase surge capacity. In this editorial, we demonstrate the changes made by an ICU of a midwest community hospital in the United States. These changes included moving patients that used to be managed in the ICU to progressive care units, such as patients requiring non-invasive ventilation and high flow nasal cannula, ST-elevation myocardial infarction patients, and post-neurosurgery patients. Additionally, newer tactics were applied to the processes of assessing oxygen supply and demand, patient care rounds, and post-ICU monitoring.

Key Words: COVID-19; Pandemics; Oxygen; Intensive care units; ST elevation myo-

cardial infarction; Nasal cannula

Core Tip: In this editorial, we demonstrate how the coronavirus disease 2019 pandemic changed our lives in the intensive care unit (ICU), especially in the management of surge capacity and allocation of resources in a 10-bed ICU of a United States suburban midwest community hospital. These strategies included managing complex patients in our progressive care unit, assessing oxygen supply and demand, performing patient care rounds, and post-ICU monitoring.

Citation: Khedr A, Rokser D, Borge J, Rushing H, Zoesch G, Johnson W, Wang HY, Lanz A, Bartlett BN, Poehler J, Surani S, Khan SA. Intensive care unit adaptations in the COVID-19 pandemic: Lessons learned. *World J Virol* 2022; 11(6): 394-398
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/394.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.394

INTRODUCTION

"Calamity tempestuous, oracle of destruction, ravishing through nations, ordained to devastation, negator of humanity, the annihilation of grace" is how our colleague depicted the coronavirus disease 2019 (COVID-19) pandemic in a recently authored poem[1]. The COVID-19 pandemic has wreaked havoc on healthcare systems all around the world[2,3]. To increase bed capacities and resources, elective surgeries were postponed[4]. Innovative approaches were implemented to perform virtual visits and perform patient care rounds[5,6]. Some hospitals have implemented structural modifications and changed strategies of resource allocation to face the intensive care unit (ICU) surge capacity and the sudden increased demand for invasive mechanical ventilation[7,8].

To meet the need for increasing demand for ICU beds, our staff at Mayo Clinic Health System (MCHS) in Mankato worked tirelessly to maximize our ICU capacity while maintaining high-quality patient care. MCHS Mankato is a 161-bed community hospital with a 15-bed multispecialty ICU staffed 24/7 by intensivists fellowship trained in critical care, a part of the Mayo Clinic enterprise in Southern Minnesota. A 19- bed progressive care unit (PCU) staffed by our hospitalist team manages patients with less acuity. Admission guidelines for both units are as per the Society of Critical Care Medicine admission criteria.

Over 80000 COVID-19 cases were diagnosed in Minnesota by September 2020[9]. Additionally, due to nationwide bed and staff shortages[2], we had to maximize our capacity to have an ICU literally without walls. Our multidisciplinary team determined that mitigation was required to overcome limited capacity[2,10,11]. Alterations to our daily routine had to be made with shared decision-making and increased communication across specialties[7]. In this editorial, we are providing a brief overview of these efforts and outcomes between November 2020 and December 2021.

PCU for do not resuscitate/do not intubate patients requiring noninvasive ventilation

Patients utilizing noninvasive ventilation (NIV) with do not resuscitate (DNR)/do not intubate (DNI) status were managed in the ICU prior to the pandemic. A collaboration between the critical care team, respiratory therapy, nursing, and hospitalist team was established to manage patients requiring NIV in the PCU. The Critical Care team managed the NIV, and the hospitalist group provided additional medical management. The challenges of this placement included a greater need for communication between very busy teams, and a potential urgent need for critical care beds if hemodynamic instability developed. Prior to November 2020, only 13 DNR/DNI patients were ever managed with NIV in the PCU. A total of 22 patients requiring NIV were managed during the last two months of 2020 (> 69.2% increase), with 79 total NIV patients being admitted to the PCU in 2021 (> 125.7% increase). This approach was found to be especially helpful for patients with prolonged respiratory failure, such as was seen with COVID-19[12,13].

ST-elevation myocardial infarction patients to the PCU

Prior to COVID-19, ST-elevation myocardial infarction (STEMI) patients were admitted to the ICU. Due to the need for more ICU beds, Critical Care, Cardiology, hospitalists, and nursing staff collaborated to manage hemodynamically stable STEMI patients in the PCU. A previous study showed that although > 80% of stable patients with STEMI are treated in the ICU after primary percutaneous coronary intervention, the risk for developing a complication requiring ICU care is 16%, which confirmed that

ICU was overutilized by stable STEMI patients[14]. Challenges to this approach included the necessity for enhanced cardiac education provided to the PCU nurses, increased requirement for more multidisciplinary coordination, and the urgent need for an ICU bed if hemodynamic instability occurs. After our adaptations, STEMI ICU admissions decreased from 107 (156 total STEMI cases) in 2020 to 51 (141 total STEMI cases) in 2021, a total reduction of 32.4%. There were no adverse events reported with this strategy.

Evaluating placement of post-operative neurosurgery patients

Before COVID-19, neurosurgical patients who underwent complex procedures were frequently managed post-operatively in the ICU regardless of hemodynamic stability. The neurosurgical and critical care teams implemented a collaborative process to assess each case for ICU appropriateness[15-17]. Those who did not need active ICU intervention (*e.g.*, pressors, intracranial monitoring, advanced oxygen therapy) were admitted to the PCU for management. Limitations of this approach included nurse training, the need for increased multidisciplinary collaboration, and the need for an emergent bed within the ICU if decompensation occurred. Prior to November, 28 of 61 post-operative neurosurgical patients were admitted to the ICU in 2020. From November 2020 through December 2020, 9 of 14 patients were managed in PCU. Sixty-two out of 109 post-operative neurosurgical cases were admitted to ICU in 2021.

High flow nasal cannula in PCU

Patients requiring greater than 0.60 FiO_2 using high flow nasal cannula (HFNC) were transferred to the ICU prior to November 2020. It was determined that all HFNC patients, regardless of code status or FiO_2 requirement, would be managed in the PCU unless the additional need for ICU admission occurred[18-20]. Nursing, respiratory therapy, and provider comfort were initial challenges. Before November 2020, 71 patients were managed in the PCU with HFNC requiring less than 0.6 FiO_2. From November 2020 until the end of 2021, a total of 187 patients were treated in PCU with HFNC, an increase of 116%. Many COVID-19 cases required prolonged HFNC without additional adjunctive critical care management, which opened ICU beds for patients requiring more complex support such as invasive mechanical ventilation[19,21].

Oxygen supply/demand assessment

Due to fixed medical gas availability, daily meetings between the respiratory therapy and critical care teams were conducted to evaluate oxygen consumption and demand. A report created in the electronic medical record delivered real-time data regarding oxygen devices in use. Medical gas pressure alarm values alerted the team to wean oxygen or change the patient to an alternative oxygen-conserving device if the gas supply reached a critical level. During times when the hospital oxygen supply reached a critically low level, ICU physicians and respiratory therapists assessed all HFNC patients for judicious use. In appropriate cases, NIV was utilized temporarily to decrease oxygen consumption while working on alternative approaches to minimize use. Additional attention was given to shutting off oxygen devices when not in use. Other tools and criteria were developed to assess oxygen resources and distribution[22,23].

Collaborate team care rounds with social distancing and visitor restrictions

A multidisciplinary approach is necessary to manage critically ill patients, and daily team rounds are an essential component of the ICU routine. Many critically ill patients cannot make medical decisions and rely on family members for assistance. During the COVID-19 pandemic, this was complicated by visitor restrictions resulting in family members calling 24/7 to receive updates and to advocate for patients. Calls were often accompanied by emotions such as anger, guilt, fear, frustration, and sadness related to the inability to be at the bedside. For the patients being alone posed a higher risk of ICU delirium. A telemedicine approach was adopted to involve the patient's family and maintain social distancing between the interdisciplinary team members, including the physician, advanced practice provider, respiratory team, nurses, pharmacist, dietician, and therapists[6,24]. During rounds *via* conference call, each team member would give a progress update and present their plan of care for the day. The physician or advanced practice provider would then summarize the plan of care and answer any questions the family had. The family was encouraged to participate throughout the rounding process actively and stay on the line for the entire process, typically about 10 min per patient[6]. Prior to the pandemic, both patients and families participated in the ICU interdisciplinary team rounds which were always conducted at the bedside. Due to the risk of exposure, the need to conserve full personal protective equipment, and the restricted visitor policy this approach was adopted. We wanted the families to receive real-time updates and assessments from the entire interdisciplinary team. Our rounds were a small gesture to lessen the emotional burden and were valued by family members. The ICU team also arranged virtual zoom or other video calls with patients and their families daily to reduce the risk of ICU delirium.

Post-ICU monitoring

Prior to the COVID-19 pandemic, ICU patients were typically monitored for 24 h in the ICU after receiving substantial life support (*e.g.*, mechanical ventilation, vasopressors, continuous renal replacement therapy). In response to increased demand for critical care beds across midwest America, ICU patients were moved to lower acuity beds at the earliest appropriate opportunity. To prevent ICU readmissions, rapid response nurses and virtual ICU providers (Mayo Clinic Enhanced Critical Care) followed every critical care discharge for 48 h regardless of hospital location. This practice has been used in different ways and has proved to decrease ICU mortality and hospital length of stay[25,26]. With this intervention, the ICU readmission rate remained low at 2% much lower than national data. Additionally, this provided extra support to hospitalists and nurses unfamiliar with managing patients immediately following ICU-level care.

CONCLUSION

Despite the significant increase in acuity within the ICU, the multidisciplinary team maintained a total ICU mortality rate index of 0.92 and a COVID-19 mortality rate index of 0.37. The length of stay index for the total ICU population was 0.95 and 1.39 for patients diagnosed with COVID-19. These numbers are impressive as they were achieved despite ICU acuity increasing as more stable patients, such as hemodynamically intact STEMI and post-operative neurosurgical patients, were transitioned to PCU care. Each member of the multidisciplinary team was crucial to our success. By maximizing our ICU resources and capacity, these interventions allowed us to better serve our community. The COVID-19 pandemic is not the last crisis that the world will face. This is the time for the call to action for the institutions to have alternative innovative strategies and learn the lesson from their shortcomings during the COVID-19 pandemic. This narrative is a prelude to our efforts and may be beneficial to other hospitals in case of another crisis.

FOOTNOTES

Author contributions: Khedr A, Rokser D, Poehler J, and Wang HY involved in the manuscript drafting; Khedr A, Rokser D, Poehler J, Wang HY, Rushing H, Bartlett BN, Zoesch G, Johnson W, Lanz A, Surani S, and Khan SA involved in the manuscript editing, and agreeing to the final accuracy of the work; Surani S and Khan SA contributed to the supervision, critical revision of the manuscript and reviewing.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: United States

ORCID number: Anwar Khedr 0000-0002-2730-3031; David Rokser 0000-0003-1299-1393; Jeanine Borge 0000-0002-9160-0487; Hannah Rushing 0000-0002-4882-598X; Greta Zoesch 0000-0003-4857-5607; Wade Johnson 0000-0002-8255-1484; Han-Yin Wang 0000-0001-7649-0892; April Lanz 0000-0003-0924-5357; Brian N Bartlett 0000-0002-4389-1806; Jessica Poehler 0000-0001-9063-8347; Salim Surani 0000-0001-7105-4266; Syed A Khan 0000-0002-2452-2079.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Khan SA**. Corona. *HCA Healthcare J Med* 2021; **2**: 6 [DOI: 10.36518/2689-0216.1377]
2 **McCabe R**, Schmit N, Christen P, D'Aeth JC, Løchen A, Rizmie D, Nayagam S, Miraldo M, Aylin P, Bottle A, Perez-Guzman PN, Ghani AC, Ferguson NM, White PJ, Hauck K. Adapting hospital capacity to meet changing demands during the COVID-19 pandemic. *BMC Med* 2020; **18**: 329 [PMID: 33066777 DOI: 10.1186/s12916-020-01781-w]
3 **Barasa EW**, Ouma PO, Okiro EA. Assessing the hospital surge capacity of the Kenyan health system in the face of the COVID-19 pandemic. *PLoS One* 2020; **15**: e0236308 [PMID: 32687538 DOI: 10.1371/journal.pone.0236308]
4 **Tonna JE**, Hanson HA, Cohan JN, McCrum ML, Horns JJ, Brooke BS, Das R, Kelly BC, Campbell AJ, Hotaling J. Balancing revenue generation with capacity generation: case distribution, financial impact and hospital capacity changes

from cancelling or resuming elective surgeries in the US during COVID-19. *BMC Health Serv Res* 2020; **20**: 1119 [PMID: 33272278 DOI: 10.1186/s12913-020-05975-z]

5 **Al-Tawfiq JA**, Al-Yami SS, Rigamonti D. Changes in healthcare managing COVID and non-COVID-19 patients during the pandemic: striking the balance. *Diagn Microbiol Infect Dis* 2020; **98**: 115147 [PMID: 32891957 DOI: 10.1016/j.diagmicrobio.2020.115147]

6 **Wang H**, Poehler JL, Ziegler JL, Weiler CC, Khan SA. Patient Care Rounds in the Intensive Care Unit During COVID-19. *Jt Comm J Qual Patient Saf* 2020; **46**: 600-601 [PMID: 32768306 DOI: 10.1016/j.jcjq.2020.06.006]

7 **Griffin KM**, Karas MG, Ivascu NS, Lief L. Hospital Preparedness for COVID-19: A Practical Guide from a Critical Care Perspective. *Am J Respir Crit Care Med* 2020; **201**: 1337-1344 [PMID: 32298146 DOI: 10.1164/rccm.202004-1037CP]

8 **Cammarota G**, Ragazzoni L, Capuzzi F, Pulvirenti S, De Vita N, Santangelo E, Verdina F, Grossi F, Vaschetto R, Della Corte F. Critical Care Surge Capacity to Respond to the COVID-19 Pandemic in Italy: A Rapid and Affordable Solution in the Novara Hospital. *Prehosp Disaster Med* 2020; **35**: 431-433 [PMID: 32423513 DOI: 10.1017/S1049023X20000692]

9 **Department of Health**. Situation Update for COVID-19. [cited 11 October 2022]. Available from: https://www.health.state.mn.us/diseases/coronavirus/stats/index.html

10 **Tyrrell CSB**, Mytton OT, Gentry SV, Thomas-Meyer M, Allen JLY, Narula AA, McGrath B, Lupton M, Broadbent J, Ahmed A, Mavrodaris A, Abdul Pari AA. Managing intensive care admissions when there are not enough beds during the COVID-19 pandemic: a systematic review. *Thorax* 2021; **76**: 302-312 [PMID: 33334908 DOI: 10.1136/thoraxjnl-2020-215518]

11 **Bravata DM**, Perkins AJ, Myers LJ, Arling G, Zhang Y, Zillich AJ, Reese L, Dysangco A, Agarwal R, Myers J, Austin C, Sexson A, Leonard SJ, Dev S, Keyhani S. Association of Intensive Care Unit Patient Load and Demand With Mortality Rates in US Department of Veterans Affairs Hospitals During the COVID-19 Pandemic. *JAMA Netw Open* 2021; **4**: e2034266 [PMID: 33464319 DOI: 10.1001/jamanetworkopen.2020.34266]

12 **Franco C**, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, Scala R, Malerba M, Carlucci A, Negri EA, Spoladore G, Arcaro G, Tillio PA, Lastoria C, Schifino G, Tabbì L, Guidelli L, Guaraldi G, Ranieri VM, Clini E, Nava S. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J* 2020; **56** [PMID: 32747398 DOI: 10.1183/13993003.02130-2020]

13 **Cammarota G**, Esposito T, Azzolina D, Cosentini R, Menzella F, Aliberti S, Coppadoro A, Bellani G, Foti G, Grasselli G, Cecconi M, Pesenti A, Vitacca M, Lawton T, Ranieri VM, Di Domenico SL, Resta O, Gidaro A, Potalivo A, Nardi G, Brusasco C, Tesoro S, Navalesi P, Vaschetto R, De Robertis E. Noninvasive respiratory support outside the intensive care unit for acute respiratory failure related to coronavirus-19 disease: a systematic review and meta-analysis. *Crit Care* 2021; **25**: 268 [PMID: 34330320 DOI: 10.1186/s13054-021-03697-0]

14 **Shavadia JS**, Chen AY, Fanaroff AC, de Lemos JA, Kontos MC, Wang TY. Intensive Care Utilization in Stable Patients With ST-Segment Elevation Myocardial Infarction Treated With Rapid Reperfusion. *JACC Cardiovasc Interv* 2019; **12**: 709-717 [PMID: 31000008 DOI: 10.1016/j.jcin.2019.01.230]

15 **Santafé Colomina M**, Arikan Abelló F, Sánchez Corral A, Ferrer Roca R. Optimization of the neurosurgical patient in Intensive Care. *Medicina Intensiva (English Edition)* 2019; **43**: 489-496 [DOI: 10.1016/j.medine.2019.02.005]

16 **Howard RS**, Kullmann DM, Hirsch NP. Admission to neurological intensive care: who, when, and why? *J Neurol Neurosurg Psychiatry* 2003; **74** Suppl 3: iii2-iii9 [PMID: 12933908 DOI: 10.1136/jnnp.74.suppl_3.iii2]

17 **de Almeida CC**, Boone MD, Laviv Y, Kasper BS, Chen CC, Kasper EM. The Utility of Routine Intensive Care Admission for Patients Undergoing Intracranial Neurosurgical Procedures: A Systematic Review. *Neurocrit Care* 2018; **28**: 35-42 [PMID: 28808901 DOI: 10.1007/s12028-017-0433-4]

18 **Zemach S**, Helviz Y, Shitrit M, Friedman R, Levin PD. The Use of High-Flow Nasal Cannula Oxygen Outside the ICU. *Respir Care* 2019; **64**: 1333-1342 [PMID: 31213571 DOI: 10.4187/respcare.06611]

19 **Xia J**, Zhang Y, Ni L, Chen L, Zhou C, Gao C, Wu X, Duan J, Xie J, Guo Q, Zhao J, Hu Y, Cheng Z, Zhan Q. High-Flow Nasal Oxygen in Coronavirus Disease 2019 Patients With Acute Hypoxemic Respiratory Failure: A Multicenter, Retrospective Cohort Study. *Crit Care Med* 2020; **48**: e1079-e1086 [PMID: 32826432 DOI: 10.1097/CCM.0000000000004558]

20 **Spoletini G**, Alotaibi M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. *Chest* 2015; **148**: 253-261 [PMID: 25742321 DOI: 10.1378/chest.14-2871]

21 **Guy T**, Créac'hcadec A, Ricordel C, Salé A, Arnouat B, Bizec JL, Langelot M, Lineau C, Marquette D, Martin F, Lederlin M, Jouneau S. High-flow nasal oxygen: a safe, efficient treatment for COVID-19 patients not in an ICU. *Eur Respir J* 2020; **56** [PMID: 32859678 DOI: 10.1183/13993003.01154-2020]

22 **ASHE**. Medical Air and Oxygen Capacity Assessment Tool. 2020. [cited 11 July 2022]. Available from: https://www.ashe.org/medical-air-and-oxygen-capacity-assessment-tool

23 **World Health Organization**. Oxygen sources and distribution for COVID-19 treatment centres: interim guidance, 4 April 2020. [cited 18 June 2022]. Available from: https://www.who.int/publications/i/item/oxygen-sources-and-distribution-for-covid-19-treatment-centres

24 **Mangram AJ**, Mccauley T, Villarreal D, Berne J, Howard D, Dolly A, Norwood S. Families' perception of the value of timed daily "family rounds" in a trauma ICU. *Am Surg* 2005; **71**: 886-891 [PMID: 16468543]

25 **Lilly CM**, Thomas EJ. Tele-ICU: experience to date. *J Intensive Care Med* 2010; **25**: 16-22 [PMID: 19752038 DOI: 10.1177/0885066609349216]

26 **Udeh C**, Udeh B, Rahman N, Canfield C, Campbell J, Hata JS. Telemedicine/Virtual ICU: Where Are We and Where Are We Going? *Methodist Debakey Cardiovasc J* 2018; **14**: 126-133 [PMID: 29977469 DOI: 10.14797/mdcj-14-2-126]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 399-410

DOI: 10.5501/wjv.v11.i6.399

ISSN 2220-3249 (online)

MINIREVIEWS

Dipeptidyl peptidase 4 inhibitors in COVID-19: Beyond glycemic control

Niya Narayanan, Dukhabandhu Naik, Jayaprakash Sahoo, Sadishkumar Kamalanathan

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Liu D, China; Trevino S, Mexico

Received: March 27, 2022
Peer-review started: March 27, 2022
First decision: May 30, 2022
Revised: June 30, 2022
Accepted: October 4, 2022
Article in press: October 4, 2022
Published online: November 25, 2022

Niya Narayanan, Department of Endocrinology, Baby Memorial Hospital, Kozhikode 673005, Kerala, India

Dukhabandhu Naik, Jayaprakash Sahoo, Sadishkumar Kamalanathan, Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

Corresponding author: Dukhabandhu Naik, MD, Additional Professor, Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, 4th Floor, Super-speciality Block, JIPMER Campus, Dhanvantri Nagar, Puducherry 605006, India. drnaik2000@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) is associated with a high risk of mortality and complications in patients with diabetes mellitus. Achieving good glycemic control is very important in diabetic patients to reduce complications and mortality due to COVID-19. Recent studies have shown the mortality benefit and anti-inflammatory effects of Dipeptidyl-peptidase-4 inhibitors (DPP-4i) in diabetic patients with COVID-19. DPP-4i may have a beneficial role in halting the severity of infection primarily by three routes, namely viral entry inhibition, anti-inflammatory and anti-fibrotic effects and glycemic control. This has raised the promising hypothesis that DPP-4i might be an optimal strategy for treating COVID-19 in patients with diabetes. This review aims to summarise the possible therapeutic non-glycemic effects of DPP-4i in diabetic patients diagnosed with COVID-19 in the light of available evidence.

Key Words: Dipeptidyl-peptidase-4; Diabetes mellitus; COVID-19; Mortality

Core Tip: Patients with pre-existing comorbidities, particularly diabetes mellitus (DM), are at increased risk of complications from coronavirus disease 2019 (COVID-19). Beyond their glycemic effects, Dipeptidyl-peptidase-4 inhibitors (DPP-4i) have proven effective in COVID-19 individuals with DM. Available observational studies and trials have shown a significant mortality reduction in COVID-19 patients with DM when DPP-4i were continued during the course of illness. As a result, COVID-19 individuals with DM may choose DPP-4i as the preferred anti-diabetic medication if it is not contraindicated.

Citation: Narayanan N, Naik D, Sahoo J, Kamalanathan S. Dipeptidyl peptidase 4 inhibitors in COVID-19: Beyond glycemic control. *World J Virol* 2022; 11(6): 399-410
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/399.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.399

INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic is caused by a novel beta coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is similar to SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)[1]. Since late 2019, the disease has spread rapidly worldwide, posing a significant threat to public health. To date more than 539 million patients have been infected across the globe leading to over 6.32 million deaths[2]. The overall mortality rate for COVID-19 ranges from 0.7% to 10.8%[3]. Nearly two-thirds of severely affected individuals have comorbidities, most commonly cardiometabolic disorders, with diabetes mellitus (DM) accounting for 17% of cases[4].

Although DM is not associated with an increased risk of COVID-19, it confers a high risk of rapid progression in the severity of the infection and hence a poor prognosis. Specifically, people with DM are more prone to invasive mechanical ventilation, intensive care unit (ICU) admission, and the development of organ dysfunction, as compared with patients without diabetes[5,6]. A recent meta-analysis of 83 eligible studies with 78874 COVID-19 hospitalized patients found that people with pre-existing DM had a doubling of the risk for severe or critical COVID-19 illness (odds ratio [OR] 2.10, 95% confidence interval [95%CI] 1.71-2.57) and a tripling of the risk for in-hospital mortality (OR 2.68, 95%CI 2.09-3.44)[7]. Putative pathogenic processes linking COVID-19 and DM include hyperglycemia-mediated immune dysregulation, inflammation, and activation of the renin-angiotensin-aldosterone pathway[8].

The increasing spread of the SAR-CoV-2 infection and the high morbidity necessitates rapid identification of an effective therapy. While developing novel therapies (such as antivirals and vaccines) is a priority, repurposing "old" medications or reconsidering previously well-characterized targets with an emerging function in COVID-19 is the need of the hour. Dipeptidyl-peptidase-4 (DPP-4), also known as cluster of differentiation 26 (CD26), has recently been suggested as a potential target receptor for SAR-CoV-2[8,9]. MERS-CoV, a beta coronavirus similar to SARS-CoV-2, uses DPP-4 as an entrance receptor. Due to its similarity with the MERS-CoV, it has also been proposed that DPP-4 may aid SARS-CoV-2 entry into the target cells[10]. In this context, DPP-4i have gained increasing interest as a therapeutic target in patients with COVID-19.

DPP-4 is a 110 kDa glycoprotein, a membrane-bound endopeptidase that cleaves many peptide hormones such as cytokines, growth factors, and incretin hormones like glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP)[11]. Also, DPP-4 interacts with cellular proteins such as adenosine deaminase and caveolin-1 to regulate immune responses[12]. DPP-4 exists in two forms in the body, a membrane-bound form or as a soluble form (sDPP-4)[13]. The extracellular portion of DPP-4 is cleaved from cell membranes to form the 727 amino acid soluble moiety sDPP-4, which circulates in the plasma with retained enzyme activity. The DPP-4 receptor is found on the surface of nearly every cell and plays a role in immune regulation, signaling, and cell apoptosis. It is widely expressed in many tissues such as the kidney, gastrointestinal tract, and lungs. The primary role of DPP-4 is to regulate glucose and insulin metabolism by degradation of incretin hormones such as GLP-1 and GIP. Visceral adipose tissue has greater expression of DPP-4 and it has been linked to adipocyte inflammation and insulin resistance. DPP-4 promotes inflammation in subjects with type 2 diabetes through both catalytic and noncatalytic pathways. DPP-4 directly regulates the immune system by activating T cells and upregulating CD86 expression and the nuclear factor kappa B (NF-kB) pathway[14].

DIPEPTIDYL- PEPTIDASE-4 INHIBITORS

DPP-4i are oral anti-diabetic drugs that affect glucose homeostasis by inhibiting the enzyme DPP-4. DPP-4i prolong the half-life of incretins by deactivating DPP-4, which cleaves and inactivates them. Incretin hormones, GLP-1 and GIP are responsible for the regulation of postprandial insulin[15]. DPP-4i have been suggested to have cardiovascular benefits. Hence, these medications are commonly used in diabetic patients with a history of cardiovascular or chronic renal disease[16]. They achieve reasonable glycemic control with no significant effect on body weight, no risk of hypoglycemic events, and a safe cardiovascular profile. They have also shown a favorable effect on surrogate vascular markers, such as lipid profile, blood pressure, and endothelial function[13].

PROPOSED MECHANISMS OF DPP-4I IN COVID-19

DPP-4i can effectively control blood glucose levels with a favorable safety profile. Good glycemic control can improve the prognosis and outcome of COVID-19[17]. Hence, DPP-4i can influence the clinical outcome in COVID-19 patients through their glycemic effects. The mechanisms by which DPP-4i influence the clinical outcomes in COVID-19 patients with DM beyond their glycemic effect are still under speculation and are detailed below (Figures 1 and 2).

DPP-4 AND SARS-COV-2 INTERACTION

Role as an alternate co-receptor

SARS-CoV-2 binds to specific host receptors on the target cell to facilitate entry into the host cell. The SARS-CoV-2 enters the cell *via* binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE-2) receptor on the surface of the host cell membrane. The binding of the S-protein causes a conformational change in the receptor, which is essential for its activation. This critical step known as priming comprises the cleaving of the spike protein by cellular serine proteases. This step enables viral fusion with the cellular membrane and promotes viral entry into the target cell[18]. Studies have shown a wide distribution of ACE-2 across human tissues, including the lung, gastrointestinal tract, and kidney. However, the expression of ACE-2 on alveolar type 2 cells, which is supposed to be the primary target cell of SARS-CoV-2, is markedly low. This has created interest in a possible role for other co-receptors for viral entry[19].

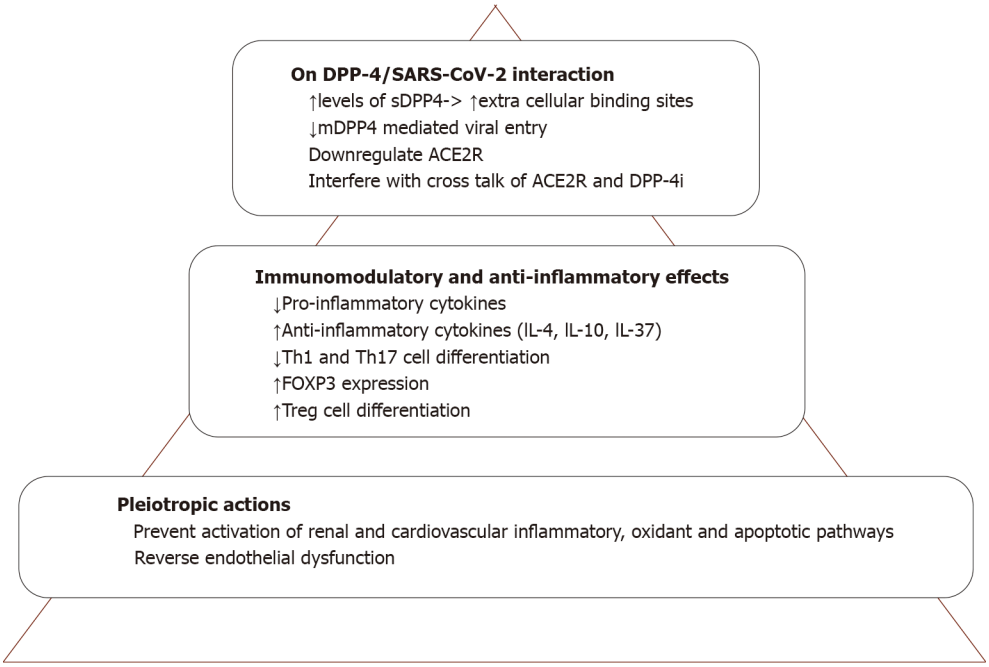
In-silico modelling of the SARS-CoV-2 spike protein, predicted a potential interaction with the DPP-4 in addition to ACE-2[20]. These models suggest that DPP-4 may be a co-receptor for SARS-CoV-2 viral entry. As DPP-4 is widely expressed in cells and tissues other than the respiratory tract, it may facilitate the spread of SARS-CoV-2 infection to a wider range of tissues[10]. DPP-4 is the receptor for the MERS-CoV spike protein, which mediates viral entrance into host cells[21]. Due to the high homology between SARS-CoV-2 and MERS-CoV, DPP-4 may also be an accessory entry receptor for SARS-CoV-2[22]. The presumed role of DPP-4 as a co-receptor for SARS-CoV-2 is still under study[14].

Cross-talk between DPP-4 and ACE-2 receptor

DPP-4 interacts with several essential proteins for viral processing, including ACE-2, implying a possible cross-talk between the two proteins[23]. *In vivo* studies have shown that the DPP-4i sitagliptin inhibits ACE activity and reduces angiotensin II levels in rats[24]. This cross-talk could interfere with viral surface binding and fusion, thereby affecting spread of the infection.

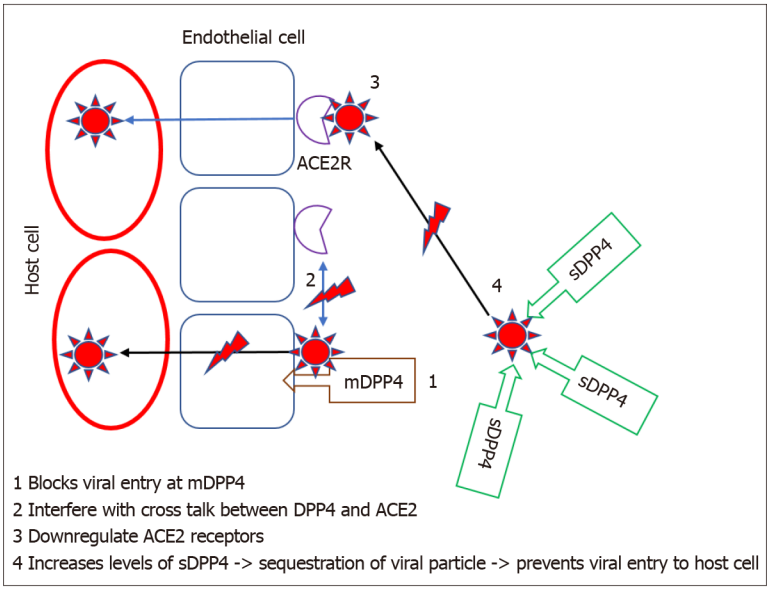
Role of soluble DPP-4

The fact that DPP-4 exists in two forms, a soluble form (sDPP-4) and membrane-bound form, adds to the intricacy of the role of DPP-4i in COVID-19. Previous research has shown that sDPP-4 acts as a decoy receptor for MERS-CoV, preventing viral replication[12]. The same may be applicable to SARS-CoV-2. sDPP-4 may bind SARS-CoV-2, preventing the virus from attaching to membrane-bound DPP-4 in the host cell, thereby hindering viral spread. A German study showed a reduced circulating level of sDPP-4 in patients with severe COVID-19[25]. A similar scenario was reported in MERS-CoV infected patients [26]. Previous studies have shown that sDPP-4 was significantly lower in older individuals than younger individuals[27]. Serum levels of sDPP-4 are also altered in various clinical diseases, such as DM, obesity, and metabolic syndrome, and are linked to insulin resistance[27,28]. This may contribute to the severe presentation of SARS-CoV-2 infection in diabetic, obese, and elderly individuals. In this regard, a recent study has shown a 50%-100% rise in the levels of sDPP-4 in mice after exposure to DPP-4i[29]. Hence, DPP-4i, in addition to interfering with viral entrance, may enhance viral particle sequestration in the circulation by increasing sDPP-4 levels, limiting viral growth in humans.



DOI: 10.5501/wjv.v11.i6.399

Figure 1 Proposed mechanisms of dipeptidyl peptidase-4 inhibitors in coronavirus disease 2019 infection. ACE2R: Angiotensin converting enzyme 2 receptor; COVID-19: Coronavirus disease 2019; DPP-4: Dipeptidyl peptidase-4; FOXP3: Forkhead box P3; IL: Interleukin; mDPP4: Membrane bound DPP4; sDPP4: Soluble DPP4; TGF-β: Transforming growth factor beta.



DOI: 10.5501/wjv.v11.i6.399

Figure 2 Hypothetical interactions between dipeptidyl peptidase-4 and severe acute respiratory syndrome coronavirus 2 virus. ACE-2: Angiotensin-converting enzyme 2; ACE2R: Angiotensin converting enzyme 2 receptor; DPP-4: Dipeptidyl peptidase-4; mDPP4: Membrane bound DPP4; sDPP4: Soluble DPP4.

Immunomodulatory role of DPP-4i

Dysregulated inflammation accounts for the severity of COVID-19. The severe presentation is linked to a hyperinflammatory state, characterized by an abnormal increase in circulating levels of pro-inflammatory cytokines such as Interleukin (IL)-1, IL-2, IL-6, Interferon-γ and tumor necrosis factor (TNF), leading to acute respiratory distress syndrome, disseminated intravascular coagulation, multi-organ failure, and death. There is significant activation of CD4+ and CD8+ T cells in COVID-19 patients and a skewing of T-cells toward the T-helper 17 functional phenotype[30]. DPP-4 is found in various cell lines involved in immune control, such as Th17 T helper cells, natural killer cells, activated B cells, macrophages, and myeloid cells[31]. DPP-4 promotes T cell proliferation, NF-kB activation, CD86

expression, and excessive production of inflammatory cytokines, all of which contribute to inflammation. Additionally, GLP-1, which DPP-4 degrades, also possesses anti-inflammatory properties[32].

DPP-4i reduce pro-inflammatory cytokines and mediators such as IL-1, IL-6, C-reactive protein (CRP), and TNF-alpha and thereby mitigate the severity of COVID-19. Many studies have shown that sitagliptin has anti-inflammatory effects in diabetic patients, which leads to an increase in the anti-inflammatory cytokine IL-10 and a decrease in several pro-inflammatory cytokines, such as TNF-alpha [13]. Therefore, the immunomodulatory effects of DPP-4i may prevent dysregulated inflammation and cytokine storms in COVID-19 patients, thereby reducing the severity of the disease.

Pleiotropic effects of DPP-4i

DPP-4i confer multiple vasculoprotective effects, which reduce the risk of comorbidities associated with DM, including hypertension, cardiovascular disease (CVD), and kidney disease. Insulin resistance, oxidative stress, dyslipidemia, adipose tissue dysfunction, and immune dysfunction may all contribute to endothelial dysfunction and arterial stiffness in DM. Beyond glycemic control, DPP-4i regulate these pathogenic mechanisms through GLP-1-dependent and independent pathways for CVD protection[33]. DPP-4i have been proven in numerous trials to prevent atherosclerosis, improve endothelial function, and promote wound healing possibly by modulating monocyte/macrophage-mediated responses, reducing oxidative stress, and decreasing neutrophil recruitment and activity[33]. As a result, Du *et al* [34] recently proposed DPP-4i as a potential therapy for preventing or treating CVD produced either directly or indirectly by the COVID-19-induced cytokine storm. Through their immune-modulatory action, DPP-4i have also been useful in obesity-related inflammation, hepatic fibrosis, myocarditis, diabetic nephropathy, and chemotherapy-induced kidney injury in animal research trials[31].

DPP-4 inhibition directly reduces lipopolysaccharide-induced lung damage in mice and human lung epithelial cells[35]. Soare *et al*[36] recently discovered that DPP-4 enhances fibroblast activation by increasing transforming growth factor β, a harbinger of tissue fibrosis. Hence, the inactivation of DPP-4 has significant anti-fibrotic effects, validated in numerous experimental models of pulmonary and skin fibrosis. Sadikot *et al*[37] have recently claimed that GLP-1 could be a new treatment for acute respiratory distress syndrome, demonstrating that human GLP-1 reduces NF-kB activation in cultured macrophages and a mouse model of acute lung damage. All these studies point to a possible anti-fibrotic role for DPP-4i.

OBSERVATIONAL STUDIES

With the above hypothesis, several observational studies have been performed to investigate the impact of DPP-4i on clinical outcomes in type 2 diabetes mellitus (T2DM) patients hospitalized for COVID-19 (Table 1).

In a cohort study conducted at the university hospital of Padova, amongst 403 patients hospitalized for COVID-19, 85 had DM, and nine were on DPP-4i. DPP-4i users and comparators had no significant difference in ICU admission or death rate[38]. In a retrospective observational study of 120 patients with diabetes, Chen *et al*[39] found that DPP-4i users and non-users had identical clinical outcomes. Users of DPP-4i had a non-significant higher rate of in-hospital death than non-users (OR 1.48, 95%CI 0.4-5.53). Similarly, after propensity score matching, Pérez-Belmonte *et al*[40] found that DPP-4i users were not at higher risk for adverse outcomes such as ICU admission, mechanical ventilation, multi-organ dysfunction, or long-term hospital admissions. In a few other observational studies there was no link between DPP-4i therapy and COVID-19-related mortality[41-46] and severity[44,47].

On the contrary, few observational studies have revealed that DPP-4i have favourable effects on COVID-19-related outcomes. In a case series encompassing 387 patients admitted to a research hospital in Lombardy (Northern Italy) with COVID-19, 90 patients were diabetic and 12.2% were on DPP-4i. After adjusting for confounders, DPP-4i use was associated with a decreased death risk [adjusted hazard ratio (HR) 0.13; 95%CI 0.02–0.92]. Furthermore, DPP-4i users required less non-invasive mechanical ventilation, implying that their pneumonia was less severe[48].

In a multicentric retrospective observational study conducted in Northern Italy, 169 age and gender-matched subjects treated with sitagliptin plus insulin were compared with a similar number of subjects treated with insulin therapy. Primary outcomes assessed were hospital discharge and death, and secondary outcomes analyzed were ICU admission, the need for mechanical ventilation, and extracorporeal membrane oxygenation. The sitagliptin users had significantly lower mortality (18% *vs* 37%, $P < 0.001$) even after adjusting for confounders like age, gender, comorbidities, and ongoing treatment (HR 0.44; 95%CI 0.29-0.66). On day 30, a larger number of patients treated with sitagliptin were discharged from the hospital than those on conventional therapy (71% *vs* 59%, $P < 0.01$). Compared to usual treatment, sitagliptin was associated with a lower probability of needing mechanical ventilation and ICU admission. At follow-up, patients treated with sitagliptin had significantly lower inflammatory markers such as procalcitonin and CRP and lower mean blood glucose levels during hospitalization[49].

Similarly, a Korean database-based retrospective study found that DPP-4i treatment was significantly associated with better clinical outcomes even after adjusting for age, gender, comorbidities, and

Table 1 Observation studies assessing coronavirus disease 2019 outcomes and dipeptidyl peptidase-4 inhibitors therapy

Sl no	Ref.	Design, location	Population	Findings
Studies with neutral outcomes with the use of DPP-4i				
1	Fadini *et al* [38], 2020	RO, Italy	Registry based DM patients with and without COVID-19. Subgroup analysis of proportion of DPP-4i users	Diabetic COVID-19 patients who were on DPP-4i had a similar disease outcome as those who were not
2	Chen *et al* [39], 2020	RO, China	Single centre hospitalised COVID-19 patients with DM; DPP-4i users (n = 20) compared with nonusers (n = 100)	Mortality OR 1.48, 95%CI 0.4-5.53, P = 0. 56
3	Pérez-Belmonte *et al*[40], 2020	RO, Spain	Registry based COVID-19 patients with DM. DPP-4i users (n = 105) compared with nonusers (n = 105)	Composite outcome of ICU admission, mechanical ventilation, or in-hospital death: OR 1.12, 95%CI 0.65-1.95, P = 0.675
4	Silverii *et al* [41], 2021	RO, Italy	Registry based all deaths due to COVID-19 infection; Subgroup analysis of DPP-4i users (n = 13) *vs* nonusers (n = 146) in DM patients	Mortality risk in COVID-19 infection. HR 1.0, 95%CI 0.5-2.1, P = 0.56
5	Kim *et al* [42], 2020	RO, Korea	Single centre hospitalised COVID-19 patients with and without DM; Subgroup analysis of DM patients using DPP-4i (n = 85) and others (n = 235)	Mortality OR 1.47, 95%CI 0.45-4.78, P = 0.52; Severe disease OR 1.05, 95%CI 0.44-2.49, P = 0.92
6	Noh *et al* [43], 2021	PO, South Korea	Registry based COVID-19 patients with DM; Mortality in DPP-4i users (n = 453) compared with nonusers (n = 133)	All-cause mortality: HR 0.74, 95%CI 0.43-1.26; Severe disease HR 0.83, 95%CI 0.45-1.53
7	Zhou *et al* [44], 2020	RO, China	Multi-centre, hospitalised COVID-19 patients with DM; Subgroup analysis of DPP-4i users (n = 142) *vs* nonusers (n = 1257)	28-d mortality: aHR = 0.44, 95%CI: 0.09-2.11, P = 0.31); Secondary outcomes such as septic shock, acute respiratory distress syndrome, organ (kidney, liver, and cardiac) injuries, were also comparable between the two groups
8	Yan *et al*[47], 2020	RO, China	Hospitalised COVID-19 patients; Subgroup analysis of DPP-4i use in patients with severe illness	No significant association between use of DPP-4i and COVID-19 severity after adjustment for age, sex, and BMI (OR 0.32, 95%CI 0.02-2.18, P = 0.31)
9	Izzi-Engbeaya *et al*[45], 2021	RO, United Kingdom	Registry based COVID-19 patients with DM admitted to 3 hospitals (n = 337); DPP-4i users (n = 93)	Admission to ICU or death OR 1.27 (0.79-2.05)
10	Israelsen *et al* [46], 2021	RO, Denmark	Registry based COVID-19 patients with DM; DPP-4i users (n = 284) compared with SGLT2i users (n = 342)	DPP-4i users- 30-d mortality aRR 2.42 (95%CI 0.99-5.89) when compared with SGLT-2i users. DPP-4i use was not associated with decreased risk of hospital admission
Studies with positive outcomes with the use of DPP-4i				
1	Mirani *et al* [48], 2020	RO, Italy	Single centre hospitalised COVID-19 patients with DM; DPP-4i users (n =11) compared with nonusers (n=79)	DPP-4i users had lower risk of mortality (aHR 0.13, 95%CI 0.02-0.92; P = 0.042)
2	Solerte *et al* [49], 2020	RO case control, Italy	Hospitalised COVID-19 patients with DM; Case sitagliptin + Standard care (n = 169) Controls – age sex matched patients with Standard care (n = 338)	Mortality: HR 0.44, 95%CI 0.29–0.66, P = 0.0001); Admission to ICU: HR: 0.51, 95%CI 0.27-0.95, P = 0.03; Mechanical ventilation HR: 0.27, 95% CI 0.11-0.62, P = 0.03; Hospital discharges 120 *vs* 89, P < 0.01
3	Rhee *et al* [50], 2021	RO, South Korea	Registry based COVID-19 patients with DM; DPP-4i users (n = 263) *vs* non users (n = 832); Assessed for severity of disease	OR for severe disease was 0.303 (95%CI 0.135-0.682) among DPP-4i users
4	Nafakhi *et al* [51], 2020	RO, Iraq	Newly diagnosed COVID-19 pneumonia; Subgroup analysis to assess predictors for adverse outcomes	DPP-4i users had decreased length of ICU stay. (OR 0.3, 95%CI 0.2-3, P = 0.04)
5	Wargny *et al* [52], 2021	PO, France	Registry based COVID-19 patients with DM. Subgroup analysis of DPP-4i use in patients succumbing to death within 28 d	The need for mechanical ventilation and death within seven days were similar in DPP-4i users compared to nonusers. (OR 0.83, 95%CI 0.65-1.05, P = 0.12). Discharge at day 28: OR 1.22, 95%CI 1.02-1.47, P = 0.03)

6	Wong *et al* [53], 2021	RO, China	Registry based COVID-19 patients with DM (n = 1214); DPP-4i users (n = 107) compared with others (n = 1107)	DPP4i users were associated with lower odds of clinical deterioration (OR 0.71, 95%CI 0.54-0.93, P = 0.013), hyperinflammatory syndrome (OR = 0.56, 95%CI 0.45-0.69, P < 0.001), invasive mechanical ventilation (OR = 0.30, 95%CI 0.21-0.42, P < 0.001), reduced length of hospitalization (-4.82 days, 95%CI -6.80 to -2.84, P < 0.001). No difference seen in mortality
Studies with negative outcomes with the use of DPP-4i				
1	Dalan *et al* [54], 2021	RO, Singapore	Single centre hospitalised COVID-19 patients with and without DM; Subgroup analysis of DM patients using DPP-4i (n = 27) and others (n = 49)	DPP-4i were at higher risk of ICU admission (aRR 4.07, 95%CI 1.42-11.66) and mechanical ventilation (aRR 2.54, 95%CI 0.43-14.99)
2	Khunti *et al* [55], 2021	RO, United Kingdom	Registry based Nationwide cohort data; HR of COVID-19-related mortality assessed in patients with diabetes on DPP-4i	HR 1.07 (1.01-1.13)

COVID-19: Coronavirus disease 2019; DPP-4i: Dipeptidyl peptidase-4 inhibitors; CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; n: Number of patients on DPP-4i; N: Number of patients with diabetes; OR: Odds ratio; PO: Prospective observational; RO: Retrospective observational; RR: Relative risk;

medications (adjusted OR 0.362, 95%CI 0.135-0.971). The study included 832 subjects with DM, of whom 263 were on DPP-4i[50]. Similarly, DPP-4i usage was related to a shorter ICU stay in 67 patients with DM admitted with COVID-19 pneumonia in a single centre in Iraq (OR 0.3, 95%CI 0.2-3)[51].

In the coronavirus disease and diabetes outcome (CORONADO) study, a multicentric prospective observational trial conducted in France, 2796 patients hospitalized for SARS-CoV-2 with DM were assessed. Around 21.6% of the participants were on DPP-4i. The primary outcome as assessed by the need for mechanical ventilation and/or death within seven days was similar in DPP-4i users compared to nonusers (OR 0.83; 95%CI 0.67-1.03)[52]. Wong *et al*[53] retrospectively analyzed 1214 T2DM patients with confirmed COVID-19 admitted to public hospitals in Hong Kong. They found a lower risk for clinical deterioration (OR = 0.71, 95%CI 0.54-0.93), hyperinflammatory syndrome (OR = 0.56, 95%CI 0.45-0.69) and invasive mechanical ventilation (OR = 0.30, 95%CI 0.21-0.42) in DPP-4i users. However, DPP-4i users had no significant in-hospital mortality reduction.

A retrospective review of 717 COVID-19 patients admitted to a health care centre in Singapore found contradictory results. Patients on DPP-4i (n = 27) showed greater odds of ICU admission than those on other glucose-lowering medicines (adjusted relative risk [RR] 5.14, 95%CI 1.5-17.7). Also, patients on DPP-4i were more likely to require mechanical ventilation; however, no data on mortality were provided[54]. Similarly, Khunti *et al*[55] in their nationwide observational cohort study in the UK analysed the HR of COVID-19-related mortality in people prescribed DPP-4i. DPP-4i users had a HR of 1.07 (95%CI 1.01-1.13) for COVID-19-related mortality.

The evidence available from observational studies on the link between DPP-4i and DM and COVID-19 outcomes suggests some heterogeneity. These outcomes were extensively evaluated in multiple meta-analyses[56-62]. Bonora *et al*[56] analyzed seven studies that reported data on mortality. There was no significant difference in death rate between patients treated with DPP-4i and other anti-diabetic medications (RR 0.74, 95%CI 0.47–1.16). Han *et al*[57] also showed similar results with a statistically non-significant lower mortality (OR 0.95, 95%CI 0.72-1.26) or poor composite outcomes (OR 1.27, 95%CI 0.91–1.77) in diabetic COVID-19 patients. Similarly, Pal *et al*[58] included nine observational studies of high quality consisting of 7008 COVID-19 patients with DM. A pooled analysis of unadjusted and adjusted data revealed no significant link between DPP-4i usage and mortality. However, subgroup analysis discovered that DPP-4i use in the hospital (rather than before admission) was related to lower mortality (adjusted OR 0.27, 95%CI 0.13-0.55). Contrary to the above studies, Nguyen *et al*[59] in their recent meta-analysis linked DPP-4i to a higher mortality risk (OR 1.23, 95%CI 1.07-1.42).

DPP-4i appear to have a neutral action in COVID-19, but the available studies are still insufficient to draw definitive conclusions. It is worth noting that all the data are from retrospective observational studies and that most of them were not specifically designed to study the effects of DPP-4i. The discrepancies reported for the connection between DPP-4i and COVID-19 outcomes could be explained by variations in methodology, baseline characteristics, and sample size.

RANDOMIZED CONTROLLED TRIALS

Two randomized controlled trials (RCTs) have evaluated DPP-4i in patients with diabetes and COVID-19 (Table 2).

Abuhasira *et al*[63] investigated 64 patients who were randomized to receive linagliptin 5 mg once daily or standard of care medication in an open-label, prospective, multicentre RCT (32 in each group).

Table 2 Randomized controlled trials assessing coronavirus disease 2019 outcomes and dipeptidyl peptidase-4 inhibitors therapy

Sl no	Ref.	Design, location	Comparators	Age (mean ± SD)	% male	Primary outcomes	Secondary outcomes	Results
1	Abuhasira *et al*[63]	Open-label, prospective, multi-centre trial, Germany	Linagliptin 5 mg + standard therapy (n = 32); Standard therapy (n = 32)	65.5 ± 16; 68.4 ± 11.5	65.6%; 53.1%	Time to clinical improvement	Proportion of patients with 2- point clinical improvement at 28 d, mortality at 28 d, length of hospitalization, ICU admissions, and MV	Time to clinical improvement (HR 1.22; 95%CI, 0.70-2.15; P = 0.49); In-hospital mortality; (OR 0.56; 95%CI, 0.16-1.93). No difference in secondary outcomes
2	Guardado-Mendoza *et al*[64]	Parallel double blind single centre trial, Mexico	LI group (n = 35) I group (n = 38)	57 ± 2; 60 ± 2	51%; 76%	Need for assisted MV and mortality	Glucose levels and insulin requirements, pulmonary parameters and clinical progression	Reduced risk of assisted MV; (HR 0.258, 95%CI 0.1-0.7, P = 0.009), improved blood glucose levels, lower insulin requirements in LI group

HR: Hazard risk, I: Insulin, LI: Linaglitin plus insulin, MV: Mechanical ventilation, OR: Odds ratio, RR: Relative risk, SD: Standard deviation.

The time to clinical improvement within 28 d of randomization was the primary outcome measured. Treatment with linagliptin in addition to standard therapy did not enhance time to resolution of symptoms (HR 1.22, 95%CI, 0.70-2.15) or death on day 28 (OR 0.56, 95%CI 0.16-1.93). Furthermore, no differences in any of the secondary outcomes, such as the proportion of patients admitted to an ICU, mechanical ventilation rates, length of hospitalization, or supplemental oxygen use, were observed between the study groups. However, due to containment of the COVID-19 epidemic in Israel, the experiment was prematurely terminated, leaving the study underpowered to identify possible differences in the primary results and mortality.

In a parallel, double-blind RCT, Guardado-Mendoza *et al*[64] evaluated the efficacy of the combination of linagliptin and insulin on metabolic control and prognosis in hospitalized patients with COVID-19 and DM. A total of 73 patients were randomly assigned to either 5 mg linagliptin plus insulin (LI group, n = 35) or insulin alone (I group, n = 38). The need for assisted mechanical ventilation and mortality were the two primary outcomes. Secondary outcomes were glucose levels and insulin requirements during the first 5-10 days in the hospital, pulmonary parameters, and clinical progression of COVID-19. Both groups had similar average hospital stays (12 ± 1 *vs* 10 ± 1 d, P = 0.343). Three patients in the LI group and twelve in the I group needed assisted mechanical ventilation (HR 0.258, 95%CI 0.092-0.719), and two patients in the LI group and six in the I group died after a 30-d follow-up period (P = 0.139). The inclusion of linagliptin reduced the relative risk of assisted mechanical ventilation by 74% and improved pre- and postprandial glucose levels, requiring less insulin and posing no increased risk of hypoglycemia.

CONCLUSION

Beyond their well-known glycemic role, DPP-4i have anti-inflammatory, immunomodulatory, and anti-fibrotic properties. They are among the non-insulin glucose-lowering medications that are safe and effective in treating T2DM, even in the presence of COVID-19, without increasing the risk of significant side effects such as hypoglycemia. As a result, practical recommendations for the management of diabetes in patients with COVID-19 do not propose stopping DPP-4i. Even though results from observational studies and a few RCTs have been inconsistent, the existing evidence suggests that DPP-4i are safe for patients with T2DM and COVID-19. Studies showed a trend towards reducing mortality in COVID-19 patients with DM, especially with continued in-hospital use of DPP-4i. As a result, it is appropriate to start or continue DPP-4i in COVID-19 individuals with DM unless contraindicated.

FOOTNOTES

Author contributions: Naik D conceptualized the work; Narayanan N wrote the first draft and provided critical inputs; Sahoo J, Naik D, and Kamalanathan S supervised the writing and critically revised the manuscript; Narayanan N edited the final draft; all authors have read and approved the final version of the manuscript

Conflict-of-interest statement: All authors have no conflicts of interest to report.

Country/Territory of origin: India

ORCID number: Niya Narayanan 0000-0001-8403-7756; Dukhabandhu Naik 0000-0003-4568-877X; Jayaprakash Sahoo 0000-0002-8805-143X; Sadishkumar Kamalanathan 0000-0002-2371-0625.

S-Editor: Liu JH
L-Editor: Webster JR
P-Editor: Liu JH

REFERENCES

1 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
2 COVID Live - Coronavirus Statistics - Worldometer. Available from: https://www.worldometers.info/coronavirus/?%3D%3D
3 **Omer SB**, Malani P, Del Rio C. The COVID-19 Pandemic in the US: A Clinical Update. *JAMA* 2020; **323**: 1767-1768 [PMID: 32250388 DOI: 10.1001/jama.2020.5788]
4 **Grasselli G**, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574-1581 [PMID: 32250385 DOI: 10.1001/jama.2020.5394]
5 **Fadini GP**, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest* 2020; **43**: 867-869 [PMID: 32222956 DOI: 10.1007/s40618-020-01236-2]
6 **Pal R**, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr* 2020; **14**: 513-517 [PMID: 32388331 DOI: 10.1016/j.dsx.2020.04.049]
7 **Mantovani A**, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis* 2020; **30**: 1236-1248 [PMID: 32571616 DOI: 10.1016/j.numecd.2020.05.014]
8 **Lim S**, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol* 2021; **17**: 11-30 [PMID: 33188364 DOI: 10.1038/s41574-020-00435-4]
9 **Iacobellis G**. COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Res Clin Pract* 2020; **162**: 108125 [PMID: 32224164 DOI: 10.1016/j.diabres.2020.108125]
10 **Li Y**, Zhang Z, Yang L, Lian X, Xie Y, Li S, Xin S, Cao P, Lu J. The MERS-CoV Receptor DPP4 as a Candidate Binding Target of the SARS-CoV-2 Spike. *iScience* 2020; **23**: 101160 [PMID: 32405622 DOI: 10.1016/j.isci.2020.101160]
11 **Lambeir AM**, Durinx C, Scharpé S, De Meester I. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV. *Crit Rev Clin Lab Sci* 2003; **40**: 209-294 [PMID: 12892317 DOI: 10.1080/713609354]
12 **Krejner-Bienias A**, Grzela K, Grzela T. DPP4 Inhibitors and COVID-19-Holy Grail or Another Dead End? *Arch Immunol Ther Exp (Warsz)* 2021; **69**: 1 [PMID: 33527308 DOI: 10.1007/s00005-020-00602-5]
13 **Kifle ZD**, Woldeyohanin AE, Demeke CA. SARS-CoV-2 and diabetes: A potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19. *Metabol Open* 2021; **12**: 100134 [PMID: 34661092 DOI: 10.1016/j.metop.2021.100134]
14 **Bassendine MF**, Bridge SH, McCaughan GW, Gorrell MD. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? *J Diabetes* 2020; **12**: 649-658 [PMID: 32394639 DOI: 10.1111/1753-0407.13052]
15 **Nauck MA**, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab* 2018; **20** Suppl 1: 5-21 [PMID: 29364588 DOI: 10.1111/dom.13129]
16 **Hanssen NM**, Jandeleit-Dahm KA. Dipeptidyl peptidase-4 inhibitors and cardiovascular and renal disease in type 2 diabetes: What have we learned from the CARMELINA trial? *Diab Vasc Dis Res* 2019; **16**: 303-309 [PMID: 31018682 DOI: 10.1177/1479164119842339]
17 **Apicella M**, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8**: 782-792 [PMID: 32687793 DOI: 10.1016/S2213-8587(20)30238-2]
18 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]
19 **Qi F**, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020; **526**: 135-140 [PMID: 32199615 DOI:

10.1016/j.bbrc.2020.03.044]
20 **Vankadari N**, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. *Emerg Microbes Infect* 2020; **9**: 601-604 [PMID: 32178593 DOI: 10.1080/22221751.2020.1739565]
21 **Lu G**, Hu Y, Wang Q, Qi J, Gao F, Li Y, Zhang Y, Zhang W, Yuan Y, Bao J, Zhang B, Shi Y, Yan J, Gao GF. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. *Nature* 2013; **500**: 227-231 [PMID: 23831647 DOI: 10.1038/nature12328]
22 **Eleftheriou P**, Amanatidou D, Petrou A, Geronikaki A. In Silico Evaluation of the Effectivity of Approved Protease Inhibitors against the Main Protease of the Novel SARS-CoV-2 Virus. *Molecules* 2020; **25** [PMID: 32485894 DOI: 10.3390/molecules25112529]
23 **Dastan F**, Abedini A, Shahabi S, Kiani A, Saffaei A, Zare A. Sitagliptin Repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and Inflammatory Cytokine Storms in the Lung. *Iran J Allergy Asthma Immunol* 2020; **19**: 10-12 [PMID: 32534505 DOI: 10.18502/ijaai.v19i(s1.r1).2849]
24 **Beraldo JI**, Benetti A, Borges-Júnior FA, Arruda-Junior DF, Martins FL, Jensen L, Dariolli R, Shimizu MH, Seguro AC, Luchi WM, Girardi ACC. Cardioprotection Conferred by Sitagliptin Is Associated with Reduced Cardiac Angiotensin II/Angiotensin-(1-7) Balance in Experimental Chronic Kidney Disease. *Int J Mol Sci* 2019; **20** [PMID: 31010001 DOI: 10.3390/ijms20081940]
25 **Schlicht K**, Rohmann N, Geisler C, Hollstein T, Knappe C, Hartmann K, Schwarz J, Tran F, Schunk D, Junker R, Bahmer T, Rosenstiel P, Schulte D, Türk K, Franke A, Schreiber S, Laudes M. Circulating levels of soluble Dipeptidylpeptidase-4 are reduced in human subjects hospitalized for severe COVID-19 infections. *Int J Obes (Lond)* 2020; **44**: 2335-2338 [PMID: 32958905 DOI: 10.1038/s41366-020-00689-y]
26 **Inn KS**, Kim Y, Aigerim A, Park U, Hwang ES, Choi MS, Kim YS, Cho NH. Reduction of soluble dipeptidyl peptidase 4 Levels in plasma of patients infected with Middle East respiratory syndrome coronavirus. *Virology* 2018; **518**: 324-327 [PMID: 29587190 DOI: 10.1016/j.virol.2018.03.015]
27 **Lamers D**, Famulla S, Wronkowitz N, Hartwig S, Lehr S, Ouwens DM, Eckardt K, Kaufman JM, Ryden M, Müller S, Hanisch FG, Ruige J, Arner P, Sell H, Eckel J. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes* 2011; **60**: 1917-1925 [PMID: 21593202 DOI: 10.2337/db10-1707]
28 **Röhrborn D**, Wronkowitz N, Eckel J. DPP4 in Diabetes. *Front Immunol* 2015; **6**: 386 [PMID: 26284071 DOI: 10.3389/fimmu.2015.00386]
29 **Varin EM**, Mulvihill EE, Beaudry JL, Pujadas G, Fuchs S, Tanti JF, Fazio S, Kaur K, Cao X, Baggio LL, Matthews D, Campbell JE, Drucker DJ. Circulating Levels of Soluble Dipeptidyl Peptidase-4 Are Dissociated from Inflammation and Induced by Enzymatic DPP4 Inhibition. *Cell Metab* 2019; **29**: 320-334.e5 [PMID: 30393019 DOI: 10.1016/j.cmet.2018.10.001]
30 **Pinheiro MM**, Fabbri A, Infante M. Cytokine storm modulation in COVID-19: a proposed role for vitamin D and DPP-4 inhibitor combination therapy (VIDPP-4i). *Immunotherapy* 2021; **13**: 753-765 [PMID: 33906375 DOI: 10.2217/imt-2020-0349]
31 **Pantanetti P**, Cangelosi G, Ambrosio G. Potential role of incretins in diabetes and COVID-19 infection: a hypothesis worth exploring. *Intern Emerg Med* 2020; **15**: 779-782 [PMID: 32592113 DOI: 10.1007/s11739-020-02389-x]
32 **Klemann C**, Wagner L, Stephan M, von Hörsten S. Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. *Clin Exp Immunol* 2016; **185**: 1-21 [PMID: 26919392 DOI: 10.1111/cei.12781]
33 **Aroor AR**, Sowers JR, Jia G, DeMarco VG. Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system. *Am J Physiol Heart Circ Physiol* 2014; **307**: H477-H492 [PMID: 24929856 DOI: 10.1152/ajpheart.00209.2014]
34 **Du H**, Wang DW, Chen C. The potential effects of DPP-4 inhibitors on cardiovascular system in COVID-19 patients. *J Cell Mol Med* 2020; **24**: 10274-10278 [PMID: 32713161 DOI: 10.1111/jcmm.15674]
35 **Kawasaki T**, Chen W, Htwe YM, Tatsumi K, Dudek SM. DPP4 inhibition by sitagliptin attenuates LPS-induced lung injury in mice. *Am J Physiol Lung Cell Mol Physiol* 2018; **315**: L834-L845 [PMID: 30188745 DOI: 10.1152/ajplung.00031.2018]
36 **Soare A**, Györfi HA, Matei AE, Dees C, Rauber S, Wohlfahrt T, Chen CW, Ludolph I, Horch RE, Bäuerle T, von Hörsten S, Mihai C, Distler O, Ramming A, Schett G, Distler JHW. Dipeptidylpeptidase 4 as a Marker of Activated Fibroblasts and a Potential Target for the Treatment of Fibrosis in Systemic Sclerosis. *Arthritis Rheumatol* 2020; **72**: 137-149 [PMID: 31350829 DOI: 10.1002/art.41058]
37 **Sadikot RT**, Rubinstein I. Long-acting, multi-targeted nanomedicine: addressing unmet medical need in acute lung injury. *J Biomed Nanotechnol* 2009; **5**: 614-619 [PMID: 20201223 DOI: 10.1166/jbn.2009.1078]
38 **Fadini GP**, Morieri ML, Longato E, Bonora BM, Pinelli S, Selmin E, Voltan G, Falaguasta D, Tresso S, Costantini G, Sparacino G, Di Camillo B, Tramontan L, Cattelan AM, Vianello A, Fioretto P, Vettor R, Avogaro A. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. *Diabetes Obes Metab* 2020; **22**: 1946-1950 [PMID: 32463179 DOI: 10.1111/dom.14097]
39 **Chen Y**, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y, Zheng L, Huang K. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care* 2020; **43**: 1399-1407 [PMID: 32409498 DOI: 10.2337/dc20-0660]
40 **Pérez-Belmonte LM**, Torres-Peña JD, López-Carmona MD, Ayala-Gutiérrez MM, Fuentes-Jiménez F, Huerta LJ, Muñoz JA, Rubio-Rivas M, Madrazo M, Garcia MG, Montes BV, Sola JF, Ena J, Ferrer RG, Pérez CM, Ripper CJ, Lecumberri JJN, Acedo IEA, Canteli SP, Cosío SF, Martínez FA, Rodríguez BC, Pérez-Martínez P, Ramos-Rincón JM, Gómez-Huelgas R; SEMI-COVID-19 Network. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. *BMC Med* 2020; **18**: 359 [PMID: 33190637 DOI: 10.1186/s12916-020-01832-2]
41 **Silverii GA**, Monami M, Cernigliaro A, Vigneri E, Guarnotta V, Scondotto S, Allotta VA, Conti M, Giordano C, Mannucci E. Are diabetes and its medications risk factors for the development of COVID-19? *Nutr Metab Cardiovasc Dis* 2021; **31**:

396-398 [PMID: 33223405 DOI: 10.1016/j.numecd.2020.09.028]
42 **Kim MK**, Jeon JH, Kim SW, Moon JS, Cho NH, Han E, You JH, Lee JY, Hyun M, Park JS, Kwon YS, Choi YK, Kwon KT, Lee SY, Jeon EJ, Kim JW, Hong HL, Kwon HH, Jung CY, Lee YY, Ha E, Chung SM, Hur J, Ahn JH, Kim NY, Chang HH, Lee YH, Lee J, Park KG, Kim HA, Lee JH. The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea. *Diabetes Metab J* 2020; **44**: 602-613 [PMID: 32794386 DOI: 10.4093/dmj.2020.0146]
43 **Noh Y**, Oh IS, Jeong HE, Filion KB, Yu OHY, Shin JY. Association Between DPP-4 Inhibitors and COVID-19-Related Outcomes Among Patients With Type 2 Diabetes. *Diabetes Care* 2021; **44**: e64-e66 [PMID: 33547204 DOI: 10.2337/dc20-1824]
44 **Zhou JH**, Wu B, Wang WX, Lei F, Cheng X, Qin JJ, Cai JJ, Zhang XJ, Zhou F, Liu YM, Li HM, Zhu LH, She ZG, Zhang X, Yang J, Li HL. No significant association between dipeptidyl peptidase-4 inhibitors and adverse outcomes of COVID-19. *World J Clin Cases* 2020; **8**: 5576-5588 [PMID: 33344548 DOI: 10.12998/wjcc.v8.i22.5576]
45 **Izzi-Engbeaya C**, Distaso W, Amin A, Yang W, Idowu O, Kenkre JS, Shah RJ, Woin E, Shi C, Alavi N, Bedri H, Brady N, Blackburn S, Leczycka M, Patel S, Sokol E, Toke-Bjolgerud E, Qayum A, Abdel-Malek M, Hope DCD, Oliver NS, Bravis V, Misra S, Tan TM, Hill NE, Salem V. Adverse outcomes in COVID-19 and diabetes: a retrospective cohort study from three London teaching hospitals. *BMJ Open Diabetes Res Care* 2021; **9** [PMID: 33408084 DOI: 10.1136/bmjdrc-2020-001858]
46 **Israelsen SB**, Pottegård A, Sandholdt H, Madsbad S, Thomsen RW, Benfield T. Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2. *Diabetes Obes Metab* 2021; **23**: 1397-1401 [PMID: 33502076 DOI: 10.1111/dom.14329]
47 **Yan H**, Valdes AM, Vijay A, Wang S, Liang L, Yang S, Wang H, Tan X, Du J, Jin S, Huang K, Jiang F, Zhang S, Zheng N, Hu Y, Cai T, Aithal GP. Role of Drugs Used for Chronic Disease Management on Susceptibility and Severity of COVID-19: A Large Case-Control Study. *Clin Pharmacol Ther* 2020; **108**: 1185-1194 [PMID: 32910830 DOI: 10.1002/cpt.2047]
48 **Mirani M**, Favacchio G, Carrone F, Betella N, Biamonte E, Morenghi E, Mazziotti G, Lania AG. Impact of Comorbidities and Glycemia at Admission and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes With COVID-19: A Case Series From an Academic Hospital in Lombardy, Italy. *Diabetes Care* 2020; **43**: 3042-3049 [PMID: 33023989 DOI: 10.2337/dc20-1340]
49 **Solerte SB**, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, Dell'Acqua M, Ippolito E, Scaranna C, Bellante R, Galliani S, Dodesini AR, Lepore G, Geni F, Fiorina RM, Catena E, Corsico A, Colombo R, Mirani M, De Riva C, Oleandri SE, Abdi R, Bonventre JV, Rusconi S, Folli F, Di Sabatino A, Zuccotti G, Galli M, Fiorina P. Sitagliptin Treatment at the Time of Hospitalization Was Associated With Reduced Mortality in Patients With Type 2 Diabetes and COVID-19: A Multicenter, Case-Control, Retrospective, Observational Study. *Diabetes Care* 2020; **43**: 2999-3006 [PMID: 32994187 DOI: 10.2337/dc20-1521]
50 **Rhee SY**, Lee J, Nam H, Kyoung DS, Shin DW, Kim DJ. Effects of a DPP-4 Inhibitor and RAS Blockade on Clinical Outcomes of Patients with Diabetes and COVID-19. *Diabetes Metab J* 2021; **45**: 251-259 [PMID: 33752274 DOI: 10.4093/dmj.2020.0206]
51 **Nafakhi H**, Alareedh M, Al-Buthabhak K, Shaghee F, Nafakhi A, Kasim S. Predictors of adverse in-hospital outcome and recovery in patients with diabetes mellitus and COVID-19 pneumonia in Iraq. *Diabetes Metab Syndr* 2021; **15**: 33-38 [PMID: 33296788 DOI: 10.1016/j.dsx.2020.12.014]
52 **Wargny M**, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou PY, Bonnet JB, Bordier L, Bourron O, Chaumeil C, Chevalier N, Darmon P, Delenne B, Demarsy D, Dumas M, Dupuy O, Flaus-Furmaniuk A, Gautier JF, Guedj AM, Jeandidier N, Larger E, Le Berre JP, Lungo M, Montanier N, Moulin P, Plat F, Rigalleau V, Robert R, Seret-Bégué D, Sérusclat P, Smati S, Thébaut JF, Tramunt B, Vatier C, Velayoudom FL, Vergès B, Winiszewski P, Zabulon A, Gourraud PA, Roussel R, Cariou B, Hadjadj S; CORONADO investigators. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia* 2021; **64**: 778-794 [PMID: 33599800 DOI: 10.1007/s00125-020-05351-w]
53 **Wong CKH**, Lui DTW, Lui AYC, Kwok ACY, Low MCH, Lau KTK, Au ICH, Xiong X, Chung MSH, Lau EHY, Cowling BJ. Use of DPP4i reduced odds of clinical deterioration and hyperinflammatory syndrome in COVID-19 patients with type 2 diabetes: Propensity score analysis of a territory-wide cohort in Hong Kong. *Diabetes Metab* 2022; **48**: 101307 [PMID: 34863934 DOI: 10.1016/j.diabet.2021.101307]
54 **Dalan R**, Ang LW, Tan WYT, Fong SW, Tay WC, Chan YH, Renia L, Ng LFP, Lye DC, Chew DEK, Young BE. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. *Eur Heart J Cardiovasc Pharmacother* 2021; **7**: e48-e51 [PMID: 32766831 DOI: 10.1093/ehjcvp/pvaa098]
55 **Khunti K**, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N, Kar P, Meace C, Sattar N, Sharp S, Wareham NJ, Weaver A, Woch E, Young B, Valabhji J. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol* 2021; **9**: 293-303 [PMID: 33798464 DOI: 10.1016/S2213-8587(21)00050-4]
56 **Bonora BM**, Avogaro A, Fadini GP. Disentangling conflicting evidence on DPP-4 inhibitors and outcomes of COVID-19: narrative review and meta-analysis. *J Endocrinol Invest* 2021; **44**: 1379-1386 [PMID: 33512688 DOI: 10.1007/s40618-021-01515-6]
57 **Han T**, Ma S, Sun C, Zhang H, Qu G, Chen Y, Cheng C, Chen EL, Ayaz Ahmed M, Kim KY, Manem R, Chen M, Guo Z, Yang H, Yan Y, Zhou Q. Association Between Anti-diabetic Agents and Clinical Outcomes of COVID-19 in Patients with Diabetes: A Systematic Review and Meta-Analysis. *Arch Med Res* 2022; **53**: 186-195 [PMID: 34412904 DOI: 10.1016/j.arcmed.2021.08.002]
58 **Pal R**, Banerjee M, Mukherjee S, Bhogal RS, Kaur A, Bhadada SK. Dipeptidyl peptidase-4 inhibitor use and mortality in COVID-19 patients with diabetes mellitus: an updated systematic review and meta-analysis. *Ther Adv Endocrinol Metab* 2021; **12**: 2042018821996482 [PMID: 33680425 DOI: 10.1177/2042018821996482]

59 **Nguyen NN**, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, Chiu HY, Chen YC. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. *Metabolism* 2022; **131**: 155196 [PMID: 35367460 DOI: 10.1016/j.metabol.2022.155196]

60 **Rakhmat II**, Kusmala YY, Handayani DR, Juliastuti H, Nawangsih EN, Wibowo A, Lim MA, Pranata R. Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19) - A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 2021; **15**: 777-782 [PMID: 33838614 DOI: 10.1016/j.dsx.2021.03.027]

61 **Zein AFMZ**, Raffaello WM. Dipeptidyl peptidase-4 (DPP-IV) inhibitor was associated with mortality reduction in COVID-19 - A systematic review and meta-analysis. *Prim Care Diabetes* 2022; **16**: 162-167 [PMID: 34952805 DOI: 10.1016/j.pcd.2021.12.008]

62 **Patoulias D**, Doumas M. Dipeptidyl Peptidase-4 Inhibitors and COVID-19-Related Deaths among Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Observational Studies. *Endocrinol Metab (Seoul)* 2021; **36**: 904-908 [PMID: 34311543 DOI: 10.3803/EnM.2021.1048]

63 **Abuhasira R**, Ayalon-Dangur I, Zaslavsky N, Koren R, Keller M, Dicker D, Grossman A. A Randomized Clinical Trial of Linagliptin vs. Standard of Care in Patients Hospitalized With Diabetes and COVID-19. *Front Endocrinol (Lausanne)* 2021; **12**: 794382 [PMID: 35002970 DOI: 10.3389/fendo.2021.794382]

64 **Guardado-Mendoza R**, Garcia-Magaña MA, Martínez-Navarro LJ, Macías-Cervantes HE, Aguilar-Guerrero R, Suárez-Pérez EL, Aguilar-García A. Effect of linagliptin plus insulin in comparison to insulin alone on metabolic control and prognosis in hospitalized patients with SARS-CoV-2 infection. *Sci Rep* 2022; **12**: 536 [PMID: 35017617 DOI: 10.1038/s41598-021-04511-1]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 411-425

DOI: 10.5501/wjv.v11.i6.411

ISSN 2220-3249 (online)

MINIREVIEWS

Effects of COVID-19 on children with autism

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Rawan Alhawamdeh, Samara Qaraghuli

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Churiso G; Mijwil MM, Iraq

Received: April 20, 2022
Peer-review started: April 20, 2022
First decision: May 12, 2022
Revised: May 12, 2022
Accepted: October 4, 2022
Article in press: October 4, 2022
Published online: November 25, 2022

Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31527, Alghrabia, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, Arabian Gulf University, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Manama, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Nermin Kamal Saeed, Department of Medical Microbiology Section, Pathology Department, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 12, Manama, Bahrain

Nermin Kamal Saeed, Department of Microbiology Section, Pathology Department, Irish Royal College of Surgeon, Busiateen 15503, Muharraq, Bahrain

Adel Salah Bediwy, Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31527, Alghrabia, Egypt

Adel Salah Bediwy, Department of Pulmonology, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Manama, Bahrain

Adel Salah Bediwy, Department of Pulmonology, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Rawan Alhawamdeh, Research and Development Department, Pediatric Occupational Therapist and Neuropsychologist, Genomics Development and Play Center (Genomisc WLL), 0000, Manama, Bahrain

Rawan Alhawamdeh, Research and Development Department, Pediatric Occupational Therapist and Neuropsychologist, Sensory Middle East (SENSORYME DWC-LLC), 282228 Dubai, United Arab Emirates

Samara Qaraghuli, Department of Pharmacognosy and Medicinal Plants, Faculty of Pharmacy, Al-Mustansiriya University, Baghdad 14022, Baghdad, Iraq

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, AlBahr street, Tanta 31527, Alghrabia, Egypt. mbelrem@hotmail.com

Abstract

The coronavirus disease 2019 (COVID-19) pandemic affects all countries and populations worldwide, significantly impacting people with autism with a high risk of morbidity and mortality due to COVID-19. Approximately 25% of children with autism have an asymptomatic or symptomatic immune deficiency or dysfunction. In addition, they frequently have various comorbid conditions that increase the severity of COVID-19. In addition, severe COVID-19 during pregnancy may increase the risk of autism in the offspring. Furthermore, severe acute respiratory syndrome coronavirus 2 could target human nervous system tissues due to its neurotrophic effects. The COVID-19 pandemic intensely impacts many patients and families in the autism community, especially the complex management of autism-associated disorders during the complete lockdown. During the complete lockdown, children with autism had difficulties coping with the change in their routine, lack of access to special education services, limited physical space available, and problems related to food and sleep. Additionally, children with autism or intellectual disabilities are more liable to be abused by others during the pandemic when the standard community supports are no longer functioning to protect them. Early detection and vaccination of children with autism against COVID-19 are highly indicated. They should be prioritized for testing, vaccination, and proper management of COVID-19 and other infectious diseases. In this review, we discuss the various effects of COVID-19 on children with autism, the difficulties they face, the increased risk of infection during pregnancy, how to alleviate the impact of COVID-19, and how to correct the inequalities in children with autism.

Key Words: Autism; ASD; Autism Spectrum Disorder; Children; COVID-19; Testing; Vaccination; Neurotropism; SARS-CoV-2

Core Tip: The pandemic of coronavirus disease 2019 (COVID-19) has dramatically impacted children with special needs. Besides the COVID-19-related high morbidity and mortality, other changes associated with the pandemic negatively impacted the educational and health-related issues of children with autism. The lockdown adversely affected sensory-motor development, cognitive abilities, sleep, morale, behavior, and social interactions in a large proportion that may reach 50% of children with special needs. Children with autism should be prioritized for testing and proper management of COVID-19 and other infectious diseases.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Alhawamdeh R, Qaraghuli S. Effects of COVID-19 on children with autism. *World J Virol* 2022; 11(6): 411-425
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/411.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.411

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic affected worldwide countries and populations. It is caused by a strain of coronaviruses called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1]. It has cast great shadows and impacts on children with special needs. It deprived them of many opportunities to improve their condition, especially with the massive interruption of medical follow-up and rehabilitation during the lockdown and the difficulty in physical communication that a child with special needs requires to develop and upgrade his mental and physical abilities, as we follow the policy of physical distancing[2]. The lockdown significantly impacted the sensory-motor development, cognitive skills, sleep, morale, behavior, and social interactions in about 50% of children with special needs. There is also plenty of evidence suggesting the adverse effects of SARS-CoV-2 and the measures we take to limit its spread to children with disabilities and their families[3]. In addition, some primary health conditions in children with disabilities and special needs may expose them to a higher risk of contracting the virus and suffering from complications to a higher degree. These children, particularly those who suffer from sensory processing and integration such as tactile, vestibular, proprioceptive, and difficulties in hearing, vision, and cognitive performance, also face problems taking necessary preventive measures during epidemic periods such as wearing masks, keeping a physical distance, washing hands, and using sanitizer[4]. Autism is a spectrum disorder (ASD) with a wide variation in clinical manifestations. In this manuscript, we will use the term autism rather than ASD.

Autism itself poses a significant burden on the family with a child affected by it. It puts a severe financial and psychological burden on the family. This effect has multiplied several times with the COVID-19 pandemic[5]. This review aims to highlight the various impacts of COVID-19 on children with autism, the difficulties they encounter, including vaccination and testing, the infection-induced risk during pregnancy, and the different suggestions to alleviate the effects of COVID-19 and correct the inequalities in children with autism.

IMMUNE STATUS OF CHILDREN WITH AUTISM

Approximately one-quarter of children with autism have an asymptomatic or symptomatic immune deficiency or dysfunction. Many of these children may have asymptomatic immune dysregulation, so it is imperative to rule it out, particularly in children with gastrointestinal disorders[6]. Rose *et al*[7] found that children with autism have more oxidative stress and less glutathione-mediated redox/antioxidant ability than typically developed children. This oxidative stress and impaired glutathione redox homeostasis have a significant role in immune dysregulation observed in children with autism. Gastrointestinal dysbiosis is frequently encountered in children with autism and causes impaired mucosal barrier, gastrointestinal dysfunction, and immune system and nervous system dysregulation. The gastrointestinal dysfunction and the increased oxidative stress induce mitochondrial dysfunction, affecting both the mental function and immune status of children with autism[8]. Thus, during long-term exposure of children with autism to toxic stress and environmental deprivation during the COVID-19 pandemic, they suffer regressions in sensory-motor, physical, and mental health development[9].

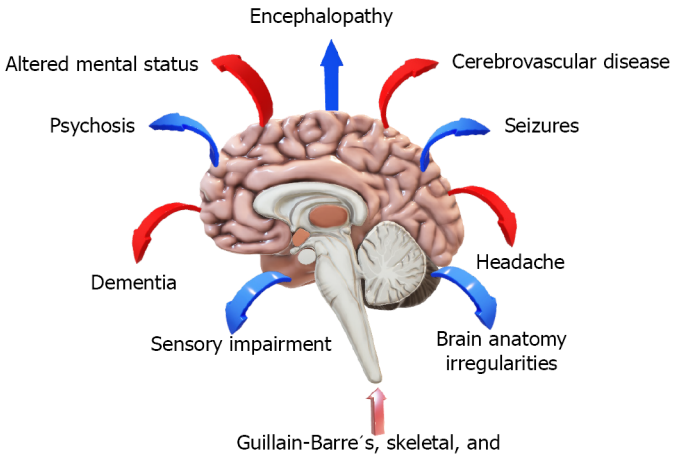
Despite children with autism having low serotonin concentrations in the brain, they have an elevated blood count of mast cells with high blood and urine serotonin levels. These elevated serotonin concentrations in tissues out of the blood-brain barrier are related to mast cell activation with increased mast cell cytokines/chemokines; another significant contributor to the immune and neuroinflammatory dysregulation observed in children with autism[10,11]. Natural killer cells may be crucial in developing neurodevelopmental disorders, including autism. Enstrom *et al*[12] found abnormal gene expression and altered natural killer cell function in children with autism with increased production of interferon-gamma (IFNgamma), granzyme B, and perforin under resting conditions and decreased production under stressful conditions. In addition, Manzardo *et al*[13] found that three cytokines involved in hematopoiesis and five cytokines involved in the attraction of T-cells, monocytes, and natural killer cells are lower in children with autism than in typically developed siblings.

Heuer *et al*[14] found significantly decreased plasma IgG and IgM levels in children with autism than in children with developmental delay or typical development. They also found that the degree of IgG and IgM levels reduction was significantly correlated with the Aberrant Behavior Checklist score; the more the drop is, the more the aberrant behavior. In addition, IgA deficiency is associated with an increase in the autism rate. Wasilewska *et al*[15] found that insidious changes in serum immunoglobulins with low-normal IgA and increased B cell activation marked by the rise in CD19/CD23-positive cells occur in children aged 3-6 years with regressive autism. These immune and neuroinflammatory dysregulations are major pathogenic components in autism, as evidenced by the high pro-inflammatory cytokines in postmortem biopsies obtained from the brain of children with autism. These immunological changes can serve as a marker for the development of autism.

Furthermore, individuals with autism have an increased prevalence of a positive family history of autoimmune disorders (such as rheumatoid arthritis and autoimmune thyroiditis), specific major histocompatibility complex haplotypes, and abnormal immunological marker levels[16]. Consequently, autism is strongly linked to abnormal immune responses, which may be an area for targeted intervention to prevent or treat children with autism. Unfortunately, COVID-19 effects on the immune system make children with autism more vulnerable to other diseases and further regression[17].

NEUROTROPIC EFFECTS OF SARS-COV-2

Besides respiratory illness, COVID-19 causes unexpected neurological complications, possibly due to direct viral effects on the central nervous system (CNS) or the peripheral nervous system (PNS) or as a part of the virus's systemic effect. Recent studies using human brain organoids showed that SARS-CoV-2 could target human nervous system tissues[18]. Although neurological disorders are relatively uncommon with coronavirus infections, two strains can enter and persist in the brain cells, including SARS-CoV and SARS-CoV-2[19]. COVID-19 showed moderately severe neurological problems (Figure 1), ranging from mild symptoms such as headache, dizziness, and smell and taste impairment to severe manifestations including Guillain–Barre syndrome, encephalitis, neuropsychiatric disorders, neurocognitive impairment, psychosis, vision impairment, dementia, and cerebrovascular defects as ischemic strokes, or intracerebral hemorrhages[20-22].



DOI: 10.5501/wjv.v11.i6.411

Figure 1 The various neurological symptoms observed in patients with coronavirus disease 2019.

The structural brain damage detected by magnetic resonance imaging and the presence of viral RNA in cerebrospinal fluid (CSF) and autopsy brain samples from patients with COVID-19 and neurological manifestations proves SARS-CoV-2-induced neurological effects. These neurological sequelae of SARS-CoV-2 are either due to the direct CNS toxic effect of the virus (as many brain cells express angiotensin-converting enzyme-2 (ACE2) receptors, the primary SARS-CoV-2 receptor, and other linked proteins and receptors such as Neuropilin-1 (NRP-1) and CD147) or as a result of a virus-mediated CNS inflammation and immune dysregulation due to the aggressive cytokine storm or the abnormal immune response[23-25].

COVID-19 AND MORTALITY RATES IN CHILDREN WITH AUTISM

COVID-19 is a systemic disease that could affect any organ or system. Many risk factors increase the rate and severity of infection with SARS-CoV-2, including male gender, older age, and medical comorbidities such as obesity, immune deficiency, autoimmune diseases, diabetes mellitus, or hypertension. Children with autism have many physical and behavioral risk factors that expose them to higher infection, morbidity, and mortality rates related to COVID-19[26]. Children with autism may require more exposure to outside caregivers and other children with a higher chance of encountering carriers of SARS-CoV-2. They frequently have persistent oral sensory-seeking behavior, which exposes them to an increased risk of contracting the virus[27]. Pica is approximately seven times more common in children with autism than in the general population, which exposes them to more infection risk. They also have challenges applying the pandemic's social distance and hygiene-related guidelines[28]. They are not able or scared to wear a mask and maintain physical distance, exposing themselves and others to a higher risk of spreading or catching COVID-19. They do not understand what COVID-19 is and cannot tolerate the sensory inputs related to preventive measures they require to protect themselves[29].

Children with autism frequently have various comorbid conditions that increase the severity of COVID-19 when encountered. Immune deficiency is commonly reported in children with autism, increasing the risk and severity of infections, including COVID-19[30]. IgA deficiency is a significant risk factor for both autism and infection with SARS-CoV-2. Serum IgA levels positively correlate with total lymphocyte counts and negatively correlate with C-reactive protein levels. Consequently, IgA deficiency, low lymphocyte count, and high C-reactive protein levels are significant risk factors for severe COVID-19[31]. Patients with autism have cytokine dysregulation with increased inflammatory cytokines production and impaired immune response at different levels[32]. Autism is four times more common in males than in females. Males are more prone to infection, particularly with SARS-CoV-2[33, 34]. Gut dysbiosis is frequently found in children with autism and is linked to many gastrointestinal and neurobehavioural symptoms[35]. There is a bidirectional relation between infection with SARS-CoV-2 and the gut microbiota. Infection with SARS-CoV-2 causes respiratory and gastrointestinal microbiota dysbiosis, which negatively impacts gastrointestinal and respiratory health. Dysbiosis of the gut microbiota produces an appropriate environment for replication of SARS-CoV-2 and subsequent pathogenic effects. Gut dysbiosis can induce pulmonary dysbiosis through the gut-lung axis, which determines the course and severity of COVID-19. On the other hand, gut microbiota diversity and the predominance of beneficial bacteria can improve the course of COVID-19 and alleviate the severity of the disease[36,37].

Schott *et al*[38] showed an increased risk of SARS-CoV-2 infection in patients with autism, especially in those who live in a residential facility, those who receive home services from outside caregivers, who need a lengthy hospitalization, and those with comorbidities. Krieger *et al*[39] showed an increased rate of infection and hospitalization in persons with autism, especially men between 40 to 60 years. Karpur *et al*[40] showed that persons with autism are nine times more likely to be hospitalized and six times more likely to have extended hospital stays than those without autism.

When hospitalized, children with autism have difficulties in social communication, the ability to express their symptoms, and understanding and following the safety guidelines. Many children with autism also have various challenging behaviors (*e.g.*, spreading and spitting saliva, pica and licking staff, and spreading stool that helps spread the virus. They strongly resist the change in the hospital environment and have aggravated stereotyped behavior patterns. Wearing protective equipment by the healthcare provider is another challenge and increases stress among children with autism[41]. In addition, people with autism may suffer some discrimination in the priority of receiving medical care depending on their counties' Intensive Care Unit (ICU) Triage Protocols and Policies. For example, the triage system in Spain used "severe baseline cognitive impairment" as an exclusion criterion for ICU admission in their triage guidance for COVID-19 ICU admission, according to the "Working Group of Bioethics of the Spanish Society of Intensive, Critical Medicine and Coronary Units." These features increase the risk of morbidity and mortality when hospitalized[41,42]. A systematic review and meta-analysis by Catalá-López *et al*[43] showed a higher mortality rate in persons with autism or attention-deficit/hyperactivity disorder than in the general population (relative risk of 2.37 and 1.97, respectively).

COULD COVID-19 DURING PREGNANCY INDUCE AUTISM?

Febrile maternal infection during pregnancy doubles the risk of autism in their offspring[44]. Currently, there is no evidence for the vertical transmission of SARS-CoV-2 from the mother to the fetus, which could be related to the preventive effect of lactoferrin at the placental interface. However, the virus could be transmitted postnatally through the mother's respiratory droplets or breastmilk[45]. In addition, severe COVID-19 during pregnancy induces the release of the inflammatory cytokine storm, which may cause fetal damage if not controlled. The brain is one of the target organs affected by inflammatory damage that could present later with autism manifestations[46]. The etiology of autism is multifactorial, with interacting genetic and environmental factors. Maternal immune activation is a significant risk factor for the offspring's neurodevelopmental diseases such as schizophrenia and autism [47]. Children with autism are more liable to many mental health disorders such as depression, sleep disorders, addiction, attention deficit, and hyperactivity behaviors since the COVID-19 pandemic started[48] (Panda).

Moreover, children with autism are among the most vulnerable populations affected by extended hours of online learning, flat-screen media, and mental health consequences during and after the COVID-19 pandemic[9,49]. Prenatal brain inflammation causes neurodegenerative changes and " short-circuiting the electrical system" in the amygdala, crucial for emotional feeling ability and fear regulation. Children with autism have exaggerated fear responses compared to their peers in neutral events. The Hypothalamic-Pituitary-Adrenal (HPA) axis system is hyper-responsive due to unpleasant sensory stimuli and/or benign social situations[50].

Insulin-like growth factor-1 (IGF-1) is a central component in perinatal oligodendrocytes-mediated neo-neuronal myelination, as it is essential for the survival of Purkinje cells in the cerebellum. IGF-1 deficiency is implicated in the pathogenesis of autism[51]. It is formed together with the growth hormone by the placenta. Maternal COVID-19 infection induces maternal immunologic activation with a marked increase in the production of pro-inflammatory cytokines, which inhibit placental IGF-1 synthesis. Reduced IGF-1 production downregulates perinatal myelination of the developing nervous system and brain dysconnectivity. If this downregulation is not corrected, a permanent neurologic deficit will occur or worsen[52,53].

In addition, SARS-CoV-2 can activate mast cells which in turn cause microglial activation. These changes release excess inflammatory molecules, stop synapses "pruning," impairing neuronal connectivity, and reduce the fear threshold, disrupting the emotional expression observed in children with autism[54]. The effects of impaired neuronal connectivity and reduction in the fear threshold worsen the problem as children with autism already have an overall sluggish HPA axis in responding to physiological or physical manipulation. These children have shown hypo-responsiveness to stressors that involve social evaluative threats[50].

The infection-induced inflammatory antenatal immune milieu is the chief trigger causing impaired fetal brain development, with long-term cognitive impairments. It is advisable to delay future pregnancy until the pandemic ends, immunization before preplanned pregnancies, follow safety guidelines with frequent hand washing, and regular testing in pregnant ladies to discover asymptomatic infection early[55]. A study in the New York metropolitan area showed that about 15% of pregnant women who presented for delivery were COVID-19 positive and mostly asymptomatic[56].

This percentage can indicate how many pregnant ladies carry the SARS-CoV-2 without symptoms worldwide, especially in areas without proper testing facilities. The effects of asymptomatic COVID-19 on the offspring are still unknown and need further research. To minimize the impact of COVID-19 infection during pregnancy, the mother is advised to have a high choline and luteolin supplement in addition to vitamin D, n-3 polyunsaturated fatty acids, and folic acid, which have beneficial effects on brain function development in infants of mothers who encountered viral infections in early pregnancy [57]. Luteolin is a potent natural flavonoid inhibitor of mast cells and microglia activation and blocks SARS-CoV-2 binding to its ACE2 receptor[54].

IMPACT OF COVID-19 ON AUTISM MANAGEMENT

To minimize the risk of COVID-19 spread, most governments imposed a near complete lockdown with extreme measures such as home confinement and shutting of special education systems. Most children with autism stopped receiving the required education and clinical therapies during the lockdown. In addition, children with autism usually resist changes in their routines. Consequently, most of them suffered during the lockdown with the closure of their kindergartens, schools, and other services they usually attend daily. At the same time, the family showed changes in its structure with the availability of a parent who is frequently absent from home, more time spent with a sibling, or separation from their grandparents who were usually present. The uncertainty about COVID-19 and the rapid and constant flow of information could devastate people with autism and increase their distress[58,59]. In addition, children with autism or intellectual disabilities are more liable to be abused by others during the pandemic when the standard community-protecting supports are no longer functioning[60]. In addition, the extended homestay increases inattentive-hyperactive behavior, screen and games addiction, and sleep disorders that lead to comorbid mental health disorders in children with autism. Depriving children with autism of their therapeutic intervention induces environmental deprivation of specific sensory tools, equipment, and inputs that help to accelerate developmental shifting and progress rates. This change is critical since online education and home training on their own cannot overcome clinical symptoms in children with autism[61].

These changes impose additional stress upon them and their families, with interrupted language development, exacerbated anxiety, more frustration, and short temper related to the fear of regression of the gained skills and sadness due to cessation of general care and support by dedicated clinical therapists and teachers. Children with autism had a significant increase in stimming, self-injury, nervousness, violence, impulsiveness, and binge eating behaviors during the pandemic[62]. Tokatly *et al* [63] showed a link between the absence of speech therapy and the increased rate of repetitive behaviors. In addition to the increased COVID-19-related infection, morbidity, and mortality rate observed in children with special needs, the pandemic deepens the gap in the healthcare inequalities provided for people with autism, adding excess risk for morbidity and mortality.

The COVID-19 pandemic poses various challenges to individuals with autism, their families, and caregivers. In recent Simons Powering Autism Research for Knowledge (SPARK) surveys, most adults with autism and caregivers of children with autism reported adverse effects in almost every field of their lives. While many are handling it well and even have encouraging experiences to share, 82% of families included in the survey reported mental health adverse effects on their children with autism. In comparison, 95% of parents and 93% of adults with autism reported adverse effects on their mental health[64]. In addition, several parents of children with autism committed suicide due to the severe psychological pressure and stress during the care of their children[65].

Mutluer *et al*[28] showed that individuals with autism had difficulties understanding what COVID-19 is and the actions it needs with challenges in applying hygiene-related and social distance regulations of the pandemic. Furthermore, the classic online learning programs do not have supportive accommodations that help children with autism learn while modulating the audio-visual sensory stimuli overload. Consequently, most of them are less likely to follow the proposed behavioral and hygienic habits such as routine hand washing that aim to prevent or reduce the risk of infection or the constant wearing of face masks due to their age, maturity, and limited developmental capacities and disabilities. The majority of the studied individuals stopped getting the required special education during the studied period of the pandemic. They also showed some features related to post-traumatic stress disorders, such as behavioral problems (including increased stereotypies and aggression), hypersensitivity, reduced and impaired sleep, and appetite alterations. They also had significant differences in all Aberrant Behavior Checklist subclasses (ABC) before and after the pandemic conditions. Their caregivers showed an increased anxiety level related to their behavior with a high ABC total score; specifically, the lethargy/social withdrawal subscale score predicted the parents' anxiety score.

Being parents of a child with autism is a real challenge, especially during the COVID-19 pandemic. During the lockdown, shutting down special education and rehabilitation facilities made the parents primarily the only full-time caregivers. Consequently, they depend on their skills to cope with their kids, with the loss of support and guidance from specialists and experts. In many cases, the caregivers of these children are not educated or trained enough to care for their children and manage them like their

typical peers. They may be unable to provide adequate care for their children's clinical symptoms such as seizures, tics, bulimic behavior, or sensory cravings and avoidances. Thus, the developmental rate drops dramatically without adequate clinical and professional special education services for children with autism[66].

Tokatly *et al*[63] showed that the most common problem encountered by the parents of children with autism is coping with the change in their routine, lack of access to special education services, limited physical space available, and food and sleep-related problems. Despite that, some children suffered worsening in their behavioral, developmental, or social domains; others succeeded in overcoming the challenges they encountered and even benefited from them. The researchers emphasized that the best way to help children with autism catch up with these severe modifications in their routine lifestyle is to provide a robust support system to their parents. Many parents lost their jobs or at least had a decrease in their income during the pandemic, with reduced affordability for the cost of special education and rehabilitation services for their children and increased anxiety levels[67]. The long-term effects of the pandemic and infection with SARS-CoV-2 on children with autism need more time to be evaluated.

In contrast, some individuals with autism and their families may manage autism more efficiently during COVID-19-related circumstances. For example, lockdown allowed the parents to spend more time with their children, allowing more sharing of activities, more co-watching, more adherence to rules and routine and limited socialization and physical contact in individuals with autism which could decrease the social-related stress and less physical contact with infected people. The lockdown also reduced the sensory overload for some children with autism and helped them enroll in online schooling that they could not attend in person due to their atypical behaviors in the classroom[68]. Asbury *et al*[68] found that a few children with autism and their families reported some positive effects of lockdown, such as decreased stress related to facing the daily routine challenges such as going to school and other public places or worrying about socializing with others. Some children could change their routines, accept new routines or make their routines. Some of them started to eat foods that they were not familiar with. Increased free time permitted for repetitive trials helped improve their abilities and skills. The availability of family time to spend together enhances the child's communication skills and allows the parent to identify these abilities[63]. The key factors that determine the successful coping of parents during the lockdown are their abilities to satisfy the child's needs, positive attitude in general, their creativity, and attending inventive problem-solving training by healthcare professionals and an occupational therapist specialized in Ayres Sensory Integration® (ASI) for sensory environmental adaptations, functional abilities, and independence in activities of daily living[69] (Dubois-Comtois).

In addition, Sergi *et al*[70] showed that children with autism involved in an Applied Behavior Analysis (ABA) based intervention during the lockdown period showed improvements in their communication, socialization, and personal autonomy. They also showed the significant effect of parents' training in avoiding delays in the generalization of socially significant behaviors following the radical treatment interruption in this group of children. Perhaps the best thing related to the COVID-19 pandemic is our awareness of how good our pre-COVID-19 lives were. Research has shown that consistent telehealth and home-based in-person occupational, physical, and speech therapies were beneficial in helping children with autism maintain their developmental rates and progress to the next level. However, parents and caregivers reported less satisfaction with telehealth services than with in-person therapy sessions. Furthermore, parents who reported higher emotional dysregulation in their children were less satisfied with ABA services[71].

INDIRECT IMPACT OF COVID-19

An indirect effect of COVID-19 was the significant reduction of the national income in most countries, which led to a lack of spending on health services related to the management of autism and giving priority to patients with COVID-19. At the same time, numerous community-based services provided by non-profit organizations and the private sector stopped due to acute financial instability. These financial crises caused a delay in the available diagnostic services and, consequently, a delay in the required therapy with a waiting list that could extend to more than a year[72]. Another significant indirect effect is the accuracy of the conducted studies during the pandemic. For example, there were difficulties in performing autism research due to social distancing and the need for the participants to wear masks. These behavioral and environmental changes increase stress conditions, making interpreting the behavior of individuals with autism difficult and affecting the research results. In addition, there is a high risk of missing scientific accuracy during moments of crisis[17].

With social distancing becoming an essential method of COVID-19 prevention, telemedicine and telehealth possibly become the ideal communication methods between caregivers and patients[73]. There has been a flood of videoconferences, "live presentations" in social networks, online training classes on online learning platforms, telepractice concerning different fields such as psychiatry, psychology, occupational therapy, speech therapy, and other remote activities that offer support, guidance, and treatment when applicable. Telemedicine requires an effective internet service, which may not be available in less developed countries or areas, which deepens the inequalities in the health

services provided to children with autism[74]. Even with strong internet, most children with autism may have difficulties following the screen during online teaching. One of the vital factors is the shortage of the sensory, motor, and cognitive accommodations needed to support the mind, brain, and body functions during the learning process. Furthermore, governments are not sufficiently drawing and applying the contributions of healthcare professionals to the academic learning process. Thus, children with autism are generally more prone to gaps in their developmental and learning processes that can be successfully implemented and reflected in the nations' economies[75].

On the other hand, there is a silver lining to the pandemic; scientists hurry to find alternative ways to continue their research and invent reasonable solutions to assist remote diagnosis, proper assessment, and manageable treatment accessible for all and increase participation in their clinical research[76]. Simultaneously, the COVID-19 pandemic represents a perfect opportunity to study the epidemiology of autism and the effects of the pandemic on environmental, genetic, and psychosocial factors on autism mechanisms over a long period worldwide[77]. We may have an unprecedented chance to study how the environment, stress, mental health comorbidities, and autism interact. The pandemic is also an excellent chance to test the efficacy of social robots for education and medical care for individuals with autism. Social robots work in a highly predictable and lawful system and provide children with autism with a highly organized learning environment that helps them focus on essential stimuli. Robots can provide these services during epidemics without the risk of transmitting infection. In addition, children with autism communicate more engagingly and have better social behaviors with robots than with human trainees[78,79].

TESTING CHILDREN WITH AUTISM FOR COVID-19

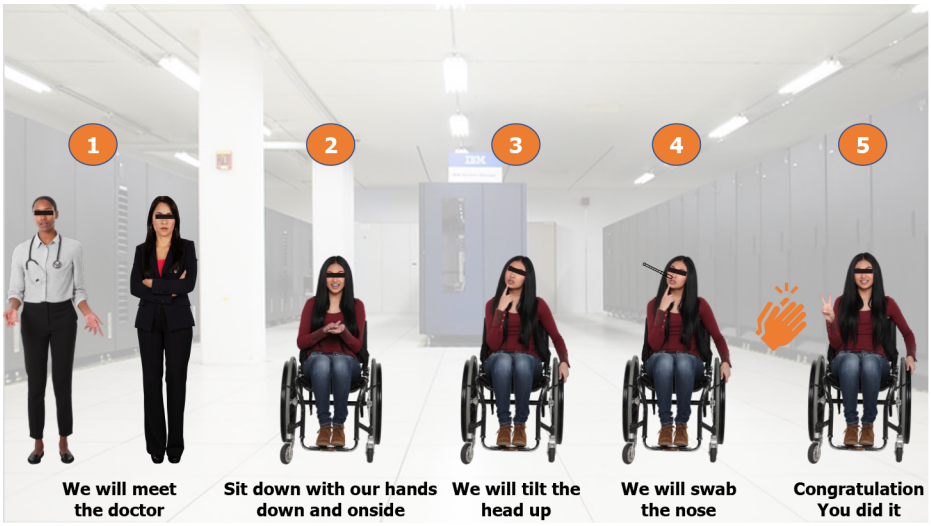
Individuals with autism should have a high priority for COVID-19 testing and other similar pandemic situations because they have an increased incidence of medical comorbidities (such as cardiovascular or respiratory diseases, hypertension, autoimmune conditions, obesity, and diabetes), high incidence of living in residential care, and difficulties in adherence to strict personal hygiene and physical distancing practices. However, most countries do not consider people with autism as a high-priority group[80]. Individuals with autism have high sensory sensitivities. Consequently, nasal and throat swabs or aspirations become a real challenge for the patient, the family, and the performing healthcare personnel. Children with autism may even need sedation to carry out testing, which may not be available in many situations. Hence, it is better to have more flexible testing procedures, such as saliva testing. People with autism may also encounter the challenge of waiting for a long time and presenting in unfamiliar places for testing. They also may have a problem using the necessary personal protective equipment[59]. Symptoms of COVID-19 may be atypical in people with autism who may indicate the need for a high index of suspicion and the need for equitable access to proactive testing and screening, especially for those with medical comorbidities or who live in high-risk settings such as those who live in supported accommodation or residential care[59].

To alleviate the testing-related anxiety, the parents can create a social narrative that tells the individual with autism what will go on and what they will do during testing. This preparation is better in enumerated steps so the parents can mark done with each completed step[81].

Figure 2 is an example of a visual demonstration of the nasopharyngeal swabbing steps. The narrative should match the person's abilities to understand with fewer words. It is better to put every step on a separate page, and to read the social narrative many times on the day before testing in order for the person to get used to the steps. The caregiver can distract the person's attention during nasal swabbing by using any distracting activities such as coloring a picture or watching a video or alleviate their anxiety by using a relaxing activity such as rubbing their hands or squeezing a squeeze ball if they are used to this[81]. The visual demonstration can also be available in the special care kits to be used by the healthcare provider when encountering persons with special needs to alleviate their tension. Light sedation or analgesia can be given before the test if the person is too anxious and cannot be calmed down[82,83]. An occupational therapist specializing in ASI in the testing and vaccination units helps children with autism have successful testing and vaccination by calibrating the sensory stimuli towards the child's brain and body using standardized and modified measurable evidence-based methods[84].

COVID-19 VACCINES IN AUTISM WHY? AND HOW?

As COVID-19 has a significant negative impact on people with autism, they need to be rapidly vaccinated. Many people with autism have a delay in COVID-19 vaccination as many families are concerned about the vaccine's effects on their children or the country's policy that shows hesitation against vaccinating children with mental and developmental disabilities[85]. A study by Choi *et al*[86] showed that only 35% of the parents of children with autism are willing to vaccinate their children with anti-COVID-19 vaccines. The vaccination rate increases with proper education and evidence-based recommendations. This delay in immunizing children with autism poses an increased risk of severe



DOI: 10.5501/wjv.v11.i6.411

Figure 2 Visual demonstration of nasopharyngeal swab testing steps.

COVID-19, especially with continuous viral mutations. With the high mortality rate of COVID-19, individuals with autism, especially with intellectual disabilities and other health problems, should be vaccinated as soon as possible, as the vaccines can prevent their death. Individuals with autism and their family members and caregivers should have the vaccine to decrease the risk of COVID-19. These individuals are less likely to adhere to the proper hygiene protocol, cannot wear masks for a long time, and cannot express their symptoms, such as sore throat. Thus, vaccination of their close contacts is also indicated. Vaccination of the parents and caregivers will decrease the chance of getting sick and reduce the possibility of leaving the child without proper care. Interestingly, Weinstein *et al*[87] found a higher rate of COVID-19 vaccination among individuals with autism aged 16-40 years across both sexes than in the controls, but not below the age of 16.

There are different types of COVID-19 vaccinations: COVID-19 Inactivated Vaccines (*e.g.*, Sinovac, Sinopharm), COVID-19 Viral Vector / Adenovirus Vaccines (*e.g.*, Oxford/AstraZeneca, the Johnson and Johnson, CanSino, and Sputnik V vaccines), genetic/mRNA vaccines (*e.g.*, Moderna and Pfizer/BioNTech COVID-19 vaccines), and live attenuated vaccines (Codagenix vaccine: under trials)[88]. Currently, the "Center for Disease Control and Prevention" (CDC) recommends two doses of Pfizer-BioNTech COVID-19 vaccine for five through 11 years of age separated by at least three weeks and an additional primary dose at least four weeks after the initial 2-dose primary series with a total of three doses. According to the CDC, Moderna, and Pfizer/BioNTech, COVID-19 vaccines are at least 90% effective in preventing symptomatic infection by SARS-CoV-2 after two weeks from the second dose [89]. The vaccines are equally effective and safe for individuals with autism as they are for others. People with various disabilities, including autism, were included in most vaccine clinical trials, which showed that the vaccines were safe and effective for everyone. To date, there is no link between COVID-19 vaccination and autism. In addition, maternal COVID-19 infection during pregnancy doubles the risk of autism, emphasizing the importance of immunization[90].

As mentioned earlier, similar to COVID-19 testing, vaccination is also a real challenge for the individual with autism, the family, and the health care provider responsible for the vaccination. Getting a vaccination poses an added challenge, especially since the shots are often not given in a typical doctor's office without a supportive occupational therapist ASI certified. This change in the routine disrupts their usual way of therapeutic care and education, which can be very upsetting. Every parent knows their child best. Therefore, they need to introduce the idea that they need to go driving somewhere, be exposed to somebody, wear protective equipment, and is going to give the vaccine. The parents should explain this many times for a week or day before the vaccination, using a narrative teaching story, video modeling, or visual social demonstration, giving the child enough time to process, understand and accept this new information and routine before the expected appointment. The parents should also help them feel better if they experience vaccine side effects. The CDC and The Autism Society of America prepared various tools, resources, and visual explainers that the parents and caregivers could use to explain the vaccine and the possible adverse effects after receiving the vaccine [91,92].

Table 1 Recommendations to minimize the effects of pandemics on people with autism

Intensive education:	Mandatory education of people with autism, their families, and caregivers about the symptoms and signs of COVID-19 and similar infections and the behavioral procedures to decrease the infection spread[28].
	Emphasize the importance of good sleep hygiene and nutrition during the pandemic[63].
	Educating, supporting, and strengthening the parents' ability to adjust could be particularly valuable in times of extreme life difficulties and during ordinary times that may not be expected[93].
	Training children with autism about how to use personal protective equipment (PPE) by their caregivers will prepare them for the social adaptations during pandemics[94].
	Launching regular mandatory education and updating all the healthcare providers about the management guidelines created for people with autism, supported by specialist providers such as psychiatrists, psychologists, occupational therapists, speech therapists, behavioral therapists, and other specialties as indicated[95].
Prioritization:	For testing and vaccination for people with autism, their families, and caregivers[86].
	For hospitalization and ICU admission in triage protocols[41,42].
	Regular or on-demand access to psychological services regardless of the enrolment[96].
During quarantine:	Allow for one-on-one home visits[97].
	Allow meeting the healthcare provider (*e.g.*, physiotherapist, behavioral therapist) in a previously disinfected open area[97].
	Allow for small classes, and preadmission testing, allowing people with COVID-19 negative testing results to enter the class[98].
	Give permitted exceptions for people with autism, granting them to leave their homes more than once daily[98].
	Providing a sensory-friendly sanitized space for children with autism to release their extra energy, or at least providing tools to help them remove their excess energy, such as a physioball or bringing a swing or trampoline at home to prevent behavioral regression. Encourage physical activity to preserve general well-being[99].
	Provide formal and informal care with psychological and financial support for the well-being and proficiency of parents of children with autism[100].
	Provide weekly or "hotline" consultations for the parents of children with autism to help manage rising general and specific COVID-19-related issues[63].
	Allowing a caregiver or support person to attend to the individual with autism in the hospital, following all required infection control protocols[97].
	During and after the pandemic, preventive measures: to implement an intensive preventive intervention program for children with autism to reduce and prevent relapse and future physical and mental health regressions in future pandemics and/or similar situations [101].

CONCLUSION

The COVID-19 pandemic affects all countries and populations worldwide, including people with autism. Besides respiratory illness, COVID-19 causes unexpected neurological complications, possibly due to direct viral effects on the nervous system. Children with autism frequently have various comorbid conditions that increase the severity of COVID-19 when encountered. There is an increased risk of SARS-CoV-2 infection in patients with autism with high morbidity and mortality rates. Children with autism should be prioritized for testing, vaccination, and proper management of COVID-19 and other infectious diseases. We must correct the inequalities children with autism face in receiving education and healthcare services by collaborating with governmental, non-profit organizations, and individuals to reach this goal.

With the hope that the COVID-19 pandemic will be in the gasping stage, we learned many lessons to be implemented to prevent its adverse effects on people with autism when similar situations occur in the future. We should regularly re-evaluate the mental and physical conditions and development of children with autism and find alternative treatment methods. The medical and rehabilitation teams are critically required to support children with autism and their families and ensure the continuity of physical and mental healthcare during and after the pandemic. Some suggested recommendations to minimize the impact of such pandemics on children with autism are shown in Table 1.

ACKNOWLEDGEMENTS

We thank the editors and the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M, Saeed NK, Bediwy AS, Alhawamdeh R, and Qaraghuli S contributed equally to this work. They collected the data and wrote and revised the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010; Rawan Alhawamdeh 0000-0003-3501-6275; Samara Qaraghuli 0000-0002-6909-2668.

Corresponding Author's Membership in Professional Societies: UMC/KAMC/AGU, Tanta University.

S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

REFERENCES

1 **Saeed NK**, Al-Khawaja S, Alsalman J, Almusawi S, Albalooshi NA, Al-Biltagi M. Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain. *World J Virol* 2021; **10**: 168-181 [PMID: 34367932 DOI: 10.5501/wjv.v10.i4.168]
2 **Cacioppo M**, Bouvier S, Bailly R, Houx L, Lempereur M, Mensah-Gourmel J, Kandalaft C, Varengue R, Chatelin A, Vagnoni J, Vuillerot C, Gautheron V, Dinomais M, Dheilly E, Brochard S, Pons C; ECHO Group. Emerging health challenges for children with physical disabilities and their parents during the COVID-19 pandemic: The ECHO French survey. *Ann Phys Rehabil Med* 2021; **64**: 101429 [PMID: 32818674 DOI: 10.1016/j.rehab.2020.08.001]
3 **Morelli M**, Cattelino E, Baiocco R, Trumello C, Babore A, Candelori C, Chirumbolo A. Parents and Children During the COVID-19 Lockdown: The Influence of Parenting Distress and Parenting Self-Efficacy on Children's Emotional Well-Being. *Front Psychol* 2020; **11**: 584645 [PMID: 33123063 DOI: 10.3389/fpsyg.2020.584645]
4 **Singh S**, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. *Psychiatry Res* 2020; **293**: 113429 [PMID: 32882598 DOI: 10.1016/j.psychres.2020.113429]
5 **Yılmaz B**, Azak M, Şahin N. Mental health of parents of children with autism spectrum disorder during COVID-19 pandemic: A systematic review. *World J Psychiatry* 2021; **11**: 388-402 [PMID: 34327131 DOI: 10.5498/wjp.v11.i7.388]
6 **Al-Beltagi M**. Autism medical comorbidities. *World J Clin Pediatr* 2021; **10**: 15-28 [PMID: 33972922 DOI: 10.5409/wjcp.v10.i3.15]
7 **Rose S**, Melnyk S, Trusty TA, Pavliv O, Seidel L, Li J, Nick T, James SJ. Intracellular and extracellular redox status and free radical generation in primary immune cells from children with autism. *Autism Res Treat* 2012; **2012**: 986519 [PMID: 22928106 DOI: 10.1155/2012/986519]
8 **Hu T**, Dong Y, He C, Zhao M, He Q. The Gut Microbiota and Oxidative Stress in Autism Spectrum Disorders (ASD). *Oxid Med Cell Longev* 2020; **2020**: 8396708 [PMID: 33062148 DOI: 10.1155/2020/8396708]
9 **Colizzi M**, Sironi E, Antonini F, Ciceri ML, Bovo C, Zoccante L. Psychosocial and Behavioral Impact of COVID-19 in Autism Spectrum Disorder: An Online Parent Survey. *Brain Sci* 2020; **10** [PMID: 32503172 DOI: 10.3390/brainsci10060341]
10 **Castellani ML**, Conti CM, Kempuraj DJ, Salini V, Vecchiet J, Tete S, Ciampoli C, Conti F, Cerulli G, Caraffa A, Antinolfi P, Galzio R, Shaik Y, Theoharides TC, De Amicis D, Perrella A, Cuccurullo C, Boscolo P, Felaco M, Doyle R, Verrocchio C, Fulcheri M. Autism and immunity: revisited study. *Int J Immunopathol Pharmacol* 2009; **22**: 15-19 [PMID: 19309548 DOI: 10.1177/039463200902200103]
11 **Patrick RP**, Ames BN. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *FASEB J* 2014; **28**: 2398-2413 [PMID: 24558199 DOI: 10.1096/fj.13-246546]
12 **Enstrom AM**, Lit L, Onore CE, Gregg JP, Hansen RL, Pessah IN, Hertz-Picciotto I, Van de Water JA, Sharp FR, Ashwood P. Altered gene expression and function of peripheral blood natural killer cells in children with autism. *Brain Behav Immun* 2009; **23**: 124-133 [PMID: 18762240 DOI: 10.1016/j.bbi.2008.08.001]
13 **Manzardo AM**, Henkhaus R, Dhillon S, Butler MG. Plasma cytokine levels in children with autistic disorder and unrelated siblings. *Int J Dev Neurosci* 2012; **30**: 121-127 [PMID: 22197967 DOI: 10.1016/j.ijdevneu.2011.12.003]
14 **Heuer L**, Ashwood P, Schauer J, Goines P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. *Autism Res* 2008; **1**: 275-283 [PMID: 19343198 DOI: 10.1002/aur.42]
15 **Wasilewska J**, Kaczmarski M, Stasiak-Barmuta A, Tobolczyk J, Kowalewska E. Low serum IgA and increased expression of CD23 on B lymphocytes in peripheral blood in children with regressive autism aged 3-6 years old. *Arch*

Med Sci 2012; **8**: 324-331 [PMID: 22662007 DOI: 10.5114/aoms.2012.28561]
16 **Mezzelani A**, Landini M, Facchiano F, Raggi ME, Villa L, Molteni M, De Santis B, Brera C, Caroli AM, Milanesi L, Marabotti A. Environment, dysbiosis, immunity and sex-specific susceptibility: a translational hypothesis for regressive autism pathogenesis. *Nutr Neurosci* 2015; **18**: 145-161 [PMID: 24621061 DOI: 10.1179/1476830513Y.0000000108]
17 **Amaral DG**, de Vries PJ. COVID-19 and Autism Research: Perspectives from Around the Globe. *Autism Res* 2020; **13**: 844-869 [PMID: 32592337 DOI: 10.1002/aur.2329]
18 **Ramani A**, Pranty AI, Gopalakrishnan J. Neurotropic Effects of SARS-CoV-2 Modeled by the Human Brain Organoids. *Stem Cell Reports* 2021; **16**: 373-384 [PMID: 33631123 DOI: 10.1016/j.stemcr.2021.02.007]
19 **Zhan WR**, Huang J, Zeng PM, Tian WY, Luo ZG. Emerging neurotropic features of SARS-CoV-2. *J Mol Cell Biol* 2021; **13**: 705-711 [PMID: 34289037 DOI: 10.1093/jmcb/mjab044]
20 **Munhoz RP**, Pedroso JL, Nascimento FA, Almeida SM, Barsottini OGP, Cardoso FEC, Teive HAG. Neurological complications in patients with SARS-CoV-2 infection: a systematic review. *Arq Neuropsiquiatr* 2020; **78**: 290-300 [PMID: 32490966 DOI: 10.1590/0004-282x20200051]
21 **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683-690 [PMID: 32275288 DOI: 10.1001/jamaneurol.2020.1127]
22 **Ellul MA**, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. *Lancet Neurol* 2020; **19**: 767-783 [PMID: 32622375 DOI: 10.1016/S1474-4422(20)30221-0]
23 **Lu Y**, Li X, Geng D, Mei N, Wu PY, Huang CC, Jia T, Zhao Y, Wang D, Xiao A, Yin B. Cerebral Micro-Structural Changes in COVID-19 Patients - An MRI-based 3-month Follow-up Study. *EClinicalMedicine* 2020; **25**: 100484 [PMID: 32838240 DOI: 10.1016/j.eclinm.2020.100484]
24 **Edler C**, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, Klein A, Langenwalder F, Lütgehetmann M, Meißner K, Püschel K, Schädler J, Steurer S, Mushumba H, Sperhake JP. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int J Legal Med* 2020; **134**: 1275-1284 [PMID: 32500199 DOI: 10.1007/s00414-020-02317-w]
25 **Song E**, Zhang C, Israelow B, Lu-Culligan A, Prado AV, Skriabine S, Lu P, Weizman OE, Liu F, Dai Y, Szigeti-Buck K, Yasumoto Y, Wang G, Castaldi C, Heltke J, Ng E, Wheeler J, Alfajaro MM, Levavasseur E, Fontes B, Ravindra NG, Van Dijk D, Mane S, Gunel M, Ring A, Kazmi SAJ, Zhang K, Wilen CB, Horvath TL, Plu I, Haik S, Thomas JL, Louvi A, Farhadian SF, Huttner A, Seilhean D, Renier N, Bilguvar K, Iwasaki A. Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J Exp Med* 2021; **218** [PMID: 33433624 DOI: 10.1084/jem.20202135]
26 **Zhou Y**, Yang Q, Chi J, Dong B, Lv W, Shen L, Wang Y. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. *Int J Infect Dis* 2020; **99**: 47-56 [PMID: 32721533 DOI: 10.1016/j.ijid.2020.07.029]
27 **Fields VL**, Soke GN, Reynolds A, Tian LH, Wiggins L, Maenner M, DiGuiseppi C, Kral TVE, Hightshoe K, Schieve LA. Pica, Autism, and Other Disabilities. *Pediatrics* 2021; **147** [PMID: 33408069 DOI: 10.1542/peds.2020-0462]
28 **Mutluer T**, Doenyas C, Aslan Genc H. Behavioral Implications of the Covid-19 Process for Autism Spectrum Disorder, and Individuals' Comprehension of and Reactions to the Pandemic Conditions. *Front Psychiatry* 2020; **11**: 561882 [PMID: 33304279 DOI: 10.3389/fpsyt.2020.561882]
29 **Imran N**, Zeshan M, Pervaiz Z. Mental health considerations for children & adolescents in COVID-19 Pandemic. *Pak J Med Sci* 2020; **36**: S67-S72 [PMID: 32582317 DOI: 10.12669/pjms.36.COVID19-S4.2759]
30 **Sabourin KR**, Reynolds A, Schendel D, Rosenberg S, Croen LA, Pinto-Martin JA, Schieve LA, Newschaffer C, Lee LC, DiGuiseppi C. Infections in children with autism spectrum disorder: Study to Explore Early Development (SEED). *Autism Res* 2019; **12**: 136-146 [PMID: 30475448 DOI: 10.1002/aur.2012]
31 **Çölkesen F**, Kandemir B, Arslan Ş, Çölkesen F, Yıldız E, Korkmaz C, Vatansev H, Evcen R, Aykan FS, Kılınç M, Aytekin G, Feyzioğlu B, Doğan M, Teke T. Relationship between Selective IgA Deficiency and COVID-19 Prognosis. *Jpn J Infect Dis* 2022; **75**: 228-233 [PMID: 34588364 DOI: 10.7883/yoken.JJID.2021.281]
32 **Lima MES**, Barros LCM, Aragão GF. Could autism spectrum disorders be a risk factor for COVID-19? *Med Hypotheses* 2020; **144**: 109899 [PMID: 32505067 DOI: 10.1016/j.mehy.2020.109899]
33 **Schuck RK**, Flores RE, Fung LK. Brief Report: Sex/Gender Differences in Symptomology and Camouflaging in Adults with Autism Spectrum Disorder. *J Autism Dev Disord* 2019; **49**: 2597-2604 [PMID: 30945091 DOI: 10.1007/s10803-019-03998-y]
34 **Ya'qoub L**, Elgendy IY, Pepine CJ. Sex and gender differences in COVID-19: More to be learned! *Am Heart J Plus* 2021; **3**: 100011 [PMID: 34169297 DOI: 10.1016/j.ahjo.2021.100011]
35 **Fattorusso A**, Di Genova L, Dell'Isola GB, Mencaroni E, Esposito S. Autism Spectrum Disorders and the Gut Microbiota. *Nutrients* 2019; **11** [PMID: 30823414 DOI: 10.3390/nu11030521]
36 **Aktas B**. Gut Microbiota Dysbiosis and COVID-19: Possible Links. *Comprehensive Gut Microbiota* 2022; 535-544 [DOI: 10.1016/B978-0-12-819265-8.00072-3]
37 **Saeed NK**, Al-Beltagi M, Bediwy AS, El-Sawaf Y, Toema O. Gut microbiota in various childhood disorders: Implication and indications. *World J Gastroenterol* 2022; **28**: 1875-1901 [PMID: 35664966 DOI: 10.3748/wjg.v28.i18.1875]
38 **Schott W**, Tao S, Shea L. COVID-19 risk: Adult Medicaid beneficiaries with autism, intellectual disability, and mental health conditions. *Autism* 2022; **26**: 975-987 [PMID: 34420427 DOI: 10.1177/13623613211039662]
39 **Krieger I**, Erez G, Weinstein O, Cohen AD, Tzur Bitan D. COVID-19 Morbidity Among Individuals with Autistic Spectrum Disorder: A Matched Controlled Population-Based Study. *J Autism Dev Disord* 2021 [PMID: 34240292 DOI: 10.1007/s10803-021-05187-2]
40 **Karpur A**, Vasudevan V, Shih A, Frazier T. Brief Report: Impact of COVID-19 in Individuals with Autism Spectrum Disorders: Analysis of a National Private Claims Insurance Database. *J Autism Dev Disord* 2022; **52**: 2350-2356 [PMID: 34041682 DOI: 10.1007/s10803-021-05100-x]
41 **Biddison LD**, Berkowitz KA, Courtney B, De Jong CM, Devereaux AV, Kissoon N, Roxland BE, Sprung CL, Dichter JR,

Christian MD, Powell T; Task Force for Mass Critical Care; Task Force for Mass Critical Care. Ethical considerations: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest* 2014; **146**: e145S-e155S [PMID: 25144262 DOI: 10.1378/chest.14-0742]

42 **Agazzi E**. The Coronavirus pandemic and the principle of common good - ScienceDirect. *Bioethics Update* 2020; 63-66 [DOI: 10.1016/j.bioet.2020.04.001]

43 **Catalá-López F**, Hutton B, Page MJ, Driver JA, Ridao M, Alonso-Arroyo A, Valencia A, Macías Saint-Gerons D, Tabarés-Seisdedos R. Mortality in Persons With Autism Spectrum Disorder or Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2022; **176**: e216401 [PMID: 35157020 DOI: 10.1001/jamapediatrics.2021.6401]

44 **Croen LA**, Qian Y, Ashwood P, Zerbo O, Schendel D, Pinto-Martin J, Daniele Fallin M, Levy S, Schieve LA, Yeargin-Allsopp M, Sabourin KR, Ames JL. Infection and Fever in Pregnancy and Autism Spectrum Disorders: Findings from the Study to Explore Early Development. *Autism Res* 2019; **12**: 1551-1561 [PMID: 31317667 DOI: 10.1002/aur.2175]

45 **Karimi-Zarchi M**, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalili SR, Behforouz A, Ferdosian F, Bahrami R. Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review. *Fetal Pediatr Pathol* 2020; **39**: 246-250 [PMID: 32238084 DOI: 10.1080/15513815.2020.1747120]

46 **Naidu SAG**, Clemens RA, Pressman P, Zaigham M, Kadkhoda K, Davies KJA, Naidu AS. COVID-19 during Pregnancy and Postpartum. *J Diet Suppl* 2022; **19**: 115-142 [PMID: 33164601 DOI: 10.1080/19390211.2020.1834049]

47 **Lins B**. Maternal immune activation as a risk factor for psychiatric illness in the context of the SARS-CoV-2 pandemic. *Brain Behav Immun Health* 2021; **16**: 100297 [PMID: 34308388 DOI: 10.1016/j.bbih.2021.100297]

48 **Panda PK**, Gupta J, Chowdhury SR, Kumar R, Meena AK, Madaan P, Sharawat IK, Gulati S. Psychological and Behavioral Impact of Lockdown and Quarantine Measures for COVID-19 Pandemic on Children, Adolescents and Caregivers: A Systematic Review and Meta-Analysis. *J Trop Pediatr* 2021; **67** [PMID: 33367907 DOI: 10.1093/tropej/fmaa122]

49 **Nonweiler J**, Rattray F, Baulcomb J, Happé F, Absoud M. Prevalence and Associated Factors of Emotional and Behavioural Difficulties during COVID-19 Pandemic in Children with Neurodevelopmental Disorders. *Children (Basel)* 2020; **7** [PMID: 32899799 DOI: 10.3390/children7090128]

50 **Taylor JL**, Corbett BA. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. *Psychoneuroendocrinology* 2014; **49**: 207-228 [PMID: 25108163 DOI: 10.1016/j.psyneuen.2014.07.015]

51 **Riikonen R**, Makkonen I, Vanhala R, Turpeinen U, Kuikka J, Kokki H. Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism. *Dev Med Child Neurol* 2006; **48**: 751-755 [PMID: 16904022 DOI: 10.1017/S0012162206001605]

52 **Patterson PH**. Maternal infection and immune involvement in autism. *Trends Mol Med* 2011; **17**: 389-394 [PMID: 21482187 DOI: 10.1016/j.molmed.2011.03.001]

53 **Steinman G**. COVID-19 and autism. *Med Hypotheses* 2020; **142**: 109797 [PMID: 32416411 DOI: 10.1016/j.mehy.2020.109797]

54 **Theoharides TC**. Ways to Address Perinatal Mast Cell Activation and Focal Brain Inflammation, including Response to SARS-CoV-2, in Autism Spectrum Disorder. *J Pers Med* 2021; **11** [PMID: 34575637 DOI: 10.3390/jpm11090860]

55 **Chatterjee S**, Kar SK. COVID 19 in pregnancy and neurodevelopmental disorder: The four-fold levels of prevention. *Asian J Psychiatr* 2022; **70**: 103046 [PMID: 35219981 DOI: 10.1016/j.ajp.2022.103046]

56 **Breslin N**, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, Ring L, Landau R, Purisch S, Friedman AM, Fuchs K, Sutton D, Andrikopoulou M, Rupley D, Sheen JJ, Aubey J, Zork N, Moroz L, Mourad M, Wapner R, Simpson LL, D'Alton ME, Goffman D. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM* 2020; **2**: 100118 [PMID: 32292903 DOI: 10.1016/j.ajogmf.2020.100118]

57 **Hoffman MC**, Freedman R, Law AJ, Clark AM, Hunter SK. Maternal nutrients and effects of gestational COVID-19 infection on fetal brain development. *Clin Nutr ESPEN* 2021; **43**: 1-8 [PMID: 34024500 DOI: 10.1016/j.clnesp.2021.04.019]

58 **Patel JA**, Badiani AA, Nielsen FBH, Assi S, Unadkat V, Patel B, Courtney C, Hallas L. COVID-19 and autism: Uncertainty, distress and feeling forgotten. *Public Health Pract (Oxf)* 2020; **1**: 100034 [PMID: 34173571 DOI: 10.1016/j.puhip.2020.100034]

59 **Oakley B**, Tillmann J, Ruigrok A, Baranger A, Takow C, Charman T, Jones E, Cusack J, Doherty M, Violland P, Wroczyńska A, Simonoff E, Buitelaar JK, Gallagher L, Murphy DGM; AIMS-2-TRIALS ECRAN & the AIMS-2-TRIALS Consortium. COVID-19 health and social care access for autistic people: European policy review. *BMJ Open* 2021; **11**: e045341 [PMID: 34001500 DOI: 10.1136/bmjopen-2020-045341]

60 **Courtenay K**, Perera B. COVID-19 and people with intellectual disability: impacts of a pandemic. *Ir J Psychol Med* 2020; **37**: 231-236 [PMID: 32404232 DOI: 10.1017/ipm.2020.45]

61 **de Figueiredo CS**, Sandre PC, Portugal LCL, Mázala-de-Oliveira T, da Silva Chagas L, Raony Í, Ferreira ES, Giestal-de-Araujo E, Dos Santos AA, Bomfim PO. COVID-19 pandemic impact on children and adolescents' mental health: Biological, environmental, and social factors. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **106**: 110171 [PMID: 33186638 DOI: 10.1016/j.pnpbp.2020.110171]

62 **Lee J**. Mental health effects of school closures during COVID-19. *Lancet Child Adolesc Health* 2020; **4**: 421 [PMID: 32302537 DOI: 10.1016/S2352-4642(20)30109-7]

63 **Tokatly Latzer I**, Leitner Y, Karnieli-Miller O. Core experiences of parents of children with autism during the COVID-19 pandemic lockdown. *Autism* 2021; **25**: 1047-1059 [PMID: 33435701 DOI: 10.1177/1362361320984317]

64 **White LC**, Law JK, Daniels AM, Toroney J, Vernoia B, Xiao S; SPARK Consortium, Feliciano P, Chung WK. Brief Report: Impact of COVID-19 on Individuals with ASD and Their Caregivers: A Perspective from the SPARK Cohort. *J Autism Dev Disord* 2021; **51**: 3766-3773 [PMID: 33387233 DOI: 10.1007/s10803-020-04816-6]

65 **Shtayermman O**, Zhang Y. Attachment Style and Mental Health Profiles of Parents Caring for a Child with Autism: Suicidal Ideation, Depression and Anxiety. *J Autism Dev Disord* 2021 [PMID: 34792710 DOI:

10.1007/s10803-021-05355-4]
66 **Schoen SA**, Lane SJ, Mailloux Z, May-Benson T, Parham LD, Smith Roley S, Schaaf RC. A systematic review of ayres sensory integration intervention for children with autism. *Autism Res* 2019; **12**: 6-19 [PMID: 30548827 DOI: 10.1002/aur.2046]
67 **Hearst MO**, Hughey L, Magoon J, Mubukwanu E, Ndonji M, Ngulube E, Makhoul Z. Rapid health impact assessment of COVID-19 on families with children with disabilities living in low-income communities in Lusaka, Zambia. *PLoS One* 2021; **16**: e0260486 [PMID: 34910762 DOI: 10.1371/journal.pone.0260486]
68 **sbury K**, Fox L, Deniz E, Code A, Toseeb U. How is COVID-19 affecting the mental health of children with special educational needs and disabilities and their families? J Autism Dev Disord. (2020). [10.1007/s10803-020-04577-2 [DOI: 10.31234/osf.io/sevyd]
69 **Dubois-Comtois K**, Suffren S, St-Laurent D, Milot T, Lemelin JP. Child Psychological Functioning During the COVID-19 Lockdown: An Ecological, Family-Centered Approach. *J Dev Behav Pediatr* 2021; **42**: 532-539 [PMID: 34518496 DOI: 10.1097/DBP.0000000000000935]
70 **Sergi L**, Mingione E, Ricci MC, Cavallaro A, Russo F, Corrivetti G, Operto FF, Frolli A. Autism, Therapy and COVID-19. *Pediatr Rep* 2021; **13**: 35-44 [PMID: 33466265 DOI: 10.3390/pediatric13010005]
71 **Ferguson EF**, Jimenez-Muñoz M, Feerst H, Vernon TW. Predictors of Satisfaction with Autism Treatment Services During COVID-19. *J Autism Dev Disord* 2022; **52**: 3686-3697 [PMID: 34448995 DOI: 10.1007/s10803-021-05232-0]
72 **Debby L**. Gerritsen, Roeslan Leontjevas, Marleen Prins, Henriëtte van der Roest. The consequences of the COVID-19 measures for the well-being of residents of long-term care institutions. *Gerontologie en Geriatrie* **53** (1): 1-14
73 **Hajjar L**, Kragen B. Timely Communication Through Telehealth: Added Value for a Caregiver During COVID-19. *Front Public Health* 2021; **9**: 755391 [PMID: 34912769 DOI: 10.3389/fpubh.2021.755391]
74 **Kichloo A**, Albosta M, Dettloff K, Wani F, El-Amir Z, Singh J, Aljadah M, Chakinala RC, Kanugula AK, Solanki S, Chugh S. Telemedicine, the current COVID-19 pandemic and the future: a narrative review and perspectives moving forward in the USA. *Fam Med Community Health* 2020; **8** [PMID: 32816942 DOI: 10.1136/fmch-2020-000530]
75 **Valencia K**, Rusu C, Quiñones D, Jamet E. The Impact of Technology on People with Autism Spectrum Disorder: A Systematic Literature Review. *Sensors (Basel)* 2019; **19** [PMID: 31623200 DOI: 10.3390/s19204485]
76 **Chen Z**, Chen L, Chen H. The impact of COVID-19 on the clinical trial. *PLoS One* 2021; **16**: e0251410 [PMID: 33974651 DOI: 10.1371/journal.pone.0251410]
77 **Fridell A**, Norrman HN, Girke L, Bölte S. Effects of the Early Phase of COVID-19 on the Autistic Community in Sweden: A Qualitative Multi-Informant Study Linking to ICF. *Int J Environ Res Public Health* 2022; **19** [PMID: 35162290 DOI: 10.3390/ijerph19031268]
78 **Kumazaki H**, Muramatsu T, Yoshikawa Y, Haraguchi H, Sono T, Matsumoto Y, Ishiguro H, Kikuchi M, Sumiyoshi T, Mimura M. Enhancing Communication Skills of Individuals With Autism Spectrum Disorders While Maintaining Social Distancing Using Two Tele-Operated Robots. *Front Psychiatry* 2020; **11**: 598688 [PMID: 33569014 DOI: 10.3389/fpsyt.2020.598688]
79 **Panceri JAC**, Freitas É, de Souza JC, da Luz Schreider S, Caldeira E, Bastos TF. A New Socially Assistive Robot with Integrated Serious Games for Therapies with Children with Autism Spectrum Disorder and Down Syndrome: A Pilot Study. *Sensors (Basel)* 2021; **21** [PMID: 34960514 DOI: 10.3390/s21248414]
80 **Shinn AK**, Viron M. Perspectives on the COVID-19 Pandemic and Individuals With Serious Mental Illness. *J Clin Psychiatry* 2020; **81** [PMID: 32369691 DOI: 10.4088/JCP.20com13412]
81 **Goh TJ**, Lim T, Foo M, Ong SKA, Aishworiya R, Nair T, Kang YQ, Agarwal PK, Sung M. Supporting individuals with Autism Spectrum Disorder in medical settings during COVID-19. *Asian J Psychiatr* 2020; **54**: 102441 [PMID: 33271720 DOI: 10.1016/j.ajp.2020.102441]
82 **Hutchins TL**, Prelock PA. Using social stories and comic strip conversations to promote socially valid outcomes for children with autism. *Semin Speech Lang* 2006; **27**: 47-59 [PMID: 16440244 DOI: 10.1055/s-2006-932438]
83 **Narzisi A**. Handle the Autism Spectrum Condition During Coronavirus (COVID-19) *Stay At Home* period: Ten Tips for Helping Parents and Caregivers of Young Children. *Brain Sci* 2020; **10** [PMID: 32244776 DOI: 10.3390/brainsci10040207]
84 **Schaaf RC**, Dumont RL, Arbesman M, May-Benson TA. Efficacy of Occupational Therapy Using Ayres Sensory Integration®: A Systematic Review. *Am J Occup Ther* 2018; **72**: 7201190010p1-7201190010p10 [PMID: 29280711 DOI: 10.5014/ajot.2018.028431]
85 **Yoon WH**. Why Fast COVID-19 Vaccination Needed for People with Disabilities and Autistics in Korea? *J Korean Med Sci* 2021; **36**: e267 [PMID: 34581522 DOI: 10.3346/jkms.2021.36.e267]
86 **Choi K**, Becerra-Culqui T, Bhakta B, Bruxvoort K, Coleman KJ. Parent intentions to vaccinate children with autism spectrum disorder against COVID-19. *J Pediatr Nurs* 2022; **63**: 108-110 [PMID: 34836713 DOI: 10.1016/j.pedn.2021.11.019]
87 **Weinstein O**, Krieger I, Cohen AD, Tzur Bitan D. COVID-19 vaccination among individuals with autism spectrum disorder: A population-based study. *Res Autism Spectr Disord* 2021; **89**: 101865 [PMID: 34548878 DOI: 10.1016/j.rasd.2021.101865]
88 **Al Khames Aga QA**, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, Shaban D, Al Khames Aga LA, Agha MYR, Traqchi M. Safety of COVID-19 vaccines. *J Med Virol* 2021; **93**: 6588-6594 [PMID: 34270094 DOI: 10.1002/jmv.27214]
89 In brief: Pfizer/BioNTech COVID-19 vaccine authorized for children 5-11 years old. *Med Lett Drugs Ther* 2021; **63**: 185 [PMID: 35085214]
90 **Center for Disease Control and Prevention**. Guidance for Vaccinating Older Adults and People with Disabilities: Ensuring Equitable COVID-19 Vaccine Access. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/older-adults-and-disability/access.html
91 **Guidance for Vaccinating Older Adults and People with Disabilities at Vaccination Sites**. Available from: Vaccinating Older Adults and People with Disabilities at Vaccination Clinics | CDC Last accessed Apr 10, 2022

92 The Autism Society of America: COVID-19 Resources. Last accessed Apr 10, 2022. Available From: https://www.covid19.autism-society.org/

93 **Steiner AM**, Koegel LK, Koegel RL, Ence WA. Issues and theoretical constructs regarding parent education for autism spectrum disorders. *J Autism Dev Disord* 2012; **42**: 1218-1227 [PMID: 21336525 DOI: 10.1007/s10803-011-1194-0]

94 **Baweja R**, Brown SL, Edwards EM, Murray MJ. COVID-19 Pandemic and Impact on Patients with Autism Spectrum Disorder. *J Autism Dev Disord* 2022; **52**: 473-482 [PMID: 33689088 DOI: 10.1007/s10803-021-04950-9]

95 **McBain RK**, Kareddy V, Cantor JH, Stein BD, Yu H. Systematic Review: United States Workforce for Autism-Related Child Healthcare Services. *J Am Acad Child Adolesc Psychiatry* 2020; **59**: 113-139 [PMID: 31150751 DOI: 10.1016/j.jaac.2019.04.027]

96 **Gunin GB**, Gravino A, Bal VH. Advancing Mental Health Supports for Autistic Postsecondary Students: A Call for Research. *Autism Adulthood* 2021; **3**: 30-36 [PMID: 34396054 DOI: 10.1089/aut.2020.0044]

97 **Hume K**, Steinbrenner JR, Odom SL, Morin KL, Nowell SW, Tomaszewski B, Szendrey S, McIntyre NS, Yücesoy-Özkan S, Savage MN. Evidence-Based Practices for Children, Youth, and Young Adults with Autism: Third Generation Review. *J Autism Dev Disord* 2021; **51**: 4013-4032 [PMID: 33449225 DOI: 10.1007/s10803-020-04844-2]

98 **Lois Mosquera M**, Mandy W, Pavlopoulou G, Dimitriou D. Autistic adults' personal experiences of navigating a social world prior to and during Covid-19 lockdown in Spain. *Res Dev Disabil* 2021; **117**: 104057 [PMID: 34371305 DOI: 10.1016/j.ridd.2021.104057]

99 **Vallefuoco E**, Purpura G, Gison G, Bonifacio A, Tagliabue L, Broggi F, Scuccimarra G, Pepino A, Nacinovich R. A Multidisciplinary Telerehabilitation Approach for Supporting Social Interaction in Autism Spectrum Disorder Families: An Italian Digital Platform in Response to COVID-19. *Brain Sci* 2021; **11** [PMID: 34827403 DOI: 10.3390/brainsci11111404]

100 **Hoefman R**, Payakachat N, van Exel J, Kuhlthau K, Kovacs E, Pyne J, Tilford JM. Caring for a child with autism spectrum disorder and parents' quality of life: application of the CarerQol. *J Autism Dev Disord* 2014; **44**: 1933-1945 [PMID: 24577786 DOI: 10.1007/s10803-014-2066-1]

101 **Marques de Miranda D**, da Silva Athanasio B, Sena Oliveira AC, Simoes-E-Silva AC. How is COVID-19 pandemic impacting mental health of children and adolescents? *Int J Disaster Risk Reduct* 2020; **51**: 101845 [PMID: 32929399 DOI: 10.1016/j.ijdrr.2020.101845]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 426-434

DOI: 10.5501/wjv.v11.i6.426

ISSN 2220-3249 (online)

MINIREVIEWS

Monkeypox: An emerging zoonotic pathogen

Masoumeh Beig, Mehrdad Mohammadi, Fatemeh Nafe Monfared, Somaieh Nasereslami

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

P-Reviewer: Panduro-Correa V, Peru; Wang T, China

Received: June 5, 2022
Peer-review started: June 5, 2022
First decision: August 1, 2022
Revised: August 22, 2022
Accepted: October 12, 2022
Article in press: October 12, 2022
Published online: November 25, 2022

Masoumeh Beig, Department of Microbiology, Pasteur Institute of Iran, Tehran 5423566512, Iran

Mehrdad Mohammadi, Department of Immunology and Microbiology, Faculty of Medicine, Kashan University of Medical Sciences, Kashan 8715973449, Iran

Fatemeh Nafe Monfared, Department of Virology, Tehran University of Medical Sciences, Tehran 5151561892, Iran

Somaieh Nasereslami, Department of Virology, Faculty of Medicine, Tarbiat Modares University, Tehran 5214632542, Iran

Corresponding author: Mehrdad Mohammadi, PhD, Researcher, Department of Immunology and Microbiology, Faculty of Medicine, Kashan University of Medical Sciences, Ghoteb-e-ravandi Street, Kashan 8715973449, Iran. mehrdad.mohammadi1984@gmail.com

Abstract

Monkeypox virus (MPXV), which belongs to the orthopoxvirus genus, causes zoonotic viral disease. This review discusses the biology, epidemiology, and evolution of MPXV infection, particularly cellular, human, and viral factors, virus transmission dynamics, infection, and persistence in nature. This review also describes the role of recombination, gene loss, and gene gain in MPXV evolvement and the role of signal transduction in MPXV infection and provides an overview of the current access to therapeutic options for the treatment and prevention of MPXV. Finally, this review highlighted gaps in knowledge and proposed future research endeavors to address the unresolved questions.

Key Words: Poxviridae; Orthopoxviruses; Monkeypox viruses; Epidemiology

Core Tip: Since May 13, 2022, cases of monkeypox have been reported to the World Health Organization (WHO) from 12 Member States that are not endemic to the monkeypox virus across three WHO regions. This emergent pathogen is a significant concern worldwide after severe acute respiratory syndrome coronavirus 2 and requires epidemiological and other data on the virus. The objective of this review is to report comprehensive data on this virus.

Citation: Beig M, Mohammadi M, Nafe Monfared F, Nasereslami S. Monkeypox: An emerging zoonotic pathogen. *World J Virol* 2022; 11(6): 426-434
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/426.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.426

INTRODUCTION

Monkeypox virus (MPXV) is one of the human orthopox viruses (OPVs), which consist of variola virus (VARV), cowpox virus (CPXV), and vaccinia virus (VACV)[1]. Monkeypox has similar clinical manifestations to smallpox, but has a milder rash and a lower fatality rate[2]. The aims of this review are to describe the current data on MPXV evolution, epidemiology, and infection-control mechanisms.

History of monkeypox virus

When two smallpox-like illnesses appeared in monkey colonies housed for scientific study, the first cases of monkeypox were discovered in 1958[3]; therefore, the name monkeypox and the first human case of the virus were registered in 1970 in the Democratic Republic of the Congo[4]. Attempts to destroy the MPXV have since been documented in humans in other Central and West African countries [5].

Morphology, genome organization, and morphogenesis

The morphology of MPXV virions has been shown to include brick- or ovoid-shaped particles[6]. Membrane links, a tightly packed core containing enzymes, transcription factors, a double-stranded DNA genome, and an outer membrane protecting the whole structure have been observed[7,8]. Although its whole life cycle occurs in the cytoplasm of infected cells, its genome contains linear double-stranded DNA (197 kb). The genome encodes all the proteins necessary for viral DNA replication, transcription, and virion assembly[6,9]. Cells infected with the poxvirus generate the intracellular mature virus and extracellular enveloped virus, two contagious viruses[10,11] (Figure 1).

INFECTION BIOLOGY, DIAGNOSIS, AND TREATMENT

Animal models

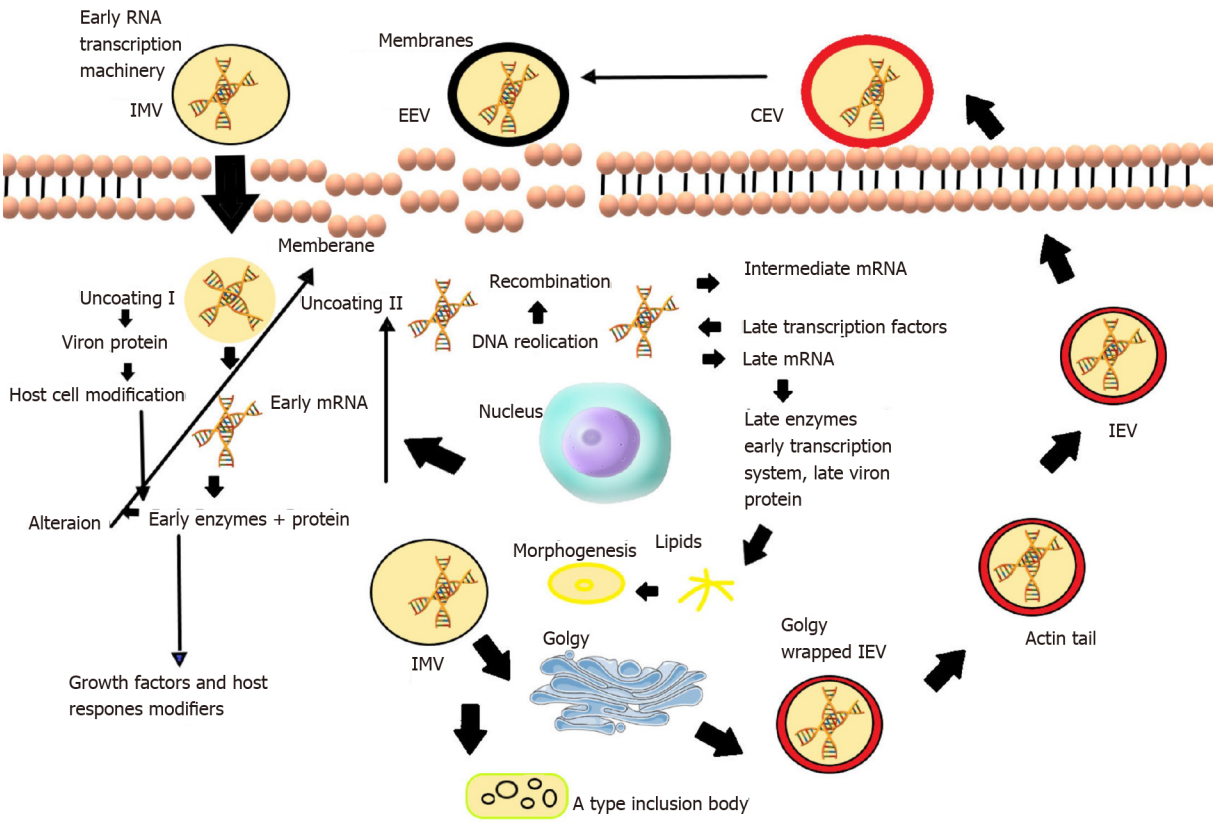
An animal model for studying ethnic illness uses a channel of contamination that matches the herbal transmission of the virus or displays development, morbidity, and death similar to those seen during ethnic infection[12,13]. The animal model also has to mirror human instances in at least one or more methods of transmission[14]. Additionally, the red patches on all MPXV-examined animals at the vaccination site showed a decrease in size compared to nearby animals, and beginning around 14 d after the challenge, a continual rise in body size across fully breathing animals in the vaccinated group[15, 16]. In a study that examined the sensitivity of 38 inbred strains of mice (32 classical inbreed stresses and six wild strains), only three of the wild-derived strains (CAST/EiJ, PERA/EiJ, and MOLF/EiJ) were highly sensitive to MPXV, whereas all other inbred lines were strong after intranasal MPXV infection[2, 17].

Transmission

Human-to-human and animal-to-human transmission are two potential MPXV transmission pathways [18]. Human-to-human transmission stability is correlated with droplet infection and interactions with body fluids, patient factors, and skin lesions in a contaminated individual[6,18]. The Congo Basin group is more virulent than the West African group and contributes more to interpersonal transport[19]. Direct contact and ingestion of the herbal viral host's food are the two routes by which transmission occurs from animals to humans[20,21]. Furthermore, zoonotic transmission can occur *via* direct touch, including blood, body fluids, and mucocutaneous lesions on a contaminated animal[22].

Sexual transmission of MPXV: MPXV outbreaks are not typical, as many patients are unrelated to travel to Central or West Africa and episodes of the virus in endemic areas. The MPXV is currently observed among men who have sex with men (MSM) in the United Kingdom. In the studies conducted, a high proportion of simultaneous sexually transmitted diseases and frequent anogenital symptoms were found, which indicates the possibility of transmission during close skin-to-skin or mucous contact during sexual activity[1,23,24].

Transmission by MPXV-contaminated surfaces: Although co-transmission between people and animals was identified as the primary method of infection dissemination in several investigations, transmission in patient care staff *via* surfaces contaminated with MPXV was seldom recorded. The



DOI: 10.5501/wjv.v11.i6.426

Figure 1 Cycle of monkeypox virus. When the virion binds and fuses with the host cell membrane, the viral core is released in the cytoplasm. Enzymes, and then factors, initiate transcription. Most virions remain in the cytoplasm. Virus- and host-encoded proteins concerning cell surface-associated enveloped virions and cell surface-associated enveloped virions guard them to complement activation. IMV: Intracellular reduced virion; EEV: Extracellular enveloped virion; CEV: Cell surface-associated enveloped virion; IEV: Intracellular enveloped virion.

MPXV may also spread indirectly *via* contaminated objects. However, the environmental contamination of surfaces with MPXV is not well understood[25].

Diagnostic methods

Phenotypic approaches: Phenotypic methods: According to the clinical diagnosis, in MPXV infection, a prodromal sickness usually accompanies it with a variety of symptoms over 3-5 d, including fever > 38.3°C, back pain, myalgia, headache, acute asthenia, pharyngitis, drenching sweats, malaise, and notably lymphadenopathy[6,26-28]. Vesiculopustular rashes begin on the face during 1-10 d of development, affecting 95% of patients[29], followed by the palms and soles (75%), oral mucosa (70%), genitalia (30%), and conjunctiva (20%). These skin lesions evolve from macules to papules, vesicles, pustules, and finally, scabs or crusts that fall[28]. Lesions in MPXV patients appear monomorphic, pea-sized, and complex, similar to smallpox[30]. The presence of lymphadenopathy in MPXV infection is one of the clinical markers that set it apart from smallpox, along with lesion appearance and limited centrifugal spread[31]. These skin manifestations compromise the skin eruption period of the disease, in which patients are contagious. Before that, patients are not able to transmit the virus. The natural history in patients without complications regularly lasts 2-4 wk[28]. Possible detection of MPXV based on clinical signs is essential to identify suspicious cases during surveillance. Nevertheless, the clinical case definition for MPXV based on unconfirmed studies has high sensitivity (93% to 98%) and low specificity (9% to 26%)[31,32]. Virus transmission occurs by direct bodily contact with pores and skin then skin lesions, along with sexual contact; or contact with contaminated materials, such as clothing, bedding and dishes, within 21 d before signs appear. Laboratory research does not validate the clinical definition, but an epidemiological link, including contact with a proven case does[28].

Genetic methods: It is recommended that genetic techniques, including polymerase chain reaction (PCR) or real-time PCR (RT-PCR), be performed in a biosafety level 3 facility[33].

Routine detection of MPXV DNA in clinical and veterinary specimens and cell cultures infected with MPXV is performed by RT-PCR targeting conserved regions of the outer coat protein (*B6R*) gene, l DNA polymerase E, the DNA-dependent RNA polymerase subunit 18 (rpo18), and the *F3L* genes[33,34]. Restriction fragment length polymorphism (RFLP) of genes or PCR-amplified gene fragments is also

used to detect MPXV DNA, but RFLP is time-consuming and requires viral culture[35]. Additionally, as RFLP of PCR products requires enzymatic digestion after gel electrophoresis, it may not be an appropriate method in a clinical setting where speed, sensitivity, and specificity are essential. Whole genome sequencing (NGS) is valuable in detecting MPXV and OPVs, but this technique is expensive, and downstream sequencing records processing requires extensive computing[36-38]. Therefore, NGS may not be a siutable detection method in resource-poor locations in sub-Saharan Africa. Although RT-PCR remains the optimal method for the identification of MPXV, this must be complemented by genome sequencing technology to provide information on the genome, which is essential for evidence-based epidemiology (Figure 2)[32].

Immunological methods: These methods include enzyme-linked immunosorbent (ELISA) and immunohistochemical assays to determine IgG and IgM antibodies and detect viral antigens[39]. Immunochemical analysis can distinguish poxvirus from herpes virus infection using polyclonal or monoclonal antibodies to all OPVs[11]. It has been shown that antibodies to the virus also have cellular responses and enhancements at the time of disease onset. Approximately 5 d and 8 d or more after the onset of the rash, IgM and IgG are formed in the serum, respectively[40]. Detection of IgM and IgG antibodies in unvaccinated individuals with a history of inflammation and severe illness may increase indirect MPXV discrimination. Despite this, these methods are not specific for MPXV detection and can detect other types of OPVs[32,41]. On the other hand, IgM can assess MPXV infection in people with a history of smallpox vaccination[42]. A positive IgM capture ELISA test indicates recent exposure to OPV (possibly MPXV in endemic areas) in vaccinated individuals.

Conversely, a positive IgG capture ELISA test indicates that a person has been exposed to OPV through vaccination or natural infection. Therefore, IgM and IgG in a sample are strong evidence of recent exposure to an OPV in previously vaccinated or naturally infected individuals. Thus, IgM in individuals vaccinated against smallpox in MPXV-endemic regions reflects recent exposure to MPXV [43,44].

Electron microscopy: MPXV under an electron microscope appears intracytoplasmic brick-shaped with lateral bodies and a central core measuring about 200–300 nm. Although this method is not a definitive diagnostic technique as OPV species cannot be differentiated morphologically, it provides a clue that the virus belongs to the Poxviridae family [45].

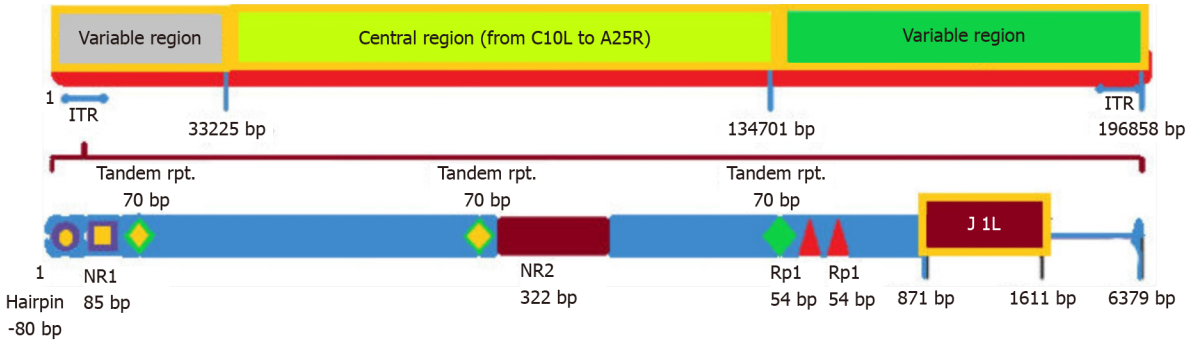
Virus-host interaction

Host and tissue tropism: Members of the OPV family are thought to exhibit diverse spectra of host tropisms[46]. Although the reservoir host for MPXV has not been definitively identified, many mammalian species are naturally infected with MPXV[47]. Thus, it is believed that MPXV has a wide host range. Previously, after the challenge with Congo Basin MPXV, large amounts of viral DNA and viable virions died in a variety of animal tissues, suggesting broad tissue tropism. The immunohistochemical and histopathological tests by Falendysz *et al*[48] found that the MPXV antigen was identified in ovarian, brain, heart, kidney, liver, pancreatic, and lung tissues, and ovarian tissues were susceptible to MPXV[49].

Host responses to the virus: PXVs develop many strategies to escape the host's immune response to infection. Natural killer (NK) cells kill virus-infected cells by secreting cytokines that stimulate the activity of other cell types, such as T cells and dendritic cells[50]. MPXV infection can change lymphocyte numbers, NK cell changes in non-human primates (NHPs), lymphadenopathy, and lymphocyte consumption in MPXV-infected NHPs. Gavin *et al*[51] using prairie pooches showed a noteworthy increment in the number of all NK subsets (CD16- CD56-, CD16+, CD56+, and CD16+ CD56+) on the seventh day after vaccination. Moreover, the expression of chemokine receptors (CXCR3, CCR5, CCR6, and CCR7) on each NK cell subset suggest that, following the MPXV challenge, receptor expression was delayed or reduced[11,52]. Hammarlund *et al*[53] anticipated that MPXV has a safe avoidance component such as CPXV. The avoidance process utilized by MPXV ensures the viral store is resistant by repressing the activation of CD4+ and CD8+ T cells after interaction with MPXV-infected cells. Acknowledgment of MPXV-infected monocytes by antiviral CD4+ and CD8+ shows that MPXV does not activate the generation of cytokines (IFN-γ or TNF-α) by virus-specific T cells[52]. Antiviral T-cell responses are substantially increased following contamination with VARV alone. However, T-cell cytokine responses decreased by 95% after co-infection, including MPXV and VARV, and by 80% when low-dose MPXV was added (VARV: MPXV ratio was 10:1)[54].

Treatment

Vaccination: The smallpox vaccine protects humans against smallpox. The smallpox vaccine incorporates a live vaccinia virus, and not a killed virus[55]. Vaccinated people must take precautions, as the vaccine can result in side effects[56]. Most humans have mild reactions such as flank pain, fever, and body aches[51]. However, some people may react differently, and some side effects can be life-threatening[57]. Although smallpox vaccination can shield humans from smallpox for approximately 3-5 years, its potential to protect humans then decreases, and for long-term protection, additional vaccinations may be needed[58]. Several reviews suggest that smallpox vaccination provides cross-protection



DOI: 10.5501/wjv.v11.i6.426

Figure 2 Genomic structure of monkeypox virus. The entire genome consists of over 196858 bp along the central genomic vicinity of 101476 bp. Both extreme variables (right is longer than left) include a 6379 bp inverted terminal repeat. ITR: Inverted terminal repeat.

against common OPV species and MPXV. Of humans vaccinated against smallpox, 85% did not develop MPXV infection[59]. The smallpox vaccine (ACAM2000™) was advocated by the Centers for Disease Control and Prevention (CDC)[60].

The attenuated vaccine, IMVAMUNE, is no longer available in MPXV areas[61]. A third-generation modified Ankara vaccine has been selected with the aid of the Food and Drug Administration (FDA) and the European Medicines Agency to prevent varicella or monkeypox in adults (age 18 years) with a high risk of VARV and MPXV infection[61,62]. Unlike the ACAM2000 vaccine, IMVAMUNE is no longer used in humans with immunodeficiency, such as immune disorders and atopic dermatitis. Neither ACAM2000 nor IMVAMUNE is used in specific populations[61,62]. Vaccination is also recommended for sexually high-risk individuals, including MSM, and those with a history of sexually transmitted diseases such as human immunodeficiency virus (HIV), syphilis, and gonorrhea. However, there are no statistics on immunization, including smallpox vaccines JYNNEOS®/IMVANEX® that may confer protection against sexually transmitted MPXV[51,63].

Antivirals: There is no approved, safe remedy for MPXV infection. A 4-trifluoromethylphenol derivative and tecovirimat (ST-246 or TPOXX®), supported by the FDA, have been examined using animal models[64]. These agents have been shown to be beneficial in infected animals. According to a CDC report, clinical trials, including on tecoirimate, show that although the treatment is well tolerated and safe, there are inadequate statistics on its usefulness in treating monkeypox in humans[61,65,66]. Similarly, *in vitro* studies with cidofovir or brincidofovir (CMX001 or hexadecyloxypropyl-cidofovir) reduced viral DNA polymerase, and is an acyclic nucleoside phosphate conjugate of cidofovir[61,66,67]. However, brincidofovir has increased cytotoxicity and higher antiviral activity than cidofovir towards VARV, MPXV, VACV, and CPXV *in vitro*.

Brincidofovir has a high selectivity index and is 25-fold greater than cidofovir. Cidofovir is a nucleotide monophosphate analog. Another dynamic agent against poxviruses is NIOCH-14, a precursor of tecovirimat[66-68]. Although the activity of NIOCH-14 towards VARV, MPXV, and ECTV is similar to that of tecovirimat in *in vitro* studies, its production is less complicated than tecovirimat, and has been recognized as an essential antiviral in the future. Ribavirin and tiazofurin inhibited the activity of every OPV tested including VARV and MPXV[59,61,68,69]. Saquinavir, ritonavir, and nelfinavir are protease inhibitors, and efavirenz, stavudine, and zidovudine are reverse transcriptase inhibitors and have been used against OPVs. In addition, two adenosine analogs (C-ca3-Ado and C3-Npc A) have been shown to have protective activity against OPVs in viral replication assays, and these analogs are also inhibitors of S-adenosylhomocysteine hydrolase (SAH)[59,61,67,68]. These SAH hydrolase inhibitors have broad antiviral activity but had no detectable effect on CPXV *in vitro*. Using specific mechanisms, cidofovir and N-(2-hydroxypropyl) methacrylamide inhibited viral duplication in PXVs. However, adefovir and dipivoxil showed no sizeable activity against poxviruses.

Furthermore, adenosine oxide N1 had a considerable effect on OPV by inhibiting CPXV viral reproduction *in vitro* by blocking viral mRNA translation[52,68,70]. Although there is no optimal therapy, MPXV is managed only by supportive than evidential treatment, and is only suitable for symptomatic individuals[66,68]. Thus, environmentally friendly MPXV vaccination and antiviral agents are required to prevent transmission from asymptomatic people.

Biocidal agents and disinfectants: On June 5, 2022, a study was conducted to assess the published data regarding the antiviral effect of biocides and disinfectants against MPXV and orthopoxviruses. Vaccinia viruses must be rendered inactive by at least four log10 using 70% ethanol (70%, 1 min), peracetic acid (0.2%, 10 min), and probiotic cleanser (1%-10%, one h) on contaminated surfaces. These tests also demonstrated the efficacy of glutaraldehyde (2%; 10 min), orthophthalaldehyde (0.55%, 5 min), iodine (0.04%-1%) and sodium hypochlorite (0.25%-2.5%; 1 min). Vaccinia virus was not affected by copper

levels (99.9%) but MPXV was at 3 min[71].

CONCLUSION

As of May 2022, instances of MPXV have been recorded in nations where the infection is not endemic and are still being reported in several endemic nations. As a result, MPXV is no longer restricted to areas where it is endemic as, in recent years, visitors from Africa have brought MPXV to the United States, the United Kingdom, Israel, and Singapore. MPXV is a dangerous reemerging pathogen. MSM males in the United Kingdom have contracted MPXV *via* community transmission without directly interacting with travelers from endemic nations. In addition, a study reported admission to the Hospital for Infectious and Tropical Diseases in Romania of a 26-year-old HIV-positive male with high fever (up to 39 ℃), chills, rectal pain, vesiculo-pustular rash, dysphagia, and skin lesions primarily in the anogenital area who had developed a mild form of the disease. This was the first MPXV case officially verified in Romania with suspicious epidemiological and clinical symptoms. Excellent knowledge on how to prevent and control MPXV infection, and improve contact tracing is required. This is particularly true in populations with high-risk characteristics. Public health officials and medical professionals should rule out MPXV in all patients who exhibit the typical rash and risky sexual behavior, especially those who have recently had sex with partners who visited countries where MPXV cases have been reported or partners who exhibit the same clinical symptoms even if they do not travel abroad[72]. As a result, it is essential to focus more on national and international research efforts for laboratory diagnosis, infection control, and treatment strategies. These strategies should also support sexual health and other specialized services in managing this condition. For MPXV outbreaks around the world, the Surveillance Outbreak Response Management Analysis System must be established and implemented.

FOOTNOTES

Author contributions: Beig M, Mohammadi M, Nafe Monfared F, and Nasereslami S were the study's principal investigators; Beig M and Mohammadi M were involved in the concept and design of the study; Mohammadi M and Nasereslami S revised the manuscript and critically evaluated the intellectual content; All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically assessed the academic ranges; All authors have read and approved the manuscript's content and confirmed the accuracy or integrity of any part of the work.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Country/Territory of origin: Iran

ORCID number: Masoumeh Beig 0000-0003-1243-3164; Mehrdad Mohammadi 0000-0002-1865-5238; Fatemeh Nafe Monfared 0000-0001-6824-6654; Somaieh Nasereslami 0000-0002-1354-8118.

S-Editor: Zhang H
L-Editor: Webster JR
P-Editor: Zhang H

REFERENCES

1 **Girometti N**, Byrne R, Bracchi M, Heskin J, McOwan A, Tittle V, Gedela K, Scott C, Patel S, Gohil J, Nugent D, Suchak T, Dickinson M, Feeney M, Mora-Peris B, Stegmann K, Plaha K, Davies G, Moore LSP, Mughal N, Asboe D, Boffito M, Jones R, Whitlock G. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. *Lancet Infect Dis* 2022; **22**: 1321-1328 [PMID: 35785793 DOI: 10.1016/S1473-3099(22)00411-X]

2 **Gong Q**, Wang C, Chuai X, Chiu S. Monkeypox virus: a re-emergent threat to humans. *Virol Sin* 2022; **37**: 477-482 [PMID: 35820590 DOI: 10.1016/j.virs.2022.07.006]

3 **Bunge EM**, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, Steffen R. The changing epidemiology of human monkeypox-A potential threat? *PLoS Negl Trop Dis* 2022; **16**: e0010141 [PMID: 35148313 DOI: 10.1371/journal.pntd.0010141]

4 **Guarner J**, Del Rio C, Malani PN. Monkeypox in 2022-What Clinicians Need to Know. *JAMA* 2022; **328**: 139-140 [PMID: 35696257 DOI: 10.1001/jama.2022.10802]

5 **Diehl MLN**, Paes J, Rott MB. Genotype distribution of Acanthamoeba in keratitis: a systematic review. *Parasitol Res* 2021; **120**: 3051-3063 [PMID: 34351492 DOI: 10.1007/s00436-021-07261-1]

6 **Luo Q**, Han J. Preparedness for a Monkeypox Outbreak. *Infect Med* 2022 [DOI: 10.1016/j.imj.2022.07.001]

7 **Hutson CL**, Damon IK. Monkeypox virus infections in small animal models for evaluation of anti-poxvirus agents. *Viruses* 2010; **2**: 2763-2776 [PMID: 21994638 DOI: 10.3390/v2122763]

8 **Kumar S**, Subramaniam G, Karuppanan K. Human monkeypox outbreak in 2022. *J Med Virol* 2022 [PMID: 35637363 DOI: 10.1002/jmv.27894]

9 **Kmiec D**, Kirchhoff F. Monkeypox: A New Threat? *Int J Mol Sci* 2022; **23** [PMID: 35887214 DOI: 10.3390/ijms23147866]

10 **Bayer-Garner IB**. Monkeypox virus: histologic, immunohistochemical and electron-microscopic findings. *J Cutan Pathol* 2005; **32**: 28-34 [PMID: 15660652 DOI: 10.1111/j.0303-6987.2005.00254.x]

11 **Sood A**, Sui Y, McDonough E, Santamaría-Pang A, Al-Kofahi Y, Pang Z, Jahrling PB, Kuhn JH, Ginty F. Comparison of Multiplexed Immunofluorescence Imaging to Chromogenic Immunohistochemistry of Skin Biomarkers in Response to Monkeypox Virus Infection. *Viruses* 2020; **12** [PMID: 32717786 DOI: 10.3390/v12080787]

12 **Saijo M**, Ami Y, Suzaki Y, Nagata N, Iwata N, Hasegawa H, Iizuka I, Shiota T, Sakai K, Ogata M, Fukushi S, Mizutani T, Sata T, Kurata T, Kurane I, Morikawa S. Virulence and pathophysiology of the Congo Basin and West African strains of monkeypox virus in non-human primates. *J Gen Virol* 2009; **90**: 2266-2271 [PMID: 19474247 DOI: 10.1099/vir.0.010207-0]

13 **Karumathil S**, Raveendran NT, Ganesh D, Kumar Ns S, Nair RR, Dirisala VR. Evolution of Synonymous Codon Usage Bias in West African and Central African Strains of Monkeypox Virus. *Evol Bioinform Online* 2018; **14**: 1176934318761368 [PMID: 29551886 DOI: 10.1177/1176934318761368]

14 **Fan C**, Wu Y, Rui X, Yang Y, Ling C, Liu S, Wang Y. Animal models for COVID-19: advances, gaps and perspectives. *Signal Transduct Target Ther* 2022; **7**: 220 [PMID: 35798699 DOI: 10.1038/s41392-022-01087-8]

15 **Mucker EM**, Shamblin JD, Raymond JL, Twenhafel NA, Garry RF, Hensley LE. Effect of Monkeypox Virus Preparation on the Lethality of the Intravenous Cynomolgus Macaque Model. *Viruses* 2022; **14**: 1741 [PMID: 36016363 DOI: 10.3390/v14081741]

16 **Mucker EM**, Golden JW, Hammerbeck CD, Kishimori JM, Royals M, Joselyn MD, Ballantyne J, Nalca A, Hooper JW. A Nucleic Acid-Based Orthopoxvirus Vaccine Targeting the Vaccinia Virus L1, A27, B5, and A33 Proteins Protects Rabbits against Lethal Rabbitpox Virus Aerosol Challenge. *J Virol* 2022; **96**: e0150421 [PMID: 34851148 DOI: 10.1128/JVI.01504-21]

17 **Hutson CL**, Kondas AV, Mauldin MR, Doty JB, Grossi IM, Morgan CN, Ostergaard SD, Hughes CM, Nakazawa Y, Kling C, Martin BE, Ellison JA, Carroll DS, Gallardo-Romero NF, Olson VA. Correction for Hutson *et al*., "Pharmacokinetics and Efficacy of a Potential Smallpox Therapeutic, Brincidofovir, in a Lethal Monkeypox Virus Animal Model". *mSphere* 2021; **6**: e00126-21 [PMID: 33597175 DOI: 10.1128/mSphere.00126-21]

18 **Jamil H**, Tariq W, Tahir MJ, Mahfooz RS, Asghar MS, Ahmed A. Human monkeypox expansion from the endemic to non-endemic regions: Control measures. *Ann Med Surg (Lond)* 2022; **79**: 104048 [PMID: 35860124 DOI: 10.1016/j.amsu.2022.104048]

19 **Parvin R**, Ali A, Abdou Nagy ZZ, Zhao S, Paul AK, Hafez M. Monkeypox virus: A comprehensive review of taxonomy, evolution, epidemiology, diagnosis, prevention, and control regiments so far. *Ger J Microbiol* 2022 [DOI: 10.51585/gjm.2022.2.0014]

20 **Patrono LV**, Pléh K, Samuni L, Ulrich M, Röthemeier C, Sachse A, Muschter S, Nitsche A, Couacy-Hymann E, Boesch C, Wittig RM, Calvignac-Spencer S, Leendertz FH. Monkeypox virus emergence in wild chimpanzees reveals distinct clinical outcomes and viral diversity. *Nat Microbiol* 2020; **5**: 955-965 [PMID: 32341480 DOI: 10.1038/s41564-020-0706-0]

21 **Peter OJ**, Kumar S, Kumari N, Oguntolu FA, Oshinubi K, Musa R. Transmission dynamics of Monkeypox virus: a mathematical modelling approach. *Model Earth Syst Environ* 2022; **8**: 3423-3434 [PMID: 34667829 DOI: 10.1007/s40808-021-01313-2]

22 **Saxena SK**, Ansari S, Maurya VK, Kumar S, Jain A, Paweska JT, Tripathi AK, Abdel-Moneim AS. Reemerging human monkeypox: A major public-health debacle. *J Med Virol* 2022; Epub ahead of print [PMID: 35652133 DOI: 10.1002/jmv.27902]

23 **Zachariou M**. Monkeypox: Symptoms seen in London sexual health clinics differ from previous outbreaks, study finds. *BMJ* 2022; **378**: o1659 [PMID: 35790223 DOI: 10.1136/bmj.o1659]

24 **Vallée A**, Farfour E, Zucman D. Monkeypox virus: A novel sexually transmitted disease? *Travel Med Infect Dis* 2022; **49**: 102394 [PMID: 35777659 DOI: 10.1016/j.tmaid.2022.102394]

25 **Nörz D**, Pfefferle S, Brehm TT, Franke G, Grewe I, Knobling B, Aepfelbacher M, Huber S, Klupp EM, Jordan S, Addo MM, Schulze Zur Wiesch J, Schmiedel S, Lütgehetmann M, Knobloch JK. Evidence of surface contamination in hospital rooms occupied by patients infected with monkeypox, Germany, June 2022. *Euro Surveill* 2022; **27** [PMID: 35775427 DOI: 10.2807/1560-7917.ES.2022.27.26.2200477]

26 **Samaranayake L**, Anil S. The Monkeypox Outbreak and Implications for Dental Practice. *Int Dent J* 2022 [PMID: 35934521 DOI: 10.1016/j.identj.2022.07.006]

27 **Bothra A**, Maheswari A, Singh M, Pawar M, Jodhani K. Cutaneous manifestations of viral outbreaks. *Australas J Dermatol* 2021; **62**: 27-36 [PMID: 32895964 DOI: 10.1111/ajd.13421]

28 **Rodriguez-Morales AJ**. Monkeypox and the importance of cutaneous manifestations for disease suspicion. *Microbes Infect Chemother* 2022; **2**: e1450 [DOI: 10.54034/mic.e1450]

29 **Patel A**, Bilinska J, Tam JCH, Da Silva Fontoura D, Mason CY, Daunt A, Snell LB, Murphy J, Potter J, Tuudah C, Sundramoorthi R, Abeywickrema M, Pley C, Naidu V, Nebbia G, Aarons E, Botgros A, Douthwaite ST, van Nispen Tot Pannerden C, Winslow H, Brown A, Chilton D, Nori A. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ* 2022; **378**: e072410 [PMID: 35902115 DOI:

10.1136/bmj-2022-072410]
30 **Mande G**, Akonda I, De Weggheleire A, Brosius I, Liesenborghs L, Bottieau E, Ross N, Gembu GC, Colebunders R, Verheyen E, Ngonda D, Leirs H, Laudisoit A. Enhanced surveillance of monkeypox in Bas-Uélé, Democratic Republic of Congo: the limitations of symptom-based case definitions. *Int J Infect Dis* 2022; **122**: 647-655 [PMID: 35809857 DOI: 10.1016/j.ijid.2022.06.060]
31 **Ortiz-Martínez Y**, Rodríguez-Morales AJ, Franco-Paredes C, Chastain DB, Gharamti AA, Vargas Barahona L, Henao-Martínez AF. Monkeypox - a description of the clinical progression of skin lesions: a case report from Colorado, USA. *Ther Adv Infect Dis* 2022; **9**: 20499361221117726 [PMID: 35910397 DOI: 10.1177/20499361221117726]
32 **Mileto D**, Riva A, Cutrera M, Moschese D, Mancon A, Meroni L, Giacomelli A, Bestetti G, Rizzardini G, Gismondo MR, Antinori S. New challenges in human monkeypox outside Africa: A review and case report from Italy. *Travel Med Infect Dis* 2022; **49**: 102386 [PMID: 35738529 DOI: 10.1016/j.tmaid.2022.102386]
33 **Isidro J**, Borges V, Pinto M, Sobral D, Santos JD, Nunes A, Mixão V, Ferreira R, Santos D, Duarte S, Vieira L, Borrego MJ, Núncio S, de Carvalho IL, Pelerito A, Cordeiro R, Gomes JP. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. *Nat Med* 2022; **28**: 1569-1572 [PMID: 35750157 DOI: 10.1038/s41591-022-01907-y]
34 **Forni D**, Molteni C, Cagliani R, Sironi M. Geographic structuring and divergence time frame of monkeypox virus in the endemic region. *J Infect Dis* 2022 [PMID: 35831941 DOI: 10.1093/infdis/jiac298]
35 **Parker S**, Buller RM. A review of experimental and natural infections of animals with monkeypox virus between 1958 and 2012. *Future Virol* 2013; **8**: 129-157 [PMID: 23626656 DOI: 10.2217/fvl.12.130]
36 **Gul I**, Liu C, Xi Y, Du Z, Zhai S, Lei Z, Qun C, Raheem MA, He Q, Zhang H, Zhang C, Wang R, Han S, Ke D, Qin P. Current and perspective sensing methods for monkeypox virus: a reemerging zoonosis in its infancy; 2022. Available from: arXiv: 220805228
37 **Brinkmann A**. Differentialdiagnostik von pockentypischen Hautveränderungen mittels Metagenomanalyse und VAmpSeq. 2021 [DOI: 10.17169/refubium-30319]
38 **Bottlender R**, Hoff P, Strauss A. Differentialdiagnostik von Paranoia und paranoider Schizophrenie mittels AMDP-Syndromen. In: Möller HJ, Engel RR, Hoff P. Befunderhebung in der Psychiatrie: Lebensqualität, Negativsymptomatik und andere aktuelle Entwicklungen. Springer: Vienna, 1996: 241-248 [DOI: 10.1007/978-3-7091-6574-4_20]
39 **Shete A**, Mohandas S, Jain R, Yadav PD. A qualitative IgG ELISA for detection of SARS-CoV-2-specific antibodies in Syrian hamster serum samples. *STAR Protoc* 2021; **2**: 100573 [PMID: 33997801 DOI: 10.1016/j.xpro.2021.100573]
40 **Adler H**, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, Osborne JC, Rampling T, Beadsworth MB, Duncan CJ, Dunning J, Fletcher TE, Hunter ER, Jacobs M, Khoo SH, Newsholme W, Porter D, Porter RJ, Ratcliffe L, Schmid ML, Semple MG, Tunbridge AJ, Wingfield T, Price NM; NHS England High Consequence Infectious Diseases (Airborne) Network. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis* 2022; **22**: 1153-1162 [PMID: 35623380 DOI: 10.1016/S1473-3099(22)00228-6]
41 **Hraib M**, Jouni S, Albitar MM, Alaidi S, Alshehabi Z. The outbreak of monkeypox 2022: An overview. *Ann Med Surg (Lond)* 2022; **79**: 104069 [PMID: 35860140 DOI: 10.1016/j.amsu.2022.104069]
42 **Bragazzi NL**, Kong JD, Mahroum N, Tsigalou C, Khamisy-Farah R, Converti M, Wu J. Epidemiological trends and clinical features of the ongoing monkeypox epidemic: A preliminary pooled data analysis and literature review. *J Med Virol* 2022 [PMID: 35692117 DOI: 10.1002/jmv.27931]
43 **Shafaati M**, Zandi M. Monkeypox virus neurological manifestations in comparison to other orthopoxviruses. *Travel Med Infect Dis* 2022; **49**: 102414 [PMID: 35926767 DOI: 10.1016/j.tmaid.2022.102414]
44 **Bethineedi LD**, Kutikuppala LVS, Kandi V. Monkeypox Epidemic: A Throwback From Smallpox Eradication. *Cureus* 2022; **14**: e26577 [PMID: 35936131 DOI: 10.7759/cureus.26577]
45 **Bano R**, Jamil M, Kashif M, Qasim M, Khan M, Ali M, Jabeen N, Ahmad S, Naz R. The Zoonotic Disease Human Monkey Pox: An Insights into Epidemiological, Clinical, and Preventative Features. *Pakistan J Med Health Sci* 2022; **16**: 1289 [DOI: 10.53350/pjmhs221651289]
46 **Swain SK**, Gadnayak A, Mohanty JN, Sarangi R, Das J. Does enterovirus 71 urge for effective vaccine control strategies? *Rev Med Virol* 2022; **32**: e2322 [PMID: 34997684 DOI: 10.1002/rmv.2322]
47 **Mariën J**, Laudisoit A, Patrono L, Baelo P, Vredendaal Rv, Musaba P, Gembu G, Mande C, Ngoy S, Mussaw M, Van Houtte N, Van de Perre F, Gryseels S, Bottieau E, Calvignac-Spencer S, Leendertz F, Leirs H, Verheyen E. Muyembe-Tamfum J, Monkeypox viruses circulate in distantly-related small mammal species in the Democratic Republic of the Congo. 2021 [DOI: 10.21203/rs.3.rs-414280/v1]
48 **Falendysz EA**, Londoño-Navas AM, Meteyer CU, Pussini N, Lopera JG, Osorio JE, Rocke TE. Evaluation of monkeypox virus infection of black-tailed prairie dogs (Cynomys ludovicianus) using in vivo bioluminescent imaging. *J Wildl Dis* 2014; **50**: 524-536 [PMID: 24779460 DOI: 10.7589/2013-07-171]
49 **Arndt WD**, Cotsmire S, Trainor K, Harrington H, Hauns K, Kibler KV, Huynh TP, Jacobs BL. Evasion of the Innate Immune Type I Interferon System by Monkeypox Virus. *J Virol* 2015; **89**: 10489-10499 [PMID: 26246580 DOI: 10.1128/JVI.00304-15]
50 **Zuo W**, Zhao X. Natural killer cells play an important role in virus infection control: Antiviral mechanism, subset expansion and clinical application. *Clin Immunol* 2021; **227**: 108727 [PMID: 33887436 DOI: 10.1016/j.clim.2021.108727]
51 **Gavin RH**. The oral apparatus of Tetrahymena pyriformis, strain WH-6. IV. Observations on the organization of microtubules and filaments in the isolated oral apparatus and the differential effect of potassium chloride on the stability of oral apparatus microtubules. *J Morphol* 1977; **151**: 239-257 [PMID: 403291 DOI: 10.1002/jmor.1051510205]
52 **Alakunle E**, Moens U, Nchinda G, Okeke MI. Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution. *Viruses* 2020; **12** [PMID: 33167496 DOI: 10.3390/v12111257]
53 **Hammarlund E**, Dasgupta A, Pinilla C, Norori P, Früh K, Slifka MK. Monkeypox virus evades antiviral CD4+ and CD8+ T cell responses by suppressing cognate T cell activation. *Proc Natl Acad Sci U S A* 2008; **105**: 14567-14572 [PMID: 18796610 DOI: 10.1073/pnas.0800589105]

54 **Demaria O**, Gauthier L, Debroas G, Vivier E. Natural killer cell engagers in cancer immunotherapy: Next generation of immuno-oncology treatments. *Eur J Immunol* 2021; **51**: 1934-1942 [PMID: 34145579 DOI: 10.1002/eji.202048953]

55 **Kaynarcalidan O**, Moreno Mascaraque S, Drexler I. Vaccinia Virus: From Crude Smallpox Vaccines to Elaborate Viral Vector Vaccine Design. *Biomedicines* 2021; **9** [PMID: 34944596 DOI: 10.3390/biomedicines9121780]

56 **Abdelaal A**, Reda A, Lashin BI, Katamesh BE, Brakat AM, AL-Manaseer BM, Kaur S, Asija A, Patel NK, Basnyat S, Rabaan AA, Alhumaid S, Albayat H, Aljeldah M, Al Shammari BR, Al-Najjar AH, Al-Jassem AK, AlShurbaji ST, Alshahrani FS, Alynbiawi, Alfaraj ZH, Alfaraj DH, Aldawood AH, Sedhai YR, Mumbo V, Rodriguez-Morales AJ, Sah R. Preventing The Next Pandemic: Is Live Vaccine Efficacious Against Monkeypox, or There is a Need for Killed Virus and mRNA Vaccines? 2022 [DOI: 10.20944/preprints202207.0232.v1]

57 **Nagata N**, Saijo M, Kataoka M, Ami Y, Suzaki Y, Sato Y, Iwata-Yoshikawa N, Ogata M, Kurane I, Morikawa S, Sata T, Hasegawa H. Pathogenesis of fulminant monkeypox with bacterial sepsis after experimental infection with West African monkeypox virus in a cynomolgus monkey. *Int J Clin Exp Pathol* 2014; **7**: 4359-4370 [PMID: 25120821]

58 **Gershon AA**, Gershon MD. Widespread Use of Varicella Vaccine Does Not Reduce Immunity to Zoster of Others. *J Infect Dis* 2022; **225**: 361-363 [PMID: 34609507 DOI: 10.1093/infdis/jiab501]

59 **Russo AT**, Grosenbach DW, Brasel TL, Baker RO, Cawthon AG, Reynolds E, Bailey T, Kuehl PJ, Sugita V, Agans K, Hruby DE. Effects of Treatment Delay on Efficacy of Tecovirimat Following Lethal Aerosol Monkeypox Virus Challenge in Cynomolgus Macaques. *J Infect Dis* 2018; **218**: 1490-1499 [PMID: 29982575 DOI: 10.1093/infdis/jiy326]

60 **Assessment RR**. Monkeypox multi-country outbreak. 2022 [DOI: 10.22541/au.165426607.74780750/v1]

61 **Russo AT**, Berhanu A, Bigger CB, Prigge J, Silvera PM, Grosenbach DW, Hruby D. Co-administration of tecovirimat and ACAM2000™ in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. *Vaccine* 2020; **38**: 644-654 [PMID: 31677948 DOI: 10.1016/j.vaccine.2019.10.049]

62 **Hatch GJ**, Graham VA, Bewley KR, Tree JA, Dennis M, Taylor I, Funnell SG, Bate SR, Steeds K, Tipton T, Bean T, Hudson L, Atkinson DJ, McLuckie G, Charlwood M, Roberts AD, Vipond J. Assessment of the protective effect of Imvamune and Acam2000 vaccines against aerosolized monkeypox virus in cynomolgus macaques. *J Virol* 2013; **87**: 7805-7815 [PMID: 23658452 DOI: 10.1128/JVI.03481-12]

63 **Petersen E**, Zumla A, Hui DS, Blumberg L, Valdoleiros SR, Amao L, Ntoumi F, Asogun D, Simonsen L, Haider N, Traore T, Kapata N, Dar O, Nachega J, Abbara A, Al Balushi A, Kock R, Maeurer M, Lee SS, Lucey DR, Ippolito G, Koopmans M. Vaccination for monkeypox prevention in persons with high-risk sexual behaviours to control on-going outbreak of monkeypox virus clade 3. *Int J Infect Dis* 2022; **122**: 569-571 [PMID: 35788415 DOI: 10.1016/j.ijid.2022.06.047]

64 **Rizk JG**, Lippi G, Henry BM, Forthal DN, Rizk Y. Prevention and Treatment of Monkeypox. *Drugs* 2022; **82**: 957-963 [PMID: 35763248 DOI: 10.1007/s40265-022-01742-y]

65 **Realegeno S**, Puschnik AS, Kumar A, Goldsmith C, Burgado J, Sambhara S, Olson VA, Carroll D, Damon I, Hirata T, Kinoshita T, Carette JE, Satheshkumar PS. Monkeypox Virus Host Factor Screen Using Haploid Cells Identifies Essential Role of GARP Complex in Extracellular Virus Formation. *J Virol* 2017; **91** [PMID: 28331092 DOI: 10.1128/JVI.00011-17]

66 **Hutson CL**, Kondas AV, Mauldin MR, Doty JB, Grossi IM, Morgan CN, Ostergaard SD, Hughes CM, Nakazawa Y, Kling C, Martin BE, Ellison JA, Carroll DS, Gallardo-Romero NF, Olson VA. Pharmacokinetics and Efficacy of a Potential Smallpox Therapeutic, Brincidofovir, in a Lethal Monkeypox Virus Animal Model. *mSphere* 2021; **6**: e00927-20 [PMID: 33536322 DOI: 10.1128/mSphere.00927-20]

67 **Davi SD**, Kissenkötter J, Faye M, Böhlken-Fascher S, Stahl-Hennig C, Faye O, Sall AA, Weidmann M, Ademowo OG, Hufert FT, Czerny CP, Abd El Wahed A. Recombinase polymerase amplification assay for rapid detection of Monkeypox virus. *Diagn Microbiol Infect Dis* 2019; **95**: 41-45 [PMID: 31126795 DOI: 10.1016/j.diagmicrobio.2019.03.015]

68 **Smith SK**, Self J, Weiss S, Carroll D, Braden Z, Regnery RL, Davidson W, Jordan R, Hruby DE, Damon IK. Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with monkeypox virus. *J Virol* 2011; **85**: 9176-9187 [PMID: 21697474 DOI: 10.1128/JVI.02173-10]

69 **Berhanu A**, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. *Antimicrob Agents Chemother* 2015; **59**: 4296-4300 [PMID: 25896687 DOI: 10.1128/AAC.00208-15]

70 **Mucker EM**, Wollen-Roberts SE, Kimmel A, Shamblin J, Sampey D, Hooper JW. Intranasal monkeypox marmoset model: Prophylactic antibody treatment provides benefit against severe monkeypox virus disease. *PLoS Negl Trop Dis* 2018; **12**: e0006581 [PMID: 29927927 DOI: 10.1371/journal.pntd.0006581]

71 **Kampf G**. Efficacy of biocidal agents and disinfectants against the monkeypox virus and other orthopoxviruses. *J Hosp Infect* 2022; **127**: 101-110 [PMID: 35777702 DOI: 10.1016/j.jhin.2022.06.012]

72 **Oprea C**, Ianache I, Piscu S, Tardei G, Nica M, Ceausu E, Popescu CP, Florescu SA. First report of monkeypox in a patient living with HIV from Romania. *Travel Med Infect Dis* 2022; **49**: 102395 [PMID: 35753658 DOI: 10.1016/j.tmaid.2022.102395]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 435-442

DOI: 10.5501/wjv.v11.i6.435

ISSN 2220-3249 (online)

MINIREVIEWS

Cholestatic liver injury: A rare but fatal complication during and after COVID-19 infection

Wachira Wongtanasarasin

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Laranjeira C, Portugal; Yu MC, Taiwan

Received: August 9, 2022
Peer-review started: August 9, 2022
First decision: August 29, 2022
Revised: September 21, 2022
Accepted: October 19, 2022
Article in press: October 19, 2022
Published online: November 25, 2022

Wachira Wongtanasarasin, Department of Emergency Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Wachira Wongtanasarasin, Department of Emergency Medicine, UC Davis School of Medicine, Sacramento, CA 95817, United States

Corresponding author: Wachira Wongtanasarasin, MD, Assistant Professor, Department of Emergency Medicine, Faculty of Medicine, Chiang Mai University, 110 Intavarorot Street, Sriphum, Chiang Mai 50200, Thailand. wachir_w@hotmail.com

Abstract

The 2019 coronavirus disease (COVID-19), resulting from the severe acute respiratory syndrome 2 virus, has transformed our globe and provided a new perspective on respiratory tract infections. However, COVID-19 would not be recognized as a condition restricted to only pneumonia. This narrative review was conducted by searching manuscripts in several databases, including PubMed/MEDLINE, Web of Science, and Reference Citation Analysis, from December 2019 to July 2022. Many studies have revealed a broad spectrum of potential systemic symptoms, including biliary complications. Although biliary injury has been observed in a very low proportion of COVID-19 patients, it is associated with increased mortalities and long-term morbidities. We identify a cholangiopathy condition in individuals during infection and after recovering from severe COVID-19, defined by a significant increase in serum alkaline phosphatase and signs of bile duct injury. Understanding the pathogeneses behind this condition would help us develop new techniques to prevent these complications. This review thoroughly discusses and summarizes the current information regarding COVID-19-associated cholangiopathy. In addition, the possible explanations for COVID-19-associated cholangiopathy are presented. Since the exact pathogenesis may not be concluded, this review could provide relevant information to encourage additional investigations shortly.

Key Words: COVID-19; Cholestatic injury; Cholangiopathy; Alkaline phosphatase

Core Tip: The 2019 coronavirus disease (COVID-19) is not only regarded as a respiratory tract disease but also demonstrates a wide range of systemic consequences, including the biliary tract. A significant increase in serum alkaline phosphatase and signs of biliary injury on imaging and/or pathology are the hallmarks of COVID-19-associated cholangiopathy. Direct viral invasion, ischemic injury related to microvascular coagulopathy, drug-induced cholestatic liver injury, alteration of gut microbiota, and cytokine release syndrome are proposed as potential explanations for cholangiopathy associated with severe COVID-19 infection.

Citation: Wongtanasarasin W. Cholestatic liver injury: A rare but fatal complication during and after COVID-19 infection. *World J Virol* 2022; 11(6): 435-442
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/435.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.435

INTRODUCTION

Since December 2019, the recent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), later confirmed as the source of the 2019 coronavirus disease (COVID-19), has turned into a global threat to public health[1]. With a rapidly increasing number of overall cases, the World Health Organization announced the disease pandemic in March 2020. Currently, COVID-19 has caused about 577 million cases and over 6 million deaths worldwide[2].

SARS-CoV-2 is greatly transmitted by droplet transmission[3], with respiratory symptoms (*i.e.*, sore throat, cough, dyspnea) being the most prevalent manifestation as a result of host seeding *via* angiotensin-converting enzyme 2 (ACE-2) receptors present primarily in type II alveolar cells of the lungs[4,5]. Although respiratory and non-specific symptoms such as fever, myalgia, and fatigue represented the most common presentations in patients with COVID-19 infection, gastrointestinal and hepatic symptoms have also been observed[6,7]. Infected individuals reported nausea, vomiting, and abdominal discomfort[6,8,9]. Current evidence has proposed pneumonia as a severe COVID-19 feature [10]. However, complications are notably distinguishable, and the virus has impacted different organ systems[11]. At initial presentation and in hospitalized patients, the incidence of abnormal serum liver function tests (LFTs) varies from 22% to 67%, with levels of elevation ranging from minor to severe[12-14]. Autopsy findings from the case series also demonstrated mild microvesicular steatosis and lobular with portal inflammation[15].

To date, the findings have concentrated on evidence of hepatocellular injury, serum aspartate aminotransferase (AST), and alanine aminotransferase (ALT) elevations[16-18]. Several studies also observed that abnormal LFTs during hospitalization had been linked with disease severity[19-22]. One article that included over 2000 patients in the United States investigated ALT increases and their associations with disease severity, also emphasizing the rarity of cholestasis[20]. Despite a myriad of research on the severe COVID-19 progression, we noticed a small number of reported reports on the consequences. Previously, Faruqui *et al*[11] described a condition characterized by increases in LFTs, particularly markedly elevated serum alkaline phosphatase (ALP), and radiographic findings indicating biliary tract inflammation, primarily bile duct stricture, similar to those seen in critically ill patients with secondary sclerosing cholangitis (SSC)[23]. Still, this condition named COVID-19-associated cholangiopathy is not antecedently reviewed and discussed. This review comprehensively summarizes up-to-date reports from studies highlighting this condition and its perspective. Moreover, possible explanations for COVID-19-associated cholangiopathy are provided and discussed. We anticipate that this review could underline the importance of this condition since it appears to have significantly negative effects on patients' recovery and may potentially result in long-term morbidities.

SEARCH STRATEGY

This narrative review was performed considering articles published from December 2019 to July 2022. The manuscripts were searched electronically using several standard databases, including PubMed/MEDLINE, Web of Science, and Reference Citation Analysis. Various search terms and Medical Subject Headings (MeSH) were used to identify potential articles: "COVID-19", "cholestasis", "alkaline phosphatase", and "obstructive jaundice" (Supplementary Table 1). This mini-review may only serve as a hypothesis-generation of all relevant articles existing in the literature. The extensive details of this condition may have been reviewed elsewhere. The included articles were only those that were published in English.

COVID-19-ASSOCIATED CHOLANGIOPATHY

COVID-19-associated cholangiopathy (COVID-C) or COVID-19 cholestasis has been proposed to describe a condition that occurs in individuals during and after severe COVID-19 infection[11]. It is characterized by elevated liver enzymes, especially substantial increases in serum ALP, and imaging-based biliary tract inflammation[11]. This condition appears to have significant negative effects on patient recovery. After other indications of COVID-19 have recovered, it may cause delayed morbidity [17], the necessity for a liver transplant, and death[11].

Elevated serum ALP and serum gamma-glutamyl transferase levels

COVID-19 is frequently linked with aberrant LFTs, despite the absence of disease-specific lesions on radiographic imaging or biopsy. Liver damage has been discovered to be a common feature of the highly deadly coronavirus-associated illness in humans[24]. Previous studies, mainly from China, have identified abnormal LFTs in infected individuals from the early stages of the recent SARS-CoV-2 pandemic[25-27]. Several systematic reviews with meta-analysis found that any abnormal LFTs were reported in 25%-47%[12-14,26]. Most abnormalities were elevated serum AST and ALT, representing hepatocellular injury[12,13]. Recent literature showed that acute hepatocellular injury during COVID-19 positively correlates with more severe COVID-19 disease[20]. Furthermore, SARS-CoV-2 can enter the liver *via* the ACE-2 receptor proteins found on the bile duct epithelium, which theoretically results in "direct viral cholangiocyte injury". Supporting this concept, the findings from meta-analyses reported serum ALP elevations occurring in up to 4.0%-13.7% of patients[12-14]. In addition, recent studies identified serum ALP elevation as an independent predictor for unfavorable outcomes, including intensive care unit (ICU) admission and hospital mortality[13,28]. Furthermore, Da *et al*[17] documented that COVID-19 patients with increased ALP levels (> 3 times of normal upper limit) were correlated with a higher likelihood of prolonged mechanical ventilation and death. In the same way, a study conducted in Iraq reported that most SARS-CoV-2 patients had abnormal liver enzyme activities, which might be associated with viral replication in the liver[16].

Similarly, serum gamma-glutamyl transferase (GGT) activity represents a sign of hepatobiliary damage, particularly cholestasis and biliary impact[29]. Previous meta-analyses revealed that COVID-19 patients had higher GGT levels than those without, ranging from 15.0-22.5%[12,13]. Although the ACE-2 receptor is primarily expressed in the biliary tree, the evidence found that both abnormal serum ALP and GGT levels were lower than abnormal serum AST and ALT levels. We hypothesize that some abnormal hepatocellular enzymes may result from baseline chronic liver diseases. Furthermore, individuals with COVID-19 and concurrent advanced-stage liver disease may be more susceptible to severe liver damage than those without.

Abnormal biliary tract imaging associated with COVID-19 infection

Faruqui *et al*[11] reported that only 0.6% of patients with severe COVID-19 infection developed aberrant radiographic findings consistent with cholestatic liver damage. All had severe pneumonia with sepsis and required mechanical ventilation during admission. Extracorporeal membrane oxygenation was used on three of them. All patients underwent magnetic resonance cholangiopancreatography, which indicated aberrant findings such as beaded intrahepatic channels, peribiliary diffusion high signal, bile duct wall thickening and hyperenhancement, and common bile duct dilatation[11]. These cholangiopathies described in that study are comparable to SSC observed in patients following prolonged ICU stays[23]. This disease has been encountered in critically ill patients with infection, polytrauma, burns, or after major surgery[30,31]. SSC also has been described in a case report or small case series[11,30,31]. It has been defined as a cholangiopathy with radiographic characteristics similar to those observed in primary SSC and comparable to ischemic cholangiopathy reported following liver transplantation[31]. Endoscopic retrograde cholangiopancreatography or liver histology was used to diagnose several individuals who had SSC following a severe illness. Gelbmann *et al*[30] recorded endoscopic observations of biliary casts with the reduced biliary flow and eventual cholangitis, as well as verified cholangitis and hemorrhagic exudates in bile ducts from liver biopsy. All 26 patients in that research had respiratory failure and required mechanical ventilation[30]. The relationship between severe SSC patients and COVID-19 cholangiopathy highlights a potential connection between hypoxic liver damage or ischemic liver failure and cholestatic liver injury[11]. The portal vein and the hepatic arteries supply the liver parenchyma or hepatocytes. On the other hand, the intrahepatic biliary tree is nourished only by hepatic artery branches *via* the peribiliary vascular plexus. Given its dependence on only arterial supply, the biliary epithelium appears more sensitive to ischemia than hepatocytes, which get dual supply[32,33]. This is illustrated by instances of hepatic artery thrombosis, which occurs in 9% of adult liver transplant patients following arterial blood supply termination, commonly leading in biliary ischemia lesions such as necrosis with biliary leakage and ischemic strictures[34].

POSSIBLE EXPLANATIONS FOR COVID-19-ASSOCIATED CHOLANGIOPATHY

Direct viral invasion

Direct viral cholangiocyte injury is a hypothetically pathogenic mechanism of the virus leading to cholestatic liver injury since SARS-CoV-2 may enter the liver *via* the ACE-2 receptor protein found on the bile duct epithelium[35]. In liver tissues taken from 4 deceased donors of liver transplants, it is demonstrated that specific ACE-2 activity was expressed in 60% of cholangiocytes, compared with 3% of hepatocytes, suggesting that the virus might directly bind to specific ACE-2 receptors on cholangiocytes[36]. They discovered that ACE-2 expression in cholangiocytes is equivalent to ACE-2 expression in type II lung alveolar cells[36]. Also, subsequent reports have found that biliary epithelial cells exhibit a high level of ACE-2[35,37]. An *in vitro* investigation of human liver cells revealed that cholangiocytes might be more vulnerable to being infected with SARS-CoV-2 than other viruses[35]. Previous literature illustrated that viral particles in cholangiocytes had been found in ultrastructural and histological studies, highlighting the possibility that cholestatic damage may be caused by SARS-CoV-2 direct infection of biliary epithelial cells[11,38]. Furthermore, transmembrane protease serine 2 (TMPRSS2), the key host protease that allows several coronaviruses to enter the cells, including SARS-CoV-2, has been found to be associated with viral invasion mechanism since its activity was expressed in cholangiocytes[39]. Its actions lead to cell apoptosis, impaired transportation of bile acids, and epithelial barrier dysfunction[35]. On the other hand, another report documented that the proportion of cells expressing ACE-2 and TMPRSS2 was only 2.50% for cholangiocytes and 0.04% for hepatocytes, questioning the uncertain hypothesis of a direct viral effect on liver and bile duct cells[40].

Ischemic injury referred to the microvascular coagulopathy

The previously discussed cholestatic injury might result from ischemic damage caused by microvascular coagulopathy and/or hypotension during critical illness or sepsis[11,19,21]. Researchers have found that SARS-CoV-2 enters the host *via* the respiratory epithelial ACE-2 receptor[41]. ACE-2 is, nevertheless, widely expressed in endothelial cells of minor and major vessels across the body[37]. The expression of ACE-2 in vascular endothelium has been proposed as a key pathogenetic factor in the widespread coagulation that contributes considerably to COVID-19 morbidity and mortality[19,21]. A recent case series discovered many platelet-fibrin microthrombi in postmortem liver cells[36]. However, another case series of 40 COVID-19 cases found sinusoidal microthrombi in only 15%, whereas most reported macrovascular steatosis (75%) and mild lobular necroinflammation and portal inflammation (50%)[42]. These controversial issues, nonetheless, did not exclude the possibility of intravascular microthrombi and thrombosis theory. More research on this topic may be warranted.

Drug-induced cholestatic liver injury

Another possible explanation for COVID-C is drug-induced cholestatic liver injury. A wide range of medications has been investigated throughout this pandemic. Among these, remsidivir[43,44], lopinavir [45], ritonavir[45], and interleukin-6 antagonists (tocilizumab)[46] have been reported as a cause of increased ALT levels. However, the pattern of biliary injury from pathological examination strongly supports this hypothesis was insufficient[43,44,46]. Besides, no single medication was constantly delivered to all patients with COVID-19 infection, resulting in inconclusive confirmation of this issue.

Alteration of gut microbiota

Interestingly, changes in the gut microbiota may also lead to cholestatic damage[47]. When SARS-CoV-2 infected the enterocytes, it inhibited the absorption of intestinal tryptophan; therefore, resulting in the generation of antimicrobial peptides, mostly through the downregulation of ACE2 following viral entrance[48,49]. It has been proposed that disruption of the gut-liver axis may increase the likelihood of developing severe COVID-19 in patients with non-alcoholic fatty liver disease[50]. In addition, the gut microbiota has been used as a prospective target for adjuvant therapy during SARS-CoV-2 infection[51, 52].

Cytokine release syndrome

Moreover, cytokine release syndrome (CRS), which occurs in both SSC and COVID-19, is another sign that the pathophysiology of SSC-associated severe illnesses and COVID-C may be pathogenetically similar[32]. Documents indicating that CRS can produce severe cholestatic liver damage suggest that the biliary epithelium is partially sensitive to CRS-immune mediated damage[53]. Overall, we may assume that the inducers, such as SARS-CoV-2 epithelial infection, microthrombosis, or the magnitude of the COVID-19 CRS, aggravate the severity and frequency of COVID-19 infection[11].

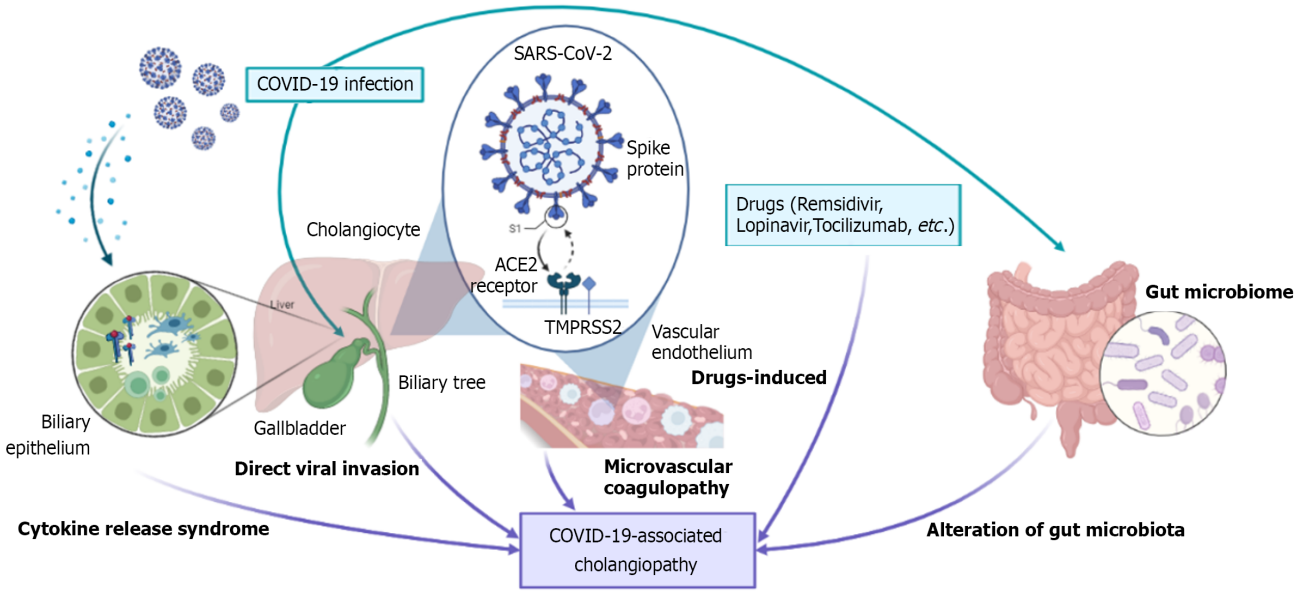
CLINICAL IMPLICATION

This review provided some important and interesting points. Recently, many researchers raised the

question of when the COVID-19 pandemic will end. One statistical report showed that the COVID-19 pandemic could terminate in 2022, but COVID-19 could be one or two times more fatal than seasonal influenza by 2023[54]. Understanding the complications and consequences after COVID-19 infection would help clinicians prevent such conditions and improve the quality of care during the post-infection period. Knowledge and evidence regarding COVID-19-associated cholangiopathy are comparably low despite the growing literature on COVID-19 and other complications. This review could pave the way for a better comprehension of this condition. Future research to completely explain the behind mechanism would advance the treatment and management paradigm. Furthermore, this mini-review will emphasize that all healthcare professionals recognize this disease and its circumstances better.

CONCLUSION

SARS-CoV-2 infection has taken our world into a disastrous situation. Severe COVID-19 patients may encounter COVID-19-associated cholangiopathy, similar to those with SSC after critical illness. COVID-19 infection initially signifies the virus's contact with ACE-2 receptors (expressed in cholangiocytes and vascular endothelium). Based on current evidence, several theories were described in this review, including direct viral invasion, microvascular coagulopathy, alteration of gut microbiota, drug-induced liver injury, and cytokine release syndrome (Figure 1). The exact underlining pathogenesis might not be concluded at this moment, raising the importance of further investigations into this issue. COVID-C may be rarely found in patients with severe COVID-19 infection but is associated with increased mortality and impaired quality of life. We anticipate that the findings described in this review will advance more translational research, resulting in a better understanding and improved treatment of COVID-C in the near future.



DOI: 10.5501/wjv.v11.i6.435

Figure 1 Possible mechanism involved in the pathogenesis of COVID-19-associated cholangiopathy during and after COVID-19 infection. ACE-2: Angiotensin-converting enzyme 2; COVID-19: 2019 coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TMPRSS2: Transmembrane protease serine 2.

FOOTNOTES

Author contributions: Wongtanasarasin W designed the protocol, contributed to data collection, data evaluation, data visualization, wrote the first draft of the manuscript, and critically reviewed the final version of the manuscript.

Conflict-of-interest statement: The author declares that they have no competing interests.

Country/Territory of origin: Thailand

ORCID number: Wachira Wongtanasarasin 0000-0002-1418-0036.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **Wang C**, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; **395**: 470-473 [PMID: 31986257 DOI: 10.1016/S0140-6736(20)30185-9]
2 **World Health Organization**. WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. [cited September 30 2022]. Available from: https://covid19.who.int/ [DOI: 10.46945/bpj.10.1.03.01]
3 **Ong SWX**, Coleman KK, Chia PY, Thoon KC, Pada S, Venkatachalam I, Fisher D, Tan YK, Tan BH, Ng OT, Ang BSP, Leo YS, Wong MSY, Marimuthu K. Transmission modes of severe acute respiratory syndrome coronavirus 2 and implications for infection control: a review. *Singapore Med J* 2022; **63**: 61-67 [PMID: 32729311 DOI: 10.11622/smedj.2020114]
4 **Kuhn JH**, Li W, Choe H, Farzan M. Angiotensin-converting enzyme 2: a functional receptor for SARS coronavirus. *Cell Mol Life Sci* 2004; **61**: 2738-2743 [PMID: 15549175 DOI: 10.1007/s00018-004-4242-5]
5 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]
6 **Patel AP**, Sanders TK, Prakash P, Law J, Alvencar S, Choi A, Shah J, Patel K, Srivoleti P, Chauhan K, Weissman S, Holzwanger E, Dhingra R, Nguyen M, Kim D, Sidhu T, Stallwood C, Dickstein A, Parekh N, Altayar O, Ciorba MA, Yu J, Chen LA, Tabibian JH, Limketkai BN. Gastrointestinal Manifestations of Coronavirus Disease 2019 Across the United States: A Multicenter Cohort Study. *Gastro Hep Adv* 2022; **1**: 909-915 [PMID: 35874930 DOI: 10.1016/j.gastha.2022.07.002]
7 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]
8 **Bangash MN**, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol* 2020; **5**: 529-530 [PMID: 32203680 DOI: 10.1016/S2468-1253(20)30084-4]
9 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
10 **Feng Z**, Yu Q, Yao S, Luo L, Zhou W, Mao X, Li J, Duan J, Yan Z, Yang M, Tan H, Ma M, Li T, Yi D, Mi Z, Zhao H, Jiang Y, He Z, Li H, Nie W, Liu Y, Zhao J, Luo M, Liu X, Rong P, Wang W. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. *Nat Commun* 2020; **11**: 4968 [PMID: 33009413 DOI: 10.1038/s41467-020-18786-x]
11 **Faruqui S**, Okoli FC, Olsen SK, Feldman DM, Kalia HS, Park JS, Stanca CM, Figueroa Diaz V, Yuan S, Dagher NN, Sarkar SA, Theise ND, Kim S, Shanbhogue K, Jacobson IM. Cholangiopathy After Severe COVID-19: Clinical Features and Prognostic Implications. *Am J Gastroenterol* 2021; **116**: 1414-1425 [PMID: 33993134 DOI: 10.14309/ajg.0000000000001264]
12 **Wijarnpreecha K**, Ungprasert P, Panjawatanan P, Harnois DM, Zaver HB, Ahmed A, Kim D. COVID-19 and liver injury: a meta-analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: 990-995 [PMID: 32639420 DOI: 10.1097/MEG.0000000000001817]
13 **Del Zompo F**, De Siena M, Ianiro G, Gasbarrini A, Pompili M, Ponziani FR. Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis. *Eur Rev Med Pharmacol Sci* 2020; **24**: 13072-13088 [PMID: 33378061 DOI: 10.26355/eurrev_202012_24215]
14 **Wu Y**, Li H, Guo X, Yoshida EM, Mendez-Sanchez N, Levi Sandri GB, Teschke R, Romeiro FG, Shukla A, Qi X. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. *Hepatol Int* 2020; **14**: 621-637 [PMID: 32710250 DOI: 10.1007/s12072-020-10074-6]
15 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]
16 **Hwaiz R**, Merza M, Hamad B, HamaSalih S, Mohammed M, Hama H. Evaluation of hepatic enzymes activities in COVID-19 patients. *Int Immunopharmacol* 2021; **97**: 107701 [PMID: 33930704 DOI: 10.1016/j.intimp.2021.107701]
17 **Da BL**, Suchman K, Roth N, Rizvi A, Vincent M, Trindade AJ, Bernstein D, Satapathy SK; Northwell COVID-19 Research Consortium. Cholestatic liver injury in COVID-19 is a rare and distinct entity and is associated with increased mortality. *J Intern Med* 2021; **290**: 470-472 [PMID: 33786906 DOI: 10.1111/joim.13292]
18 **Goel H**, Harmouch F, Garg K, Saraiya P, Daly T, Kumar A, Hippen JT. The liver in COVID-19: prevalence, patterns, predictors, and impact on outcomes of liver test abnormalities. *Eur J Gastroenterol Hepatol* 2021; **33**: e274-e281 [PMID: 33369962 DOI: 10.1097/MEG.0000000000002021]
19 **Ferm S**, Fisher C, Pakala T, Tong M, Shah D, Schwarzbaum D, Cooley V, Hussain S, Kim SH. Analysis of

Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY. *Clin Gastroenterol Hepatol* 2020; **18**: 2378-2379.e1 [PMID: 32497637 DOI: 10.1016/j.cgh.2020.05.049]

20 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: 32473607 DOI: 10.1002/hep.31404]

21 **Fan Z**, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]

22 **Hundt MA**, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology* 2020; **72**: 1169-1176 [PMID: 32725890 DOI: 10.1002/hep.31487]

23 **Laurent L**, Lemaitre C, Minello A, Plessier A, Lamblin G, Poujol-Robert A, Gervais-Hasenknopf A, Pariente EA, Belenotti P, Mostefa-Kara N, Sogni P, Legrand M, Cournac JM, Tamion F, Savoye G, Bedossa P, Valla DC, Vilgrain V, Goria O. Cholangiopathy in critically ill patients surviving beyond the intensive care period: a multicentre survey in liver units. *Aliment Pharmacol Ther* 2017; **46**: 1070-1076 [PMID: 29023905 DOI: 10.1111/apt.14367]

24 **Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: 32170806 DOI: 10.1111/Liv.14435]

25 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

26 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]

27 **Wu J**, Liu J, Zhao X, Liu C, Wang W, Wang D, Xu W, Zhang C, Yu J, Jiang B, Cao H, Li L. Clinical Characteristics of Imported Cases of Coronavirus Disease 2019 (COVID-19) in Jiangsu Province: A Multicenter Descriptive Study. *Clin Infect Dis* 2020; **71**: 706-712 [PMID: 32109279 DOI: 10.1093/cid/ciaa199]

28 **Aghemo A**, Piovani D, Parigi TL, Brunetta E, Pugliese N, Vespa E, Omodei PD, Preatoni P, Lleo A, Repici A, Voza A, Cecconi M, Malesci A, Bonovas S, Danese S; Humanitas COVID-19 Task Force. COVID-19 Digestive System Involvement and Clinical Outcomes in a Large Academic Hospital in Milan, Italy. *Clin Gastroenterol Hepatol* 2020; **18**: 2366-2368.e3 [PMID: 32437870 DOI: 10.1016/j.cgh.2020.05.011]

29 **Chand K**, Thakur S. "Significance of serum gamma glutamyl transpeptidase in cholestatic jaundice". *Indian J Med Sci* 1997; **51**: 270-274 [PMID: 9491680]

30 **Gelbmann CM**, Rümmele P, Wimmer M, Hofstädter F, Göhlmann B, Endlicher E, Kullmann F, Langgartner J, Schölmerich J. Ischemic-like cholangiopathy with secondary sclerosing cholangitis in critically ill patients. *Am J Gastroenterol* 2007; **102**: 1221-1229 [PMID: 17531010 DOI: 10.1111/j.1572-0241.2007.01118.x]

31 **Lin T**, Qu K, Xu X, Tian M, Gao J, Zhang C, Di Y, Zhang Y, Liu C. Sclerosing cholangitis in critically ill patients: an important and easily ignored problem based on a German experience. *Front Med* 2014; **8**: 118-126 [PMID: 24415157 DOI: 10.1007/s11684-014-0306-6]

32 **Leonhardt S**, Veltzke-Schlieker W, Adler A, Schott E, Hetzer R, Schaffartzik W, Tryba M, Neuhaus P, Seehofer D. Trigger mechanisms of secondary sclerosing cholangitis in critically ill patients. *Crit Care* 2015; **19**: 131 [PMID: 25886728 DOI: 10.1186/s13054-015-0861-5]

33 **Gudnason HO**, Björnsson ES. Secondary sclerosing cholangitis in critically ill patients: current perspectives. *Clin Exp Gastroenterol* 2017; **10**: 105-111 [PMID: 28694703 DOI: 10.2147/CEG.S115518]

34 **Mourad MM**, Liossis C, Gunson BK, Mergental H, Isaac J, Muiesan P, Mirza DF, Perera MT, Bramhall SR. Etiology and management of hepatic artery thrombosis after adult liver transplantation. *Liver Transpl* 2014; **20**: 713-723 [PMID: 24652787 DOI: 10.1002/Lt.23874]

35 **Zhao B**, Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, Liang J, Zhang Q, Xu W, Xie Y, Wang X, Yuan Z, Zhang R, Lin X. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell* 2020; **11**: 771-775 [PMID: 32303993 DOI: 10.1007/s13238-020-00718-6]

36 **Chai X**, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Lan F. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv (e-pub ahead of print 1 January 2020; DOI:10.1101/2020.02.03.931766). [DOI: 10.1101/2020.02.03.931766]

37 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

38 **Wang Y**, Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; **73**: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]

39 **Schönfelder K**, Breuckmann K, Elsner C, Dittmer U, Fistera D, Herbstreit F, Risse J, Schmidt K, Sutharsan S, Taube C, Jöckel KH, Siffert W, Kribben A, Möhlendick B. *Transmembrane serine protease 2* Polymorphisms and Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Type 2 Infection: A German Case-Control Study. *Front Genet* 2021; **12**: 667231 [PMID: 33968142 DOI: 10.3389/fgene.2021.667231]

40 **De Smet V**, Verhulst S, van Grunsven LA. Single cell RNA sequencing analysis did not predict hepatocyte infection by SARS-CoV-2. *J Hepatol* 2020; **73**: 993-995 [PMID: 32473193 DOI: 10.1016/j.jhep.2020.05.030]

41 **Zamorano Cuervo N**, Grandvaux N. ACE2: Evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. *Elife* 2020; **9** [PMID: 33164751 DOI: 10.7554/eLife.61390]

42 **Lagana SM**, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, Del Portillo A, De Michele S, de Gonzalez AK, Saqi A, Khairallah P, Chong AM, Park H, Uhlemann AC, Lefkowitch JH, Verna EC. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol* 2020; **33**: 2147-2155 [PMID: 32792598 DOI: 10.1038/s41379-020-00649-x]

43 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**: 1813-1826 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

44 **Wang Y**, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569-1578 [PMID: 32423584 DOI: 10.1016/S0140-6736(20)31022-9]

45 **European Association for the Study of the Liver**; Clinical Practice Guideline Panel: Chair:; Panel members; EASL Governing Board representative:. EASL Clinical Practice Guidelines: Drug-induced liver injury. *J Hepatol* 2019; **70**: 1222-1261 [PMID: 30926241 DOI: 10.1016/j.jhep.2019.02.014]

46 **Guaraldi G**, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, Santoro A, Di Gaetano M, Puzzolante C, Carli F, Bedini A, Corradi L, Fantini R, Castaniere I, Tabbì L, Girardis M, Tedeschi S, Giannella M, Bartoletti M, Pascale R, Dolci G, Brugioni L, Pietrangelo A, Cossarizza A, Pea F, Clini E, Salvarani C, Massari M, Viale PL, Mussini C. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; **2**: e474-e484 [PMID: 32835257 DOI: 10.1016/S2665-9913(20)30173-9]

47 **Zuo T**, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology* 2020; **159**: 944-955.e8 [PMID: 32442562 DOI: 10.1053/j.gastro.2020.05.048]

48 **Hashimoto T**, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 Links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487**: 477-481 [PMID: 22837003 DOI: 10.1038/nature11228]

49 **Liévin-Le Moal V**, Servin AL. The front line of enteric host defense against unwelcome intrusion of harmful microorganisms: mucins, antimicrobial peptides, and microbiota. *Clin Microbiol Rev* 2006; **19**: 315-337 [PMID: 16614252 DOI: 10.1128/CMR.19.2.315-337.2006]

50 **Assante G**, Williams R, Youngson NA. Is the increased risk for MAFLD patients to develop severe COVID-19 Linked to perturbation of the gut-liver axis? *J Hepatol* 2021; **74**: 487-488 [PMID: 32574578 DOI: 10.1016/j.jhep.2020.05.051]

51 **Gasbarrini G**, Dionisi T, Franceschi F, Gasbarrini A. Editorial - COVID-19 and the microbiota: new kids on the block. *Eur Rev Med Pharmacol Sci* 2020; **24**: 5189-5191 [PMID: 32432790 DOI: 10.26355/eurrev_202005_21218]

52 **Di Renzo L**, Merra G, Esposito E, De Lorenzo A. Are probiotics effective adjuvant therapeutic choice in patients with COVID-19? *Eur Rev Med Pharmacol Sci* 2020; **24**: 4062-4063 [PMID: 32374010 DOI: 10.26355/eurrev_202004_20977]

53 **Abdalian R**, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. *Hepatology* 2006; **44**: 1063-1074 [PMID: 17058222 DOI: 10.1002/hep.21405]

54 **Chen JM**. Novel statistics predict the COVID-19 pandemic could terminate in 2022. *J Med Virol* 2022; **94**: 2845-2848 [PMID: 35150458 DOI: 10.1002/jmv.27661]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 443-452

DOI: 10.5501/wjv.v11.i6.443

ISSN 2220-3249 (online)

MINIREVIEWS

COVID-19-induced liver injury in adult patients: A brief overview

Martina Grando, Massimiliano Balbi, Marco Zeppieri

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Kreisel W, Germany; Reiche W, United States

Received: August 17, 2022
Peer-review started: August 17, 2022
First decision: September 2, 2022
Revised: September 7, 2022
Accepted: October 12, 2022
Article in press: October 12, 2022
Published online: November 25, 2022

Martina Grando, Massimiliano Balbi, Department of Internal Medicine, Azienda Sanitaria Friuli Occidentale, San Vito al Tagliamento 33078, Italy

Marco Zeppieri, Department of Ophthalmology, University Hospital of Udine, Udine 33100, Italy

Corresponding author: Marco Zeppieri, BSc, MD, PhD, Doctor, Department of Ophthalmology, University Hospital of Udine, p.le SM Misericordia, Udine 33100, Italy.
markzeppieri@hotmail.com

Abstract

Coronavirus disease has spread worldwide since 2019, causing important pandemic issues and various social health problems to date. Little is known about the origin of this virus and the effects it has on extra-pulmonary organs. The different mechanisms of the virus and the influence it has on humans are still being studied, with hopes of finding a cure for the disease and the pathologies associated with the infection. Liver damage caused by coronavirus disease 2019 (COVID-19) is sometimes underestimated and has been of important clinical interest in the past few years. Hepatic dysfunctions can manifest in different forms which can sometimes be mild and without specific signs and symptoms or be severe with important clinical implications. There are several studies that have tried to explain the mechanism of entry (hepatotropism) of the virus into hepatocytes and the effects the virus has on this important organ. What clearly emerges from the current literature is that hepatic injury represents an important clinical aspect in the management of patients infected with COVID-19, especially in frail patients and those with comorbidities. The aim of our brief overview is to summarize the current literature regarding the forms of hepatic damage, complications, mechanisms of pathology, clinical features of liver injury, influence of comorbidities and clinical management in patients with COVID-19 infection.

Key Words: COVID-19; SARS-CoV-2; Hepatotropism; Hepatic injury; Cirrhosis; Cytokine storm; Angiotensin-converting enzyme 2

Core Tip: Liver damage can occur in patients infected by coronavirus disease 2019 (COVID-19). The organ damage can be due to various mechanisms such as direct infection, immune injury, drug-induced damage, hypoxia or inflammation response. It is of clinical importance to manage hepatic damage in COVID-19-positive patients. Patient outcomes, the success of therapy, prevention of life-threatening complications and management of existing comorbidities depend on proper organ functioning.

Citation: Grando M, Balbi M, Zeppieri M. COVID-19-induced liver injury in adult patients: A brief overview. *World J Virol* 2022; 11(6): 443-452
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/443.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.443

INTRODUCTION

In December 2019, a new ribonucleic acid (RNA) virus in humans was reported in China, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This viral infection has spread quickly throughout the world ever since the first outbreak. The virus causes coronavirus disease 2019 (COVID-19) which has had a great global impact[1]. SARS-CoV-2 started as a zoonotic infection but currently also affect humans. The disease propagates quickly between humans *via* air droplets, sneezing and coughing, especially amongst people that are in close contact with each other. Studies have also shown the possibility of fecal-oral transmission[2]. The majority of SARS-CoV-2 infected patients can be asymptomatic or can present with mild symptoms which range from coughing, fever, headache, anosmia, *etc*. About 15% of cases, however, can show severe pulmonary disease leading to respiratory dysfunction, which can progress to multiorgan failure, coagulopathy and even death[3-5]. Common risk factors for severe disease progression include male sex, advanced age and coexisting comorbidities (*i.e.* heart disease, tumors, diabetes, hypertension, *etc*)[6,7].

Possible hepatic involvement has been shown in two recent types of pathogenic Coronaviruses, which include SARS-CoV-2 and middle east respiratory syndrome coronavirus. These two viruses show striking genetic similarities, thus hepatic involvement is not entirely unexpected[8]. COVID-19 patients showing injury of the liver can present with abnormal liver biochemical indicators, such as elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin, in addition to low levels of albumin[9,10]. The possible mechanisms involved in viral infections include: a direct effect of the virus on hepatocytes or biliary epithelium; liver injury related to accentuated immune response (cytokine storm) and immune-mediated damage; drug toxicity; and ischemic hepatitis. These complications can be favored in patients having multiorgan dysfunction and hemodynamic instability [11]. COVID-19 can give rise to a worsening of existing chronic liver disease (CLD) which can lead to higher mortality due to acute-on-chronic liver failure and/or hepatic decompensation.

Our overview provides a brief summary based on the various forms of hepatic damage, complications, mechanisms, clinical features of liver injury, influence of comorbidities and clinical management in patients with infection of SARS-CoV-2.

SEARCHING OF THE LITERATURE

We conducted a search of the literature published between January 1, 2011 to June 1, 2022, using PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (https://www.referencecitationanalysis.com). The database was first searched using the key words "SARS-CoV-2 AND hepatic injury, hepatic damage AND therapy". We considered only studies in English and those referring to humans and with abstract, thus reducing the count to 350 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. Only articles with abstracts were considered. Each study was independently assessed by at least two reviewers (Grando M and Balbi M), and rating decisions were based on the consensus of the reviewing authors. Our manuscript was based on the most relevant and pertinent studies which included 76 references listed in the paper.

Mechanism and hepatotropism of SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) is expressed in about 80% of pulmonary alveolar cells, but also in other organs. It seems to be a susceptible receptor for SARS-CoV-2. In vitro studies during the SARS epidemic showed that ACE2 acts as the host receptor for viral entry[12]. Moreover, furin gene and transmembrane serine protease 2 (TMPRSS2) have also shown to play an important role in infection. Cells expressing these specific receptors can be indicative of putative hepatic permissive cells[13].

Hepatic distribution of ACE2 is particular. Single-cell RNA sequencing analyzed from livers from normal patients have shown higher levels of gene expression in cholangiocytes, sinusoidal endothelial cells and hepatocytes[14,15]. The ACE2 expression levels in cholangiocytes are like those found in pulmonary type 2 alveolar cells of the lungs, thus indicating that the liver could be a potential target for SARS-CoV-2[16]. In addition, studies have reported that furin and TMPRSS2 have shown a broad gene expression profile in many types of liver cells[14]. In three single-cell RNA combined analysis from sequencing obtained from healthy liver tissue, relatively few hepatocytes co-expressed ACE2 and TMPRSS2[17]. Zhao *et al*[18] conducted studies on liver ductal organoids that expressed ACE2 and TMPRSS2. These were shown to recapitulate infection of SARS-CoV-2, which could be indicative that the epithelium of the bile duct may support entry of pseudo particles[18]. The exact reasons to explain these findings are not known. It may be possible, however, that the virus may show low levels of replication in cholangiocytes *in vivo* in the absence of cell death.

The effects of coexisting liver disease and injury on SARS-CoV-2 hepatotropism is still not known. Studies performed before COVID-19 have reported an increase in liver ACE2 expression in patients with cirrhosis due to hepatitis virus C when compared with normal patients[19]. Moreover, liver mRNA TMPRSS2 and ACE2 expression have shown to be upregulated in non-infected obese individuals and non-alcoholic steatohepatitis patients[20]. Studies based on liver injury in animal models using ligation of the bile ducts have shown elevated expression and activity of hepatic ACE2 and the presence of hypoxia markers[19,21]. Inflammation and injury of the liver may potentially enhance hepatotropism of SARS-CoV-2 by influencing the expression of viral receptors, with ACE2 shown as an interferon-inducible gene in the epithelia of the respiratory system in humans[22,23]. While the tissue specific factors involved in the infection of SARS-CoV-2 are not completely known, the importance of accessory receptors like the receptor B type 1 high-density lipoprotein scavenger (SR-B1) can help better understand *in vitro* facilitated coronavirus attachment[24].

Clinical presentation

Liver biochemistries abnormalities are frequent in COVID-19 patients which has been reported to be seen in 15-65% of individuals infected with SARS-CoV-2[13]. Liver biochemistry abnormalities are generally characterized by mild to moderate elevated ALT and AST levels, accompanied by a slight increase in bilirubin levels and gamma-glutamyl transferase (GGT)[25]. Hypoalbuminemia, a typical manifestation of a hepatic synthetic dysfunction, has been reported to be associated with a worsening in COVID-19 outcomes[26-28]. Despite the presence of ACE2 in cholangiocytes, patients have shown to have elevated levels of transaminases. Several studies, however, have reported the development of cholangiopathy after severe COVID-19, which was characterized by marked elevation in serum alkaline phosphatase (ALP) accompanied by bile duct injury shown in imaging scans. ALP peaks can be seen in patients with worse prognosis. AST elevations can also be seen as a result of myositis[29]. Studies have showed that levels of AST at hospital admission tended to correlate with ferritin[30]. However, further studies are needed to determine whether COVID-19 aggravates cholestasis in individuals with primary sclerosing cholangitis and primary biliary cholangitis[31,32]. The clinical manifestation[10,13,28,32] of the disease can include gastrointestinal alterations like nausea, anorexia, vomiting, diarrhea, *etc*. Patients can also complain of abdominal pain, especially in the right upper quadrant region.

Prognosis

The prognostic significance of elevated liver enzymes in COVID-19 patients is currently debatable. Unpublished data from Wuhan, China showed increased GGT levels in severe cases of COVID-19[8]. Several reports have demonstrated that high levels of AST and ALT can be associated with negative outcomes including mechanical ventilation and management in an intensive care unit (ICU)[33-36]. A recent review showed that the pooled frequency of elevations of ALT and AST was similar in all COVID-19 cases, however, the prevalence of AST elevations was more than ALT in patients with severe COVID-19 disease[37]. Increased liver enzymes are commonly seen in patients needing severe critical care. Studies have reported raised AST in 62% of patients in the ICU compared to 25% in a non-ICU setting[38]. The current literature in this field can potentially be prone to bias considering that infected individuals with severe health issues tend to undergo more laboratory testing than patients with mild symptoms.

The influence of liver enzymes on mortality is debatable. Several studies have stated that there are no apparent associations between mortality rates and elevations in levels of liver enzymes[33,39]. Other studies, however, have reported elevated levels of liver enzymes (*i.e.* AST and ALT elevations higher than five times the normal ranges) in patients with greater risk of mortality[27,40]. Some authors have suggested that indicators based on liver biochemical levels can be useful predictors of prognosis and severity in COVID-19 individuals, however, it is important to note that the prognostic significance could also be due to enhanced host response and active treatments that could be more aggressive in patients with important signs and symptoms[41].

Hepatic damage

The complex mechanisms of liver injury during SARS-CoV-2 infection are of important clinical

importance but are still not all completely known. Hepatic damage could be related to the direct cytopathic effect of the virus. Huang *et al*[42] found that liver injury as the first clinical manifestation in COVID-19 patients was very rare and that hepatic damage in COVID-19 patients appeared mostly due to secondary liver injury. Numerous studies have speculated that in addition to the virus itself causing initial liver injury, other factors involved could cause secondary liver injury. These mechanisms include: an uncontrolled immune reaction; systemic inflammatory response syndrome (SIRS); ischemia and reperfusion; cytokine storm injury; and liver injury induced by drugs[38,41,43].

Direct damage: Liver injury in patients with COVID-19 could be partially caused by direct SARS-CoV-2 viral invasion and hepatocyte destruction. Several studies have reported hepatic necrosis foci located near peri-portal areas and terminal hepatic veins, without signs of surrounding inflammatory cellular infiltration (consistent with acute liver injury patterns)[43,44]. Amongst hospitalized patients with COVID-19, elevations of serum AST levels have been shown to be positively correlated with levels of ALT, which have not been seen with markers of systemic inflammation like ferritin and C-reactive protein (CRP)[30]. Increased liver enzyme levels in COVID-19 patients could possibly be due to direct hepatic injury. Bile duct epithelium shows ACE2 expression which tends to be much greater than that seen in hepatocytes. Compensatory proliferation in parenchymal cells of the liver arising from cells of the bile duct may lead to the upregulation of ACE2 expression in the liver. This could be an important mechanism involved in SARS-CoV-2 induced liver injury.

The direct hepatic damage caused by the virus is still a hypothesis, especially considering the low number of autopsies performed in COVID-19 patients and the relatively low ACE2 expression in the liver. The direct toxic attack of SARS-CoV-2 on the liver is still questionable and remains debatable. Moreover, biomarkers for cholangiocyte injury, such as GGT and ALP have also been seen in some patients, which tends to be consistent with injury to biliary epithelial cells[39]. COVID-19 patients can show elevated total bilirubin levels. These results could be indicative that SARS-CoV-2 can directly bind to cholangiocytes expressing ACE2, thus giving rise to cholangiocyte injury. Further clinical and histopathological studies are needed to confirm these hypothetical mechanisms.

SIRS and cytokine storm: Like numerous other diseases, SARS-CoV-2 is associated with systemic inflammation, which could cause elevations in biochemistries in the liver due to the release of cytokine [45]. Individuals with relatively high serum ALT levels tend to show elevated levels of CRP, D-dimer, ferritin and IL6[46]. Studies have shown elevated serum levels of interleukin (IL) IL2 receptor and IL6 in COVID-19 individuals which tend to correlate with the severity of the disease[47]. Moreover, other cytokines such as tumor necrosis factor IL18, IL4 and IL 10 have shown to be increased, as do peripheral blood pro-inflammatory CCR4+, CCR6+ and Th17 cells[48]. After being infected, a large number of immune cells may be overactivated and induced to secret excessive cytokines and chemokines. This can lead to acute respiratory syndrome and SIRS which can give rise to cell damage and necrosis.

Ischemia and reperfusion injury: Individuals with COVID-19 tend to show different degrees of hypoxemia. Systemic hypoxia might also have a contributory role. Studies have shown raised AST levels with other viral pneumonias including influenza A (H1N1) infection[49]. With hypoxia and ischemia, glycogen consumption, lipid accumulation and adenosine triphosphate depletion of hepatocytes can inhibit cell survival signal transduction which can lead to hepatocyte death. It is important to note that hepatic ischemia-reperfusion injury (HIRI) is considered as a normal pathophysiological process. The mechanisms behind this injury are closely related to neutrophils, Kupffer cells, reactive oxygen species and calcium overload. HIRI can induce neutrophils, Kupffer cells and platelets which induce destructive cellular processes that can cause inflammation and injury to cells [11]. Ischemia and hypoxia could surely be involved in the mechanisms of liver damage in patients with severe and critical COVID-19 disease.

Histological studies have showed altered intrahepatic blood vessel derangement, coagulopathy, antiphospholipid antibodies and abnormal hepatic perfusion which could be indicative of micro thrombotic disease[50,51].

Antibody-dependent enhancement: Antibody-dependent enhancement (ADE) involves the interaction between the Fc receptor and/or complement receptor with the virus-specific antibody to enhance the virus' ability to enter granulocytes, macrophages and monocytes. Studies have shown that antibodies against the SARS-CoV-2 spike protein trigger ADE causing the virus to enter immune cells that do not express ACE2[52-54]. The liver has numerous immune-response cells. ADE could also mediate SARS-CoV-2 in immune cell infection by a pathway not dependent on ACE2 and be involved in injury to the liver.

Drug induced injury: Drug-induced liver injury may have been more common during the initial periods of the pandemic which could have been favored by the use of experimental therapies[53]. It is also important to note that the common symptom in COVID-19 patients tends to be fever which may lead to the abundant use of antipyretic agents that contain acetaminophen, which is known to cause liver damage when excessively used without prescription in certain patients.

Antiviral drugs that are currently available have not proven to be very effective in controlling the disease. During the outbreak, patients were given ritonavir, lopinavir, oseltamivir, *etc*. Raised hepatic enzyme levels have been reported in patients receiving lopinavir/ritonavir therapy (56.1% *vs* 25%)[54, 55]. Remdesivir is another antiviral drug that is used to inhibit the replication of SARS-CoV-2 virus and studies have shown increased levels of blood creatinine, acute kidney injury and higher levels of liver enzymes in patients using the drug[56]. A study published in 2019 showed that CYP3A4 may have an important role in hepatotoxicity mediated by ritonavir and that oxygen free radical can be produced by the CYP3A4 metabolic pathways[56]. Covalent binding could occur with substances found in the cells of the liver which can cause peroxidation of membrane lipid, damage the integrity and ca2+-ATPase pathway of the membrane, influence the homeostasis of external and internal cell levels of Ca2+ and impair the function of critical organelles within the liver cells. This can eventually lead to tissue damage and cell death. In addition, the overuse of ritonavir and lopinavir could activate the endoplasmic reticulum stress pathway, induce apoptosis, inhibit the replication of hepatocytes, induce inflammatory reactions and accelerate liver injury by aggravating oxidative stress[11]. Drug-induced damage needs to be included in the differential diagnosis. This requires a thorough and accurate medical history in addition to pertinent examinations and testing to exclude other forms of liver injury and diseases.

Other mechanisms: There are several other potential contributors that can help provide a better understanding of abnormal liver biochemistries in COVID-19. Current literature has also described COVID-19 as a vascular disease, in which endothelial cells can be infected and cause endothelitis. Subsequent microvascular dysfunction can lead to hypercoagulability, tissue edema and organ ischemia [57,58]. Moreover, some studies have shown that AST levels can exceed ALT during the disease which is not typical in classic hepatocellular patterns of liver injury. This is commonly seen in alcohol-related liver disease and cirrhosis. These alternative factors that may play a role in hepatic damage in COVID-19 patients remain unknown and require future clinical and histological studies. The mechanisms may include mitochondrial dysfunction related to COVID-19 and hepatic steatosis induced by SARS-CoV-2 [59].

Aggravation or recurrence of existing liver disease

Patients with pre-existing CLD can get COVID-19. Whether or not CLD patients tend to be more susceptible to infection of SARS-CoV-2 is still not known. Data from large case series based on health records do not suggest that these patients are over-represented[60]. CLD patients tend to have immune disfunction due to the disease and/or to long-term immunosuppressants treatments (as in immune hepatitis). These chronic patients have been reported to have worse clinical outcomes when compared to patients without underlying liver diseases. Preliminary studies have reported a potentially higher mortality rate and a more severe disease course in these patients, however, further studies with large cohorts are needed[61-63].

Cirrhosis: Acute hepatic decompensation (AHD) is typical in individuals with COVID-19 and cirrhosis. Studies have reported that about 50% of patients with cirrhosis and COVID-19[62] show AHD which typically manifests as worsening ascites and encephalopathy. Amongst COVID-19 infected patients with cirrhosis, studies have shown an increase in mortality and morbidity with increasing disease severity based on the Child-Pugh class. The number of hospitalized individuals reported in COVID-Hep the SECURE-Cirrhosis registries have showed no significant differences amongst patients with CLD and CP classes A, B and C[63]. Studies however, have reported an increase in: ICU admissions; patients needing renal replacement therapy; individuals using mechanical ventilation; and mortality rates.

SARS-CoV-2 infection does not seem to cause the progression of liver disease beyond the natural clinical course of cirrhosis. The composition of the gut microbiota may play an important role in regulating disease severity and host immune responses. Considering that cirrhosis can induce changes in the function and composition of the gut microbiota, in addition to influencing the intestinal permeability, gut-liver axis alterations may play a role in the clinical severity in COVID-19 patients[13].

Non-alcoholic fatty liver disease: The influence of non-alcoholic fatty liver disease (NAFLD) on COVID-19 infected individuals is debatable. Studies have reported that it may be difficult to identify the effects of NAFLD from other metabolic conditions and viral-induced steatosis. A retrospective series based on about 200 SARS-CoV-2 patients showed NAFLD to be a risk factor in: COVID-19 infection severity; elevated levels of liver enzyme; and longer shedding times of the virus[13].

Immune hepatitis, viral chronic hepatitis: Studies have reported that individuals with autoimmune hepatitis tend to show COVID-19-related mortality rates similar to normal matched-individuals of the population[64]. Immunosuppression use does not seem to be an independent mortality risk factor. With regards to chronic hepatitis B individuals in the phase of immune tolerance, studies still need to be performed to show if these individuals have persistent liver injury after infection. Studied based on guidelines from the Chinese Medical Association reported that for hepatitis-B individuals using antiviral drugs, discontinuation of anti-HBV therapy could favor replication and reactivation of HBV after high-dose hormone therapy (*i.e.* estrogens, estradiol, progesterone, ethisterone, medroxyprogesterone, norethindrone, cyproterone, norgestrel, clomiphene, *etc*) during SARS-CoV-2 infection[65].

Clinicians that deal with autoimmune liver disease know that an unspecific infection may induce a flare of these diseases. It could be possible that SARS-Cov2 favors the onset of several types of autoimmune disease and/or induces an autoimmune phenomena.

Liver transplant: It is not yet clear if liver transplant (LT) recipients are more susceptible to COVID-19. A prospective study based on more than 100 individuals showed that patients that underwent liver transplantation had an increased risk of SARS-CoV-2 infection which could probably be due to the chronic immunosuppression therapy[66]. Moreover, data from the United Kingdom and Spain have shown that SARS-CoV-2 diagnoses tend to be greater in LT patients when compared to normal individuals. Biases in the data could be present, however, considering the increased testing and intense management in LT patients[67,68]. Studies have reported that LT recipients tended to be more likely to present gastrointestinal symptoms when compared to non-LT patients[69]. Clinical data incorporating adjustments for concurrent comorbidity suggest that LT individuals do not seem to be at greater risk of COVID-19 severity or mortality when compared to normal individuals[67,68].

Treatment

In the presence of acute liver injury, clinicians should first assess the probable causes of injury before taking on applicable measures. Although liver injury is a normal complication of COVID-19 infection, most infected individuals show mild abnormalities in liver function that are not permanent and tend to resolve without therapy[38]. COVID-19 individuals showing liver damage can be treated with anti-jaundice, hepatoprotective or anti-inflammatory drugs (*i.e.* glycyrrhizic acid, polyene phosphatidylcholine, adenosylmethionine and ursodeoxycholic acid)[70]. Hepatoprotective drugs should be administered prudently. It is preferable to avoid administering more than 2 types of these drugs at the same time. For individuals with critical and severe COVID-19 disease with liver injury, the clinician should consider carefully managing the respiratory and circulatory support systems. Xu *et al*[71] showed that an artificial liver blood purification system may be beneficial in severe patients. This could be due to the rapid removal of inflammatory mediators, thus limiting cytokine storms, and enhancing the balance of water-electrolytes. In COVID-19 individuals with suspected liver damage caused by drugs, clinicians should consider dose reduction or suspension. Acetaminophen (paracetamol) can be useful in patients with COVID-19, however, dosing (preferably not exceeding 2000 mg in a 24 h period) must be carefully monitored[72]. Future studies in large cohorts having long-follow-ups are needed in determining the long-term effects of COVID-19 induced liver injury.

CONCLUSION

Liver damage caused by COVID-19 is very common, especially in individuals with severe or critical disease. This aspect is also more relevant in patients with pre-existing CLD. The damage can be caused by various mechanisms such as direct infection, immune injury, drug induced, hypoxia or inflammation response. Further studies, however, are needed to understand the pathogenic mechanisms that lead to this damage and the hepatotropic mechanism of the virus. It is of utmost importance to monitor and manage abnormal liver function in COVID-19 positive patients, considering that the success of therapy, prevention of life-threatening complications and worsening of comorbidities also depends on proper hepatic functioning in the global management of these patients.

FOOTNOTES

Author contributions: Grando M, Balbi M and Zeppieri M wrote the outline and the paper, assisted in the editing and making critical revisions of the manuscript; Grando M did the research and writing of the manuscript; Zeppieri M was responsible for the conception and design of the study and completed the English and scientific editing (a native English speaking MD, PhD); All authors provided the final approval of the article.

Conflict-of-interest statement: All authors declare no conflict of interests for this article.

Country/Territory of origin: Italy

ORCID number: Martina Grando 0000-0002-1877-3621; Massimiliano Balbi 0000-0002-4757-1009; Marco Zeppieri 0000-0003-0999-5545.

S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

REFERENCES

1 **COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE)**. [cited 20 July 2022]. Available from: https://coronavirus.jhu.edu/map.html (2021)
2 **Leung WK**, To KF, Chan PK, Chan HL, Wu AK, Lee N, Yuen KY, Sung JJ. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology* 2003; **125**: 1011-1017 [PMID: 14517783 DOI: 10.1016/s0016-5085(03)01215-0]
3 **Berlin DA**, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020; **383**: 2451-2460 [PMID: 32412710 DOI: 10.1056/NEJMcp2009575]
4 **Tay MZ**, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]
5 **World Health Organization**. Clinical Management of COVID-19: Interim Guidance (2020)
6 **Williamson EJ**, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584**: 430-436 [PMID: 32640463 DOI: 10.1038/s41586-020-2521-4]
7 **Ioannou GN**, Locke E, Green P, Berry K, O'Hare AM, Shah JA, Crothers K, Eastment MC, Dominitz JA, Fan VS. Risk Factors for Hospitalization, Mechanical Ventilation, or Death Among 10 131 US Veterans With SARS-CoV-2 Infection. *JAMA Netw Open* 2020; **3**: e2022310 [PMID: 32965502 DOI: 10.1001/jamanetworkopen.2020.22310]
8 **Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: 32170806 DOI: 10.1111/Liv.14435]
9 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
10 **Wang Q**, Zhao H, Liu LG, Wang YB, Zhang T, Li MH, Xu YL, Gao GJ, Xiong HF, Fan Y, Cao Y, Ding R, Wang JJ, Cheng C, Xie W. Pattern of liver injury in adult patients with COVID-19: a retrospective analysis of 105 patients. *Mil Med Res* 2020; **7**: 28 [PMID: 32507110 DOI: 10.1186/s40779-020-00256-6]
11 **Tian D**, Ye Q. Hepatic complications of COVID-19 and its treatment. *J Med Virol* 2020; **92**: 1818-1824 [PMID: 32437004 DOI: 10.1002/jmv.26036]
12 **Li W**, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454 [PMID: 14647384 DOI: 10.1038/nature02145]
13 **Marjot T**, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 348-364 [PMID: 33692570 DOI: 10.1038/s41575-021-00426-4]
14 **Pirola CJ**, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: putative mechanisms of liver involvement in COVID-19. *Liver Int* 2020; **40**: 2038-2040 [DOI: 10.1111/Liv.14500]
15 **Qi F**, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020; **526**: 135-140 [PMID: 32199615 DOI: 10.1016/j.bbrc.2020.03.044]
16 **Chai X**, Hu L, Zhang Y, Han W, Lu Z, Ke A. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. BioRxiv, 2020 [DOI: 10.1101/2020.02.03.931766]
17 **De Smet V**, Verhulst S, van Grunsven LA. Single cell RNA sequencing analysis did not predict hepatocyte infection by SARS-CoV-2. *J Hepatol* 2020; **73**: 993-995 [PMID: 32473193 DOI: 10.1016/j.jhep.2020.05.030]
18 **Zhao B**, Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, Liang J, Zhang Q, Xu W, Xie Y, Wang X, Yuan Z, Zhang R, Lin X. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell* 2020; **11**: 771-775 [PMID: 32303993 DOI: 10.1007/s13238-020-00718-6]
19 **Paizis G**, Tikellis C, Cooper ME, Schembri JM, Lew RA, Smith AI, Shaw T, Warner FJ, Zuilli A, Burrell LM, Angus PW. Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. *Gut* 2005; **54**: 1790-1796 [PMID: 16166274 DOI: 10.1136/gut.2004.062398]
20 **Fondevila MF**, Mercado-Gómez M, Rodríguez A, Gonzalez-Rellan MJ, Iruzubieta P, Valentí V, Escalada J, Schwaninger M, Prevot V, Dieguez C, Crespo J, Frühbeck G, Martinez-Chantar ML, Nogueiras R. Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points. *J Hepatol* 2021; **74**: 469-471 [PMID: 33096086 DOI: 10.1016/j.jhep.2020.09.027]
21 **Herath CB**, Warner FJ, Lubel JS, Dean RG, Jia Z, Lew RA, Smith AI, Burrell LM, Angus PW. Upregulation of hepatic angiotensin-converting enzyme 2 (ACE2) and angiotensin-(1-7) levels in experimental biliary fibrosis. *J Hepatol* 2007; **47**: 387-395 [PMID: 17532087 DOI: 10.1016/j.jhep.2007.03.008]
22 **Chua RL**, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, Debnath O, Thürmann L, Kurth F, Völker MT, Kazmierski J, Timmermann B, Twardziok S, Schneider S, Machleidt F, Müller-Redetzky H, Maier M, Krannich A,

Schmidt S, Balzer F, Liebig J, Loske J, Suttorp N, Eils J, Ishaque N, Liebert UG, von Kalle C, Hocke A, Witzenrath M, Goffinet C, Drosten C, Laudi S, Lehmann I, Conrad C, Sander LE, Eils R. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat Biotechnol* 2020; **38**: 970-979 [PMID: 32591762 DOI: 10.1038/s41587-020-0602-4]

23 **Ziegler CGK**, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM, Feldman J, Muus C, Wadsworth MH 2nd, Kazer SW, Hughes TK, Doran B, Gatter GJ, Vukovic M, Taliaferro F, Mead BE, Guo Z, Wang JP, Gras D, Plaisant M, Ansari M, Angelidis I, Adler H, Sucre JMS, Taylor CJ, Lin B, Waghray A, Mitsialis V, Dwyer DF, Buchheit KM, Boyce JA, Barrett NA, Laidlaw TM, Carroll SL, Colonna L, Tkachev V, Peterson CW, Yu A, Zheng HB, Gideon HP, Winchell CG, Lin PL, Bingle CD, Snapper SB, Kropski JA, Theis FJ, Schiller HB, Zaragosi LE, Barbry P, Leslie A, Kiem HP, Flynn JL, Fortune SM, Berger B, Finberg RW, Kean LS, Garber M, Schmidt AG, Lingwood D, Shalek AK, Ordovas-Montanes J; HCA Lung Biological Network. Electronic address: lung-network@humancellatlas.org; HCA Lung Biological Network. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. *Cell* 2020; **181**: 1016-1035.e19 [PMID: 32413319 DOI: 10.1016/j.cell.2020.04.035]

24 **Wei C**, Wan L, Yan Q, Wang X, Zhang J, Yang X, Zhang Y, Fan C, Li D, Deng Y, Sun J, Gong J, Wang Y, Li J, Yang H, Li H, Zhang Z, Wang R, Du P, Zong Y, Yin F, Zhang W, Wang N, Peng Y, Lin H, Feng J, Qin C, Chen W, Gao Q, Zhang R, Cao Y, Zhong H. HDL-scavenger receptor B type 1 facilitates SARS-CoV-2 entry. *Nat Metab* 2020; **2**: 1391-1400 [PMID: 33244168 DOI: 10.1038/s42255-020-00324-0]

25 **Zhong P**, Xu J, Yang D, Shen Y, Wang L, Feng Y, Du C, Song Y, Wu C, Hu X, Sun Y. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. *Signal Transduct Target Ther* 2020; **5**: 256 [PMID: 33139693 DOI: 10.1038/s41392-020-00373-7]

26 **Elmunzer BJ**, Spitzer RL, Foster LD, Merchant AA, Howard EF, Patel VA, West MK, Qayed E, Nustas R, Zakaria A, Piper MS, Taylor JR, Jaza L, Forbes N, Chau M, Lara LF, Papachristou GI, Volk ML, Hilson LG, Zhou S, Kushnir VM, Lenyo AM, McLeod CG, Amin S, Kuftinec GN, Yadav D, Fox C, Kolb JM, Pawa S, Pawa R, Canakis A, Huang C, Jamil LH, Aneese AM, Glamour BK, Smith ZL, Hanley KA, Wood J, Patel HK, Shah JN, Agarunov E, Sethi A, Fogel EL, McNulty G, Haseeb A, Trieu JA, Dixon RE, Yang JY, Mendelsohn RB, Calo D, Aroniadis OC, LaComb JF, Scheiman JM, Sauer BG, Dang DT, Piraka CR, Shah ED, Pohl H, Tierney WM, Mitchell S, Condon A, Lenhart A, Dua KS, Kanagala VS, Kamal A, Singh VK, Pinto-Sanchez MI, Hutchinson JM, Kwon RS, Korsnes SJ, Singh H, Solati Z, Willingham FF, Yachimski PS, Conwell DL, Mosier E, Azab M, Patel A, Buxbaum J, Wani S, Chak A, Hosmer AE, Keswani RN, DiMaio CJ, Bronze MS, Muthusamy R, Canto MI, Gjeorgjievski VM, Imam Z, Odish F, Edhi AI, Orosey M, Tiwari A, Patwardhan S, Brown NG, Patel AA, Ordiah CO, Sloan IP, Cruz L, Koza CL, Okafor U, Hollander T, Furey N, Reykhart O, Zbib NH, Damianos JA, Esteban J, Hajidiacos N, Saul M, Mays M, Anderson G, Wood K, Mathews L, Diakova G, Caisse M, Wakefield L, Nitchie H, Waljee AK, Tang W, Zhang Y, Zhu J, Deshpande AR, Rockey DC, Alford TB, Durkalski V; North American Alliance for the Study of Digestive Manifestations of COVID-19. Digestive Manifestations in Patients Hospitalized With Coronavirus Disease 2019. *Clin Gastroenterol Hepatol* 2021; **19**: 1355-1365.e4 [PMID: 33010411 DOI: 10.1016/j.cgh.2020.09.041]

27 **Fu Y**, Zhu R, Bai T, Han P, He Q, Jing M, Xiong X, Zhao X, Quan R, Chen C, Zhang Y, Tao M, Yi J, Tian D, Yan W. Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. *Hepatology* 2021; **73**: 1509-1520 [PMID: 32602604 DOI: 10.1002/hep.31446]

28 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]

29 **Panteghini M**. Aspartate aminotransferase isoenzymes. *Clin Biochem* 1990; **23**: 311-319 [PMID: 2225456 DOI: 10.1016/0009-9120(90)80062-n]

30 **Bloom PP**, Meyerowitz EA, Reinus Z, Daidone M, Gustafson J, Kim AY, Schaefer E, Chung RT. Liver Biochemistries in Hospitalized Patients With COVID-19. *Hepatology* 2021; **73**: 890-900 [PMID: 32415860 DOI: 10.1002/hep.31326]

31 **Meersseman P**, Blondeel J, De Vlieger G, van der Merwe S, Monbaliu D; Collaborators Leuven Liver Transplant program. Secondary sclerosing cholangitis: an emerging complication in critically ill COVID-19 patients. *Intensive Care Med* 2021; **47**: 1037-1040 [PMID: 34185115 DOI: 10.1007/s00134-021-06445-8]

32 **Tafreshi S**, Whiteside I, Levine I, D'Agostino C. A case of secondary sclerosing cholangitis due to COVID-19. *Clin Imaging* 2021; **80**: 239-242 [PMID: 34364072 DOI: 10.1016/j.clinimag.2021.07.017]

33 **Ponziani FR**, Del Zompo F, Nesci A, Santopaolo F, Ianiro G, Pompili M, Gasbarrini A; "Gemelli against COVID-19" group. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2-positive patients. *Aliment Pharmacol Ther* 2020; **52**: 1060-1068 [PMID: 32628793 DOI: 10.1111/apt.15996]

34 **Yip TC**, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut* 2021; **70**: 733-742 [PMID: 32641471 DOI: 10.1136/gutjnl-2020-321726]

35 **Weber S**, Hellmuth JC, Scherer C, Muenchhoff M, Mayerle J, Gerbes AL. Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: a prospective cohort study. *Gut* 2021; **70**: 1925-1932 [PMID: 33514597 DOI: 10.1136/gutjnl-2020-323800]

36 **Ding ZY**, Li GX, Chen L, Shu C, Song J, Wang W, Wang YW, Chen Q, Jin GN, Liu TT, Liang JN, Zhu P, Zhu W, Li Y, Zhang BH, Feng H, Zhang WG, Yin ZY, Yu WK, Yang Y, Zhang HQ, Tang ZP, Wang H, Hu JB, Liu JH, Yin P, Chen XP, Zhang B; Tongji Multidisciplinary Team for Treating COVID-19 (TTTC). Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol* 2021; **74**: 1295-1302 [PMID: 33347952 DOI: 10.1016/j.jhep.2020.12.012]

37 **Kumar-M P**, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R, Mandavdhare HS, Dutta U, Sharma V. Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. *Hepatol Int* 2020; **14**: 711-722 [PMID: 32623633 DOI: 10.1007/s12072-020-10071-9]

38 **Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]

39 **Zhang Y**, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int* 2020; **40**: 2095-2103 [PMID: 32239796 DOI: 10.1111/Liv.14455]

40 **Lei F**, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, Zhang XJ, Cai J, Lin L, Ouyang S, Wang X, Yang C, Cheng X, Liu W, Li H, Xie J, Wu B, Luo H, Xiao F, Chen J, Tao L, Cheng G, She ZG, Zhou J, Wang H, Lin J, Luo P, Fu S, Ye P, Xiao B, Mao W, Liu L, Yan Y, Chen G, Huang X, Zhang BH, Yuan Y. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. *Hepatology* 2020; **72**: 389-398 [PMID: 32359177 DOI: 10.1002/hep.31301]

41 **Bangash MN**, Patel JM, Parekh D, Murphy N, Brown RM, Elsharkawy AM, Mehta G, Armstrong MJ, Neil D. SARS-CoV-2: Is the liver merely a bystander to severe disease? *J Hepatol* 2020; **73**: 995-996 [PMID: 32502510 DOI: 10.1016/j.jhep.2020.05.035]

42 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

43 **Li Y**, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol* 2020; **92**: 1491-1494 [PMID: 32369204 DOI: 10.1002/jmv.25973]

44 **Tian S**, Xiong Y, Liu H, Niu L, Guo J, Liao M, Xiao SY. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol* 2020; **33**: 1007-1014 [PMID: 32291399 DOI: 10.1038/s41379-020-0536-x]

45 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

46 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: 32473607 DOI: 10.1002/hep.31404]

47 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

48 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

49 **Papic N**, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. *Influenza Other Respir Viruses* 2012; **6**: e2-e5 [PMID: 21951624 DOI: 10.1111/j.1750-2659.2011.00287.x]

50 **Sonzogni A**, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, Morotti D, Zerbi P, Carsana L, Rossi R, Lauri E, Pellegrinelli A, Nebuloni M. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. *Liver Int* 2020; **40**: 2110-2116 [PMID: 32654359 DOI: 10.1111/Liv.14601]

51 **Zhang Y**, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med* 2020; **382**: e38 [PMID: 32268022 DOI: 10.1056/NEJMc2007575]

52 **Wang SF**, Tseng SP, Yen CH, Yang JY, Tsao CH, Shen CW, Chen KH, Liu FT, Liu WT, Chen YM, Huang JC. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochem Biophys Res Commun* 2014; **451**: 208-214 [PMID: 25073113 DOI: 10.1016/j.bbrc.2014.07.090]

53 **Olry A**, Meunier L, Délire B, Larrey D, Horsmans Y, Le Louët H. Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. *Drug Saf* 2020; **43**: 615-617 [PMID: 32514859 DOI: 10.1007/s40264-020-00954-z]

54 **Karthik K**, Senthilkumar TMA, Udhayavel S, Raj GD. Role of antibody-dependent enhancement (ADE) in the virulence of SARS-CoV-2 and its mitigation strategies for the development of vaccines and immunotherapies to counter COVID-19. *Hum Vaccin Immunother* 2020; **16**: 3055-3060 [PMID: 32845733 DOI: 10.1080/21645515.2020.1796425]

55 **Dawood DRM**, Salum GM, El-Meguid MA. The Impact of COVID-19 on Liver Injury. *Am J Med Sci* 2022; **363**: 94-103 [PMID: 34752738 DOI: 10.1016/j.amjms.2021.11.001]

56 **Singh A**, Kamath A. Assessment of adverse events associated with remdesivir use for coronavirus disease 2019 using real-world data. *Expert Opin Drug Saf* 2021; **20**: 1559-1564 [PMID: 34328807 DOI: 10.1080/14740338.2021.1962846]

57 **Shehu AI**, Lu J, Wang P, Zhu J, Wang Y, Yang D, McMahon D, Xie W, Gonzalez FJ, Ma X. Pregnane X receptor activation potentiates ritonavir hepatotoxicity. *J Clin Invest* 2019; **129**: 2898-2903 [PMID: 31039134 DOI: 10.1172/JCI128274]

58 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

59 **Fraser J**, Mousley J, Testro A, Smibert OC, Koshy AN. Clinical Presentation, Treatment, and Mortality Rate in Liver Transplant Recipients With Coronavirus Disease 2019: A Systematic Review and Quantitative Analysis. *Transplant Proc* 2020; **52**: 2676-2683 [PMID: 32891405 DOI: 10.1016/j.transproceed.2020.07.012]

60 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI:

10.1001/jama.2020.6775]

61 **Mohammed A**, Paranji N, Chen PH, Niu B. COVID-19 in Chronic Liver Disease and Liver Transplantation: A Clinical Review. *J Clin Gastroenterol* 2021; **55**: 187-194 [PMID: 33394628 DOI: 10.1097/MCG.0000000000001481]

62 **Del Zompo F**, De Siena M, Ianiro G, Gasbarrini A, Pompili M, Ponziani FR. Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis. *Eur Rev Med Pharmacol Sci* 2020; **24**: 13072-13088 [PMID: 33378061 DOI: 10.26355/eurrev_202012_24215]

63 **Elnaggar M**, Abomhya A, Elkhattib I, Dawoud N, Doshi R. COVID-19 and liver diseases, what we know so far. *World J Clin Cases* 2022; **10**: 3969-3980 [PMID: 35665122 DOI: 10.12998/wjcc.v10.i13.3969]

64 **Marjot T**, Buescher G, Sebode M, Barnes E, Barritt AS 4th, Armstrong MJ, Baldelli L, Kennedy J, Mercer C, Ozga AK, Casar C, Schramm C; contributing Members and Collaborators of ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis, Moon AM, Webb GJ, Lohse AW. SARS-CoV-2 infection in patients with autoimmune hepatitis. *J Hepatol* 2021; **74**: 1335-1343 [PMID: 33508378 DOI: 10.1016/j.jhep.2021.01.021]

65 **Wei L**. The protocol for prevention, diagnosis and treatment of corona virus infective disease 2019. *J Clin Exp Hepatol* 2020; **28**: E004

66 **Hashemi N**, Viveiros K, Redd WD, Zhou JC, McCarty TR, Bazarbashi AN, Hathorn KE, Wong D, Njie C, Shen L, Chan WW. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: A multicentre United States experience. *Liver Int* 2020; **40**: 2515-2521 [PMID: 32585065 DOI: 10.1111/Liv.14583]

67 **Colmenero J**, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, Nuño J, Gastaca M, Bustamante-Schneider J, Cachero A, Lladó L, Caballero A, Fernández-Yunquera A, Loinaz C, Fernández I, Fondevila C, Navasa M, Iñarrairaegui M, Castells L, Pascual S, Ramírez P, Vinaixa C, González-Dieguez ML, González-Grande R, Hierro L, Nogueras F, Otero A, Álamo JM, Blanco-Fernández G, Fábrega E, García-Pajares F, Montero JL, Tomé S, De la Rosa G, Pons JA. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021; **74**: 148-155 [PMID: 32750442 DOI: 10.1016/j.jhep.2020.07.040]

68 **Ravanan R**, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, Friend P, Parameshwar J, Currie I, Burnapp L, Baker R, Dudley J, Oniscu GC, Berman M, Asher J, Harvey D, Manara A, Manas D, Gardiner D, Forsythe JLR. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: A national cohort study. *Am J Transplant* 2020; **20**: 3008-3018 [PMID: 32780493 DOI: 10.1111/ajt.16247]

69 **Gordon DE**, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, Eckhardt M, Soucheray M, Bennett MJ, Cakir M, McGregor MJ, Li Q, Meyer B, Roesch F, Vallet T, Mac Kain A, Miorin L, Moreno E, Naing ZZC, Zhou Y, Peng S, Shi Y, Zhang Z, Shen W, Kirby IT, Melnyk JE, Chorba JS, Lou K, Dai SA, Barrio-Hernandez I, Memon D, Hernandez-Armenta C, Lyu J, Mathy CJP, Perica T, Pilla KB, Ganesan SJ, Saltzberg DJ, Rakesh R, Liu X, Rosenthal SB, Calviello L, Venkataramanan S, Liboy-Lugo J, Lin Y, Huang XP, Liu Y, Wankowicz SA, Bohn M, Safari M, Ugur FS, Koh C, Savar NS, Tran QD, Shengjuler D, Fletcher SJ, O'Neal MC, Cai Y, Chang JCJ, Broadhurst DJ, Klippsten S, Sharp PP, Wenzell NA, Kuzuoglu-Ozturk D, Wang HY, Trenker R, Young JM, Cavero DA, Hiatt J, Roth TL, Rathore U, Subramanian A, Noack J, Hubert M, Stroud RM, Frankel AD, Rosenberg OS, Verba KA, Agard DA, Ott M, Emerman M, Jura N, von Zastrow M, Verdin E, Ashworth A, Schwartz O, d'Enfert C, Mukherjee S, Jacobson M, Malik HS, Fujimori DG, Ideker T, Craik CS, Floor SN, Fraser JS, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**: 459-468 [PMID: 32353859 DOI: 10.1038/s41586-020-2286-9]

70 **Cai Y**, Ye LP, Song YQ, Mao XL, Wang L, Jiang YZ, Que WT, Li SW. Liver injury in COVID-19: Detection, pathogenesis, and treatment. *World J Gastroenterol* 2021; **27**: 3022-3036 [PMID: 34168405 DOI: 10.3748/wjg.v27.i22.3022]

71 **Xu K**, Cai H, Shen Y, Ni Q, Chen Y, Hu S, Li J, Wang H, Yu L, Huang H, Qiu Y, Wei G, Fang Q, Zhou J, Sheng J, Liang T, Li L. [Management of COVID-19: the Zhejiang experience]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020; **49**: 147-157 [PMID: 32391658 DOI: 10.3785/j.issn.1008-9292.2020.02.02]

72 **Pergolizzi JV Jr**, Varrassi G, Magnusson P, LeQuang JA, Paladini A, Taylor R, Wollmuth C, Breve F, Christo P. COVID-19 and NSAIDS: A Narrative Review of Knowns and Unknowns. *Pain Ther* 2020; **9**: 353-358 [PMID: 32447629 DOI: 10.1007/s40122-020-00173-5]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 453-466

DOI: 10.5501/wjv.v11.i6.453

ISSN 2220-3249 (online)

MINIREVIEWS

Hepatic manifestations of coronavirus disease 2019 infection: Clinical and laboratory perspective

Farina M Hanif, Zain Majid, Shoaib Ahmed, Nasir H Luck, Muhammed Mubarak

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Arumugam VA, India; Corrales FJ, Spain; Iannolo G, Italy

Received: September 12, 2022
Peer-review started: September 12, 2022
First decision: September 29, 2022
Revised: October 17, 2022
Accepted: November 7, 2022
Article in press: November 7, 2022
Published online: November 25, 2022

Farina M Hanif, Zain Majid, Shoaib Ahmed, Nasir H Luck, Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi 74200, Sindh, Pakistan

Muhammed Mubarak, Department of Pathology, Sindh Institute of Urology and Transplantation, Karachi 74200, Sindh, Pakistan

Corresponding author: Muhammed Mubarak, FCPS, Professor, Department of Pathology, Sindh Institute of Urology and Transplantation, Dewan Farooque Medical Complex, Chand Bibi Road, Karachi 74200, Sindh, Pakistan. drmubaraksiut@yahoo.com

Abstract

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has become a global challenge of unprecedented nature since December 2019. Although most patients with COVID-19 exhibit mild clinical manifestations and upper respiratory tract involvement, in approximately 5%-10% of patients, the disease is severe and involves multiple organs, leading to multi-organ dysfunction and failure. The liver and gastrointestinal tract are also frequently involved in COVID-19. In the context of liver involvement in patients with COVID-19, many key aspects need to be addressed in both native and transplanted organs. This review focuses on the clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19 with no prior liver disease, patients with pre-existing liver diseases and liver transplant recipients. A brief overview of the history of COVID-19 and etiopathogenesis of the liver injury will also be described as a prelude to better understanding the above aspects.

Key Words: COVID-19; Liver injury; SARS-CoV-2; Clinical manifestations; Liver function tests; Cirrhosis

Core Tip: The novel coronavirus disease 2019 (COVID-19) has affected the entire globe with devastating consequences on the health and economy of all countries. Primarily a disease of the upper respiratory tract, it may involve multiple organs in severe cases, which are fortunately rare. The liver and gastrointestinal tract are also frequently involved in COVID-19. Involvement of the liver is multifaceted and may be asymptomatic or may lead to acute liver failure. This review article focused on various clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19. This will help in creating awareness among the general physicians, gastroenterologists, hepatologists and infectious disease consultants regarding this important complication.

Citation: Hanif FM, Majid Z, Ahmed S, Luck NH, Mubarak M. Hepatic manifestations of coronavirus disease 2019 infection: Clinical and laboratory perspective. *World J Virol* 2022; 11(6): 453-466
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/453.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.453

INTRODUCTION

During the past 20 years, three major outbreaks by coronaviruses have occurred. These include severe acute respiratory distress syndrome (SARS), Middle East respiratory syndrome and coronavirus disease 2019 (COVID-19)[1]. Among these, COVID-19, caused by SARS coronavirus 2 (SARS-CoV-2) was reported for the first time in Wuhan, China in December 2019, which later spread in pandemic form throughout the world[2]. In patients with COVID-19 infection, upper and lower respiratory tract involvement, *e.g.*, common cold, bronchiolitis, and pneumonia, are the dominant manifestations. Primary clinical symptoms of COVID-19 patients are fever, dry cough, fatigue and myalgia. However, in many cases, SARS-CoV-2 affects other organs such as the heart, gastrointestinal tract, liver and kidneys with organ-specific symptoms (Table 1). Many patients with severe disease may die from multiorgan failure. In this review, we described liver involvement in COVID-19, which can be studied from many aspects. The focus of this review, however, was on clinical and laboratory manifestations of liver disease in COVID-19 patients, in the native healthy liver, native diseased liver and in the transplanted liver.

For this narrative review, we searched the electronic databases of Web of Science, Scopus, Embase, PubMed and Google Scholar. The search terms used were: COVID-19, combined with the following terms; acute liver injury (ALI), acute-on-chronic liver failure (ACLF), chronic liver disease (CLD), cirrhosis of liver, hepatitis, deranged liver function tests (LFTs), liver failure, SARS-CoV-2, angiotensin-converting enzyme 2, hepatocellular carcinoma (HCC), liver transplantation, autoimmune liver disease, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV) and hepatitis C virus (HCV). The search was carried out within the time frame of January 1, 2020 to May 2022. We found 4758 records and used 85 (mainly original articles or guidelines) for extracting information to be presented in this review.

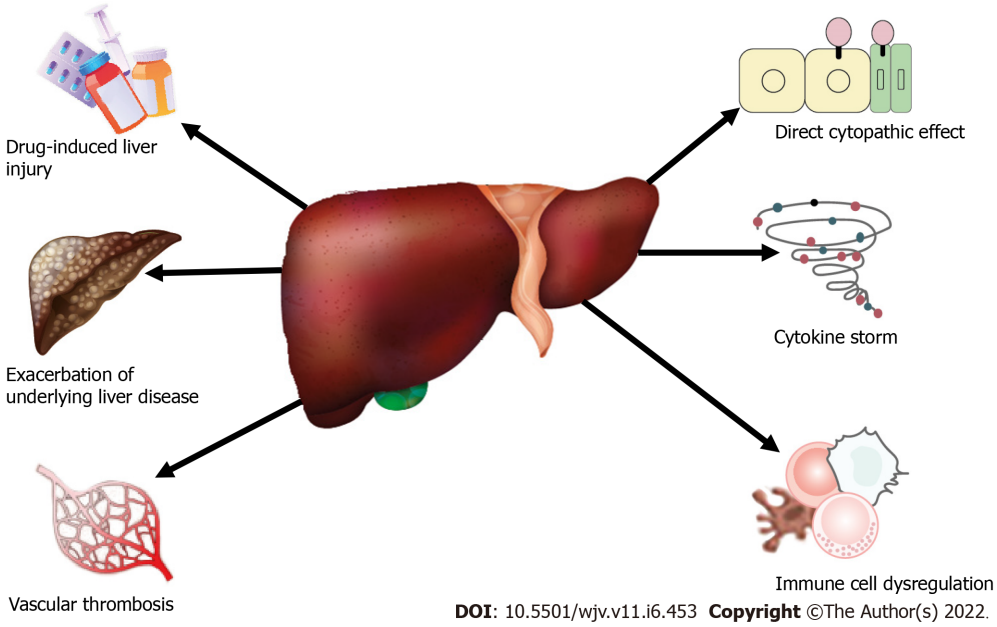
PATHOGENESIS OF LIVER INJURY

COVID-19 causes liver damage that is mostly hepatocellular in nature as demonstrated by increased transaminase levels. It is often asymptomatic and manifests with derangement in liver functions on laboratory testing. COVID-19-induced liver injury is due to a multitude of reasons, which possibly differ from case to case according to various clinical scenarios[1]. Various mechanisms have been proposed including the direct cytopathic effect of the virus itself, immune dysfunction, systemic inflammatory response syndrome, cytokine storm, sepsis, vascular thrombosis, hypoxia and ischemia-reperfusion injury, as shown in Figure 1. Additionally, drug-induced liver injury has also been implicated as a possible secondary mechanism of liver impairment in patients with COVID-19[3].

The entry of SARS-CoV-2 into human host cells with resultant injury is primarily mediated *via* a metalloproteinase enzyme, called angiotensin-converting enzyme 2 (ACE2) receptor, located in various tissues, including the lungs, liver and gastrointestinal tract[4]. The previous RNA-seq data in the Human Protein Atlas database (www.proteinatlas.org) has demonstrated relatively low expression of ACE2 in the liver that, in all respects, could be considered a potential target. In particular, ACE2 expression is limited to the cholangiocytes of normal hepatic tissue and, to a minimal extent, in the hepatocytes[4]. A low throughput study of ACE2 protein expression in selected cell types of multiple organs showed a low frequency of ACE2 occurrence in cholangiocytes but not in hepatocytes, Kupffer cells and endothelial cells[5]. However, the antibody detection might be subjected to nonspecificity and sensitivity issues. Neither data sources could provide a definitive conclusion of cell type specific expression of the *ACE2* gene in the liver.

Table 1 Major clinical manifestations and laboratory abnormalities in coronavirus disease 2019

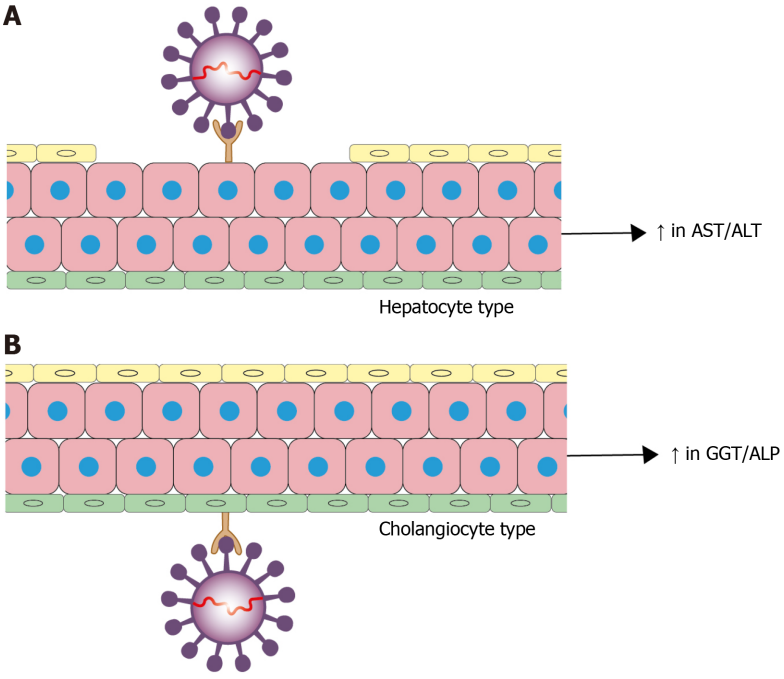
Signs/symptoms
Systemic and respiratory system manifestations
Fever, cough, malaise, dyspnea, fatigue, sputum
Cardiovascular system manifestations
Heart failure, arrhythmia, shock, tight chest, acute myocarditis
Gastrointestinal manifestations
Anorexia, diarrhea, loss of appetite, loss of taste, gastrointestinal bleeding, nausea and vomiting, abdominal pain, mild pancreatitis, mild colitis
Hepatobiliary manifestations
Abnormal liver function tests, jaundice, hypoalbuminemia, new-onset decompensation, acute-on-chronic liver failure, cholangiopathy, acalculous cholecystitis
Kidney manifestations
Acute kidney injury, proteinuria, hematuria
Neurological manifestations
Dizziness, headache, skeletal muscle injury, acute cerebrovascular disease, seizures



DOI: 10.5501/wjv.v11.i6.453

Figure 1 Schematic illustration of possible mechanisms of liver injury in coronavirus disease 2019. Other mechanisms (not shown) may be involved.

Recent advances of single cell technologies allow unbiased profiling of all cell types in given tissues at an unparalleled scale. Chai *et al*[5] performed an unbiased evaluation of cell type specific expression of ACE2 in healthy hepatic tissues employing scRNA-seq data of two independent cohorts. This study revealed significant enrichment of ACE2 expression in cholangiocyte clusters (59.7% of cells) compared to hepatocytes (2.6% of cells) suggesting that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes, and the liver abnormalities of COVID-19 patients may not be due to a direct hepatocyte damage but, probably, to cholangiocyte dysfunction. It is well established that cholangiocytes play an essential role in liver regeneration and immune response; hence, their dysfunction may contribute to liver damage (Figure 2). Overexpression of the ACE2 receptor on hepatocytes has been observed in patients with liver fibrosis/cirrhosis and in cases of hypoxia. This might explain the high probability of liver injury in these populations[6]. Since liver biopsies of COVID-19 patients show focal hepatic necrosis without significant surrounding inflammatory infiltration, this points toward direct viral injury. However, considering high receptor levels in cholangiocytes rather than hepatocytes and as most of the COVID-19 patients manifest with elevated transaminases, the possibility of direct viral attack is less likely[7]. Other possible pathways of virus entry in hepatocytes have also been suggested to play a



DOI: 10.5501/wjv.v11.i6.453

Figure 2 Two principal types of severe acute respiratory syndrome coronavirus 2 infection of the liver parenchyma. A: Direct severe acute respiratory syndrome coronavirus 2 infection targeted to hepatocytes is designated as hepatocellular type; B: Direct viral entry into biliary epithelial cells is known as the cholangiocyte type. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-Glutamyltransferase; ALP: Alkaline phosphatase.

role in liver involvement in COVID-19 (Figure 3).

Another mechanism potentially associated with hepatic injury is the cytokine storm generated by the coronavirus infection. Excess inflammatory burden and potential immune-mediated damage lead to increased vascular permeability, multiorgan failure and death[1,3]. Similarly, studies have documented a correlation between high levels of interleukins, a group of cytokines, and severity of COVID-19[8].

In addition, COVID-19-related vascular thrombotic complications with consequent hypoxia and shock can lead to liver injury mediated by the ischemia-reperfusion injury mechanism. Ischemia-reperfusion injury involves a biphasic process of ischemia-induced cell injury and reperfusion-induced inflammatory response. Thus, an activated proinflammatory immune cascade due to the aforementioned processes can be a possible mechanism of liver injury in COVID-19 patients[3,6,9].

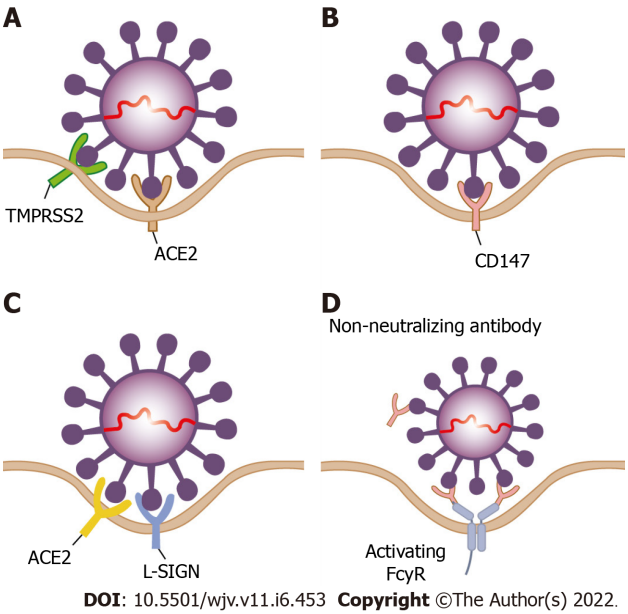
Finally, studies have also reported variable degrees of hepatotoxicity with medications used in the treatment of COVID-19[10,11]. Hundt *et al*[12] reported the use of medications needed to treat COVID-19 virus (remdesivir, hydroxychloroquine, lopinavir/ritonavir and tocilizumab) as a significant predictor of raised transaminases [> 5 × upper limit of normal (ULN)] during hospitalization for COVID-19. Cai *et al*[13] described lopinavir/ritonavir as a risk factor for liver injury in COVID-19 patients [odds ratio (OR): 4.44; 95% confidence interval: 1.50-13.17]. However, these authors did not report significant risk with the use of antibiotics, nonsteroidal anti-inflammatory drugs, ribavirin, herbal medications and interferon.

Muhović *et al*[14] reported severe drug-induced liver injury with tocilizumab in patients previously treated with chloroquine and lopinavir/ritonavir. As interleukin-6 is known to be associated with liver regeneration and metabolism, it is postulated that inhibition of interleukin-6 by tocilizumab may be the potential cause of liver enzyme derangement[11,15]. Hepatotoxicity can be expected in COVID-19 patients as the liver metabolizes nearly all medications used in COVID-19. Several mechanisms, like upregulation of ACE2 receptors and downregulation of cytochrome p450, sensitize the hepatocytes to the SARS-CoV-2 virus or therapeutic agents. While on the other hand, the pharmacological features of medications may increase susceptibility to liver injury[11].

In summary, the progression of COVID-19 from a mild to severe form is associated with a dysregulated immune response, which leads to uncontrolled viral replication and cellular damage, thus further exacerbating the immune-mediated damage, which includes liver damage[16].

CLINICAL MANIFESTATIONS

The SARS-CoV-2 genomic sequence has shown similarity with the SARS coronavirus and Middle East respiratory syndrome coronavirus. Like these viruses, respiratory symptoms along with gastrointestinal



DOI: 10.5501/wjv.v11.i6.453

Figure 3 Possible pathways of virus entry in hepatocytes. A: The angiotensin converting enzyme-2 in conjunction with transmembrane protease serine protease 2 is considered the predominant receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into cells; B: CD147 is another possible receptor for SARS-CoV-2 entry into hepatocytes. CD147 is highly expressed in tumor tissues, inflamed tissues and pathogen-infected cells including hepatocytes; C: L-SIGN (CD209L) may serve as a liver-specific cell receptor for SARS-CoV-2 infection of hepatocytes; D: Antibody-dependent enhancement may also facilitate SARS-CoV-2 infection of hepatocytes. During antibody-dependent enhancement of infection, suboptimal non-neutralizing antibodies cannot completely neutralize the virus; instead, they bind with the Fc receptors expressed on hepatocytes, leading to virus entry and infection. ACE2: Angiotensin-converting enzyme 2.

and liver involvement have been reported in SARS-CoV-2[17]. Clinical manifestations in COVID-19 infected patients with no previous liver comorbidities may range from asymptomatic liver function abnormalities to liver failure, as shown in Table 1[1,18].

ABNORMAL LIVER FUNCTIONS

The reported prevalence of liver injury in COVID-19 varies widely from 10.5% to 58.0% depending on many factors[4,19]. Various studies have reported a slight derangement of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin levels[19,20]. The reported figures of complications in COVID-19 are slightly lower as compared to SARS-CoV and Middle East respiratory syndrome-CoV infections, as shown in Table 2. A systemic review reported a 15.0% elevation of AST and ALT, while a 16.7% elevation of bilirubin was reported[21]. Similarly, a meta-analysis pooled 13251 COVID-19 patients and reported a mild decrease in albumin in 39.8% cases, with a mild increase in AST in 22.8% and ALT levels in 20.6%[19]. Parohan *et al*[22] reported older age, male sex, obesity and underlying liver disease as commonly associated risk factors for deranged LFTs.

Furthermore, the extent of liver enzyme derangement has been associated with the severity of COVID-19 infection and its prognosis. Marjot *et al*[23] and Wang *et al*[24] reported higher levels of AST in intensive care unit (ICU) admitted COVID-19 patients. Similarly, Guan *et al*[25] reported 18.2% liver enzyme derangement in non-severe disease as compared to 39.4% with severe disease in 1099 Chinese patients affected by COVID-19 infection. The authors also described higher bilirubin, ALT and AST levels in COVID-19 patients that had either passed away or required ICU admission and/or the need for mechanical ventilation as compared to those patients who did not[25].

Different studies have reported different prognoses of deranged LFTs in COVID-19 patients. Moreover, different studies have used different definitions of liver injury. Ding *et al*[26] labeled liver injury as a 3 × ULN increase in ALT or AST or 2 × ULN increase in total bilirubin, direct bilirubin or alkaline phosphatase. The authors documented ALI in 0.5% of the COVID-19 patients without underlying liver disease. In addition, all patients had concomitant debilitating conditions like acute respiratory distress syndrome, septic shock, kidney injury, *etc*. Hajifathalian *et al*[27] defined ALI as elevation of any parameter of a liver biochemistry panel and demonstrated a higher risk of ICU admission and death in patients with ALI. Phipps *et al*[28] retrospectively studied a large cohort of in-hospital patients based on raised ALT levels, graded liver injury into no/mild (< 2 × ULN), moderate (2-5 × ULN) or severe (> 5 × ULN) forms. Although only 6.4% of the study population developed severe injury, it was significantly associated with severe clinical outcomes including death. The authors also proposed that severe liver injury can be used as a prognostic factor in hospitalized patients. Considering

Table 2 Rates of hepatic complications in different clinically significant human coronavirus infectious diseases

Hepatic complications	SARS-CoV-2, %	SARS-CoV, %	MERS-CoV, %
Increase in ALT	13.3-28.0	52.5-8.07	11.0-56.3
Increase in AST	22.0-58.0	37.1-86.9	15.0-86.8
Increase in TB	10.5-18.0	30.0	NA
Decrease in serum albumin	36.8	40.4-72.0	NA
Co-morbidity with liver disease	HBV-positive patients were more prone to develop severe disease (32.9%) *vs* HBV-negative patients (15.3%)	HBV infection was not associated with worse clinical outcomes	NA

ALT: Alanine transaminase; AST: Aspartate transaminase; HBV: Hepatitis B virus; MERS: Middle east respiratory syndrome; NA: Not applicable; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SARS-CoV: Severe acute respiratory distress syndrome; TB: Total bilirubin.

the association of deranged LFTs with disease severity and prognosis, Tian and Ye[17] suggested that changes in LFTs should be vigilantly monitored for early identification and management.

Although, the majority of studies have reported higher levels of liver enzymes with the severity of COVID-19, a few case reports also documented liver failure in patients without underlying liver disease. Gurala *et al*[18] and Weber *et al*[29] documented acute liver failure in patients without comorbidities and presenting with worsening pulmonary symptoms. However, Orandi *et al*[30] reported acute liver failure documented by replicating SARS-COV-2 RNA in hepatocytes in a young female with COVID-19 presenting with non-respiratory symptoms. Moreover, Busani *et al*[31] reported two fatal cases of acute liver failure in patients with COVID-19 secondary to herpes simplex virus 1 infection. Both patients were treated with tocilizumab.

The resolution of liver injury post-COVID-19 hospitalization is not well studied. A large retrospective study demonstrated persistent deranged LFTs post-discharge in 31.7% of the study population. Thus, it was suggested that recovery from liver injury after resolution of COVID-19 symptoms could be delayed [26]. Hence, the European Association for the Study of the Liver (EASL) position paper recommends monitoring LFTs not only during hospitalization but also post-discharge in COVID-19 patients with persistent deranged laboratory parameters[32].

CHRONIC LIVER DISEASE

CLD, an immunocompromised state, makes the patient susceptible to various diseases including COVID-19 virus[4]. The reported prevalence of CLD amongst COVID-19 patients ranges between 2%-11%[23]. Studies have reported contradictory outcomes for CLD patients with COVID-19. Some have documented higher mortality rates while others negated these findings.

An international registry study between March 2020 and July 2020 documented 745 CLD patients from 29 countries infected with COVID-19 virus. Of the total study population, 386 (51.8%) had cirrhosis, 345 were hospitalized, 108 required ICU admission, and 71 required mechanical ventilation. Among these, 123 (32%) cirrhotic patients died mainly due to pulmonary complications (64%). Moreover, in comparison with non-cirrhotic CLD patients, multivariate analysis documented age, higher Child-Turcotte-Pugh (CTP) score and ALD as significant prognostic factors. Additionally, increased morbidity and mortality were observed with an incremental increase in CTP score[33]. Similarly, a preliminary report of 152 CLD patients documented 39.8% mortality in patients with cirrhosis with CTP B and CTP C scores serving as significant predictors of mortality (P = 0.03 and < 0.001, respectively)[34].

A large National COVID Cohort Collaborative dataset study reported 220727 COVID-19 patients with CLD. Among which, 8941 were patients with cirrhosis, out of which, 8.8% required mechanical ventilation, while 8.9% of patients died at 30 d. In contrast, amongst 29446 non-cirrhotic patients, 2.0% required mechanical ventilation while 30 d mortality was documented in 1.7% of patients. The multivariate analysis documented higher odds of mortality among patients with cirrhosis compared to patients without cirrhosis with COVID-19 (adjusted hazard ratio: 3.31)[35]. However, a pooled analysis of six studies documented no significant association between the severity of COVID-19 and death in patients with CLD[36].

Similarly, in a nationwide Swedish cohort, a nonsignificant association was documented between mortality and COVID-19 in CLD patients. In addition, the presence or absence of cirrhosis did not have an impact on this association. However, the authors did document a slightly higher risk of hospitalization and development of severe COVID-19 in CLD patients as compared to matched controls (adjusted hazard ratio: 1.08 and 1.23, respectively)[37].

ALI at the admission of COVID-19-affected patients was documented in 14 (32.6%) patients, while (39.5%) developed ALI during the hospital stay. Acute decompensation was reported in 9.1%, while 11.6% developed acute-on-chronic liver failure. Further analysis documented higher mortality and complications (liver-related and overall) in decompensated cirrhotic patients with COVID-19. In non-cirrhotic patients with liver injury there was a higher propensity of ICU admission, but the recovery, hospital stay and mortality were comparable to those without liver injury[38]. In another study of 179 patients with cirrhosis with acute decompensation, 50% developed acute-on-chronic liver failure, and this complication was associated with a higher rate of mortality ($P < 0.001$)[33]. Thus, it may be concluded that not only the underlying liver disease but also the existing liver reserve may predict a patient's outcomes with COVID-19 infection. Hence, active and dynamic management of these patients should be done considering their high associated risk of morbidity and mortality.

Recognizing high-risk groups and those predisposed to the severe clinical courses are of utmost importance to plan preventive strategies and management. A limited number of studies have documented the variable impact of etiology on the severity of COVID-19 infection[37].

In a nationwide cohort of 42320 CLD patients, underlying etiology was not associated with a significant risk of hospitalization or development of severe COVID-19. In this study, 32.7% had viral hepatitis, 15.0% had NAFLD, 2.1% had ALD, and 44.0% had other etiologies. However, an international registry of 745 CLD patients with COVID-19 documented ALD as a predictor of mortality ($P = 0.04$). However, no significant association was documented with NAFLD, hepatitis B and C[33]. Similarly, a United States multicenter study also documented ALD along with decompensated cirrhosis and HCC as a liver-specific predictor of mortality in COVID-19 patients[39]. The authors suggested that the added cytokine storm of the SARS-CoV-2 virus to the already heightened inflammatory state in alcoholics could be the cause of the detrimental outcomes. Moreover, increased use of alcohol due to economic and social burdens during the COVID-19 era could be a contributing factor[39,40]. Wang *et al*[41], in a large case-control study, documented that patients with CLD secondary to alcohol-related liver damage and alcoholic liver cirrhosis have odds of 7.05 and 7.00, respectively, of developing COVID-19.

Viral hepatitides, mainly hepatitis B and C, have infected millions of people worldwide. A case-control study of electronic health records documented that adjusted odds of developing COVID-19 were 8.93 and 4.37 with chronic hepatitis C and chronic hepatitis B, respectively[41].

A higher prevalence of hepatitis B has been reported in COVID-19 patients in Asian studies, ranging from 0.8%-6.3%, while a lower prevalence rate of 0.1% has been reported in a United States-based study [41-43]. Although, the pathogenesis is unclear, studies have documented the variable associations of HBV on clinical outcomes of patients with COVID-19. In 105 COVID-19 and HBV co-infected patients, Zhang *et al*[44] reported 23 cases of HBV-related CLD patients with COVID-19. Among which, two patients with cirrhosis (8.7%) became critically ill. Yet, no mortality was reported.

Chen *et al*[45] retrospectively analyzed 20 HBV-positive patients amongst 326 COVID-19 patients. Authors reported three deaths in hepatitis B surface antigen-negative patients, while no patients in the hepatitis B surface antigen-positive group died. Moreover, no statistically significant difference was noted in LFTs, hospital stay and disease severity[45]. In another retrospective analysis of 5639 chronic hepatitis B patients with COVID-19, the authors concluded that current or past hepatitis B infection is not associated with increased mortality[46]. However, another Chinese study documented higher COVID-19 severity and mortality in HBV-infected patients[47]. Zou *et al*[48] observed liver injury as a significant cause of disease severity and mortality in chronic hepatitis B patients with COVID-19.

A chronic immunosuppressed state potentiates the risk of HBV reactivation in patients with chronic or resolved hepatitis B. Moreover, HBV reactivation is associated with high morbidity and mortality [49]. Few case reports have documented HBV reactivation in patients with COVID-19. Aldhaleei *et al*[50] reported a case of HBV reactivation in a patient with COVID-19 presenting with an altered level of consciousness and deranged LFTs. However, high HBV DNA levels were interpreted as reactivation without prior DNA levels.

It is postulated that the immunosuppressive therapy used in COVID-19 can attenuate the host immunity against HBV, thus leading to increased HBV replication. Moreover, with the later withdrawal of immunosuppressants, the reconstituted immune system might mount a heightened immune response against HBV antigen-laden hepatocytes, thus leading to liver injury[51]. Sagnelli *et al*[52] reported HBV reactivation in a patient with COVID-19 pneumonia 7 d after stopping corticosteroid therapy. Wu *et al* [53] also documented HBV reactivation in a COVID-19 patient on entecavir treated with recombinant interferon-alpha-2b, lopinavir/ritonavir and subsequently with methylprednisolone. However, Yip *et al* [46] did not document HBV reactivation in 10 patients on no treatment treated with corticosteroids for severe COVID-19. Nevertheless, the detrimental risk of hepatitis B reactivation persists with COVID-19 treatment. Thus, the Asian Pacific Association for the Study of the Liver (APASL) COVID-19 Taskforce recommends screening all COVID-19 patients for hepatitis B surface antigen. Moreover, antiviral treatment should be prescribed to hepatitis B-positive patients especially treated with interleukin-6 monoclonal antibodies or other immunosuppressive therapy[3].

The prevalence of HCV in COVID-19 is not well reported. A case series from the United States of 5700 hospitalized patients with COVID-19 reported < 0.1% incidence of HCV infection[54]. However, a retrospective single-center study reported a higher incidence of 4.1%. In the latter study, the authors also reported HCV, age, D-dimers and serum ferritin as predictors of in-hospital mortality[55]. The

authors suggested that vascular endothelial dysfunction, elevated cytokine levels and the role of overexpressed transmembrane protease serine 2 could be the potential cause of morbidity and mortality of COVID-19 in HCV-infected patients.

Lensen *et al*[56] reported reactivation of HCV leading to patient mortality in an elderly patient following COVID-19 vaccination. However, the patient had multiple comorbidities along with HBV and HCV co-infection-related cirrhosis[56]. Although, a large veteran database study of HCV-positive patients documented a higher rate of hospitalization, the rates of ICU admission and mortality were similar to negative patients. Moreover, the rate of hospitalization increased with higher fibrosis[57]. The American Association for the Study of Liver Diseases recommends continuing therapy for HBV and HCV if patients are already on treatment when infected with COVID-19. In addition, HBV treatment should be considered in patients with a risk of HBV flare[58].

With the increasing prevalence of NAFLD, it is not surprising that a higher incidence of NAFLD is noted among COVID-19 patients. The prevalence varies from 30% to 55%. The range may be an overestimate, as most of the studies were concentrated on hospitalized patients[59]. NAFLD (recently renamed metabolic dysfunction-associated fatty liver disease) is associated with factors like diabetes and obesity, which are known to aggravate COVID-19 severity[60]. An electronic health records-based study reported that CLD patients have an increased risk of acquiring COVID-19 with the highest odds in patients with NAFLD (adjusted OR: 13.11), nonalcoholic cirrhosis (adjusted OR: 11.5) and chronic hepatitis C (adjusted OR: 8.7)[41]. A systemic review and meta-analysis of 14 studies reported an increased risk of COVID-19 severity and ICU admission in patients with NAFLD. However, no difference in mortality was observed in comparison to non-NAFLD patients[61]. Similar findings have also been reported in other studies[60,62,63]. However, a single-center study from India reported a nonsignificant difference in hospital stay and mortality in COVID-19 patients with or without NAFLD [64]. Similarly, Madan *et al*[65] also documented no association of fatty liver with COVID-19 morbidity and mortality.

Thromboembolism risk is high in COVID-19 patients and is associated with high mortality[66]. A prospective cohort documented a statistically significant association of NAFLD with the development of pulmonary thrombosis in COVID-19 patients. Increased levels of proinflammatory proteins and cytokines may be the contributing factor in this debilitating disease process[59].

Like hepatitis B and C, the underlying liver fibrosis plays an important role in COVID-19 outcomes. Targher *et al*[67] determined the impact of non-invasive fibrosis scores, FIB-4 or NAFLD fibrosis score on COVID-19 severity. After adjustment for sex, obesity and diabetes, the authors documented a significant association of severe COVID-19 with high/intermediate FIB-4 or NAFLD fibrosis score[67].

Regarding autoimmune hepatitis (AIH), a database study of three large registries with 70 AIH patients documented no differences in rates of hospitalization, ICU admission and death between patients with and without AIH-related CLD. However, a higher risk of mortality was observed in the AIH cohort with CTP B and C. Interestingly, the use of immunosuppression was not associated with mortality[68]. Another case series reported uneventful clinical course of 10 AIH patients on immunosuppression[69].

Thus, liver disease etiology may play a role, but the underlying liver fibrosis is the cornerstone to determining susceptibility to COVID-19 and its outcomes. Furthermore, no studies have documented increased predisposition to COVID-19 infection or adverse outcomes in patients with CLD secondary to AIH, primary biliary cholangitis or primary sclerosing cholangitis[70].

HEPATOCELLULAR CARCINOMA

Studies amongst oncological patients have reported a higher risk of acquiring COVID-19 infection along with a greater risk of morbidity and mortality. Moreover, recent cancer treatment may also worsen the outcomes[71,72]. The reported mortality in cancer patients with COVID-19 ranges from 11% to 28%. Nevertheless, concomitant comorbidities, functional class and cancer activity status are associated with a poorer prognosis. Hence, the immunodeficient status of cancer patients determines clinical outcomes [72].

It is estimated that more than 70% of HCC patients have underlying CLD or cirrhosis[73]. It has been shown that the SARS-CoV-2 virus can aggravate liver damage in patients with underlying disease, thus making patients with HCC more susceptible to COVID-19-related morbid complications[74]. Yet, data on the outcomes of HCC with COVID-19 is scarce. A large United States-based multicenter study involving CLD patients infected with COVID-19 reported 52% mortality among patients with HCC (n = 22). Additionally, the authors concluded that decompensated cirrhosis, ALD and HCC were independent liver-related risk factors of mortality[75].

HCC is an aggressive tumor with a tumor volume doubling time of nearly 70 to 120 d[76]. A monthly ultrasound for 6 mo for HCC surveillance is thus recommended under normal circumstances. However, during the pandemic, the delay of 2-3 mo in surveillance has been considered acceptable[58,77]. Inchingolo *et al*[78] suggested prioritizing patients who are at high risk of incidence and/or recurrence of HCC and patients eligible for liver transplantation.

Since the majority of resources were diverted in managing and treating COVID-19 patients during the COVID-19 pandemic, various hepatological associations and societies drafted recommendations for the management of patients with HCC in these times[58,77,79].

Regarding the treatment of HCC, hepatology societies have recommended tailoring the treatment on a case-by-case basis. The American Association for the Study of Liver Diseases proposes that during the COVID-19 pandemic, HCC treatment with curative intent should not be delayed[58]. In addition, APASL recommends postponing surgical treatment and suspending vascular intervention if there is high risk of decompensation or comorbidities since it increases the risk of severe COVID-19. Moreover, ablation therapy could be considered an alternative therapy during this time[77]. Like APASL, EASL guidelines recommend postponing locoregional therapies as these are mostly for the purpose of cytoreduction[77,79]. Similarly, radiation therapy should only be considered in case of functional or life-threatening situations[77].

Although, APASL suggests a preference for oral tyrosine kinase inhibitors over intravenous therapy, EASL proposes dose reduction based on the individual patients[77,79]. Moreover, EASL recommends temporary withdrawal of immune-checkpoint inhibitor therapy in patients with HCC[79].

In general, in all patients with HCC, it is of utmost importance to screen patients for the SARS-CoV-2 virus prior to diagnosis or intervention. Assessment and/or treatment should be postponed until noninfective status is achieved in COVID-19-positive patients. Limited staff with protective gear along with hygienic measures should always be followed during each intervention to curtail the spread of the novel viruses[77].

SOLID ORGAN TRANSPLANTS

Globally, solid organ transplantation has been profoundly affected by the COVID-19 pandemic, resulting in decreased rates of organ procurement and transplantation[80,81]. Liver is the second most common solid organ transplanted in the world after kidney[82]. Although prolonged immunocompromised status and post-transplant associated comorbidities theoretically increase the susceptibility to COVID-19 severity, the data on liver transplant recipients is scarce. Contradictory to the initial reports, a recent multicenter and large database studies have reported similar outcomes in transplanted and non-transplanted COVID-19 populations[80,83,84]. The studies were performed on only hospitalized patients, so it could not be concluded that transplanted patients are prone to be hospitalized due to COVID-19[80]. Centers for Medicare and Medicaid Services has labelled transplant surgery in Tier 3b that is not to be postponed[85]. Owing to diverted and limited resources amidst the pandemic, hepatology societies have restricted liver transplants to urgent transplants only. Table 3 describes a summary of recommendations from various societies regarding liver transplantation activities during the COVID-19 pandemic.

LIMITATIONS

There are certain limitations to this study. We addressed the clinical presentation and laboratory abnormalities primarily, and pathogenesis and particularly pathology were not described. We also did not cover management and prognostic aspects of this infection in detail. New variants of COVID-19 virus were also not discussed nor the vaccination of patients with liver diseases.

FUTURE DIRECTIONS

There is a need for international collaboration for carrying out basic research for better understanding the pathogenesis of hepatobiliary injury in COVID-19 as it can pave the path for the development of targeted therapy and personalized medicine. The role of direct virus infection of the liver with consequent cytopathic effects *vs* indirect liver injury needs to be explored further. Expression profiles of various SARS-CoV-2 entry receptors vary across different *in vitro* and *in vivo* liver models; however, evidence of specific viral hepatotropism of SARS-CoV-2 is inadequate. Abnormal LFT values are common in patients with COVID-19; both the prognostic significance of these derangements and whether they are directly attributable to hepatic SARS-CoV-2 infection remain to be explored in future focused research.

CONCLUSION

In conclusion, liver involvement is common in patients with COVID-19 infection, particularly in those

Table 3 Summary of recommendations from various hepatology societies regarding liver transplantation during the coronavirus disease 2019 pandemic

Step	AASLD	EASL	APASL	Indian Transplant Society
Indications	Develop a hospital-specific policy for organ acceptance in consideration to community incidence of COVID-19 infection	Restrict transplant with poor short-term prognosis like ALF, ACLF, high MELD score and HCC at upper limit of Milan criteria	Can limit transplant to urgent cases (ALF, high MELD, high risk of HCC progression) according to resources and infection status of country	Until April 2020, elective transplants were withheld. However, in ALF and ACLF transplant could proceed
Pre- transplant evaluation	Test all recipients and donors for SARS-CoV-2 before transplantation. In case of COVID-19 infection in potential recipient, transplant can be considered after at least 14-21 d if symptoms are resolved and repeat SARS-CoV-2 test is negative. Vaccination of potential recipient is encouraged	All recipients and donors should be tested for SARS-CoV-2 before transplantation. Reduction of hospital stay for transplant evaluation and consultation	All recipients and donors should be tested for SARS-CoV-2 before transplantation. Donor should also be evaluated for evidence of COVID-19 infection on chest CT	All recipients and donors should be tested for SARS-CoV-2 before transplantation
Post-transplant management without COVID-19	Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage COVID-19 vaccination at least 6 wk post-transplant if partially vaccinated pretransplant than vaccination can be completed 1 mo after transplant	Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza	Standard immunosuppression protocols should be followed in new transplant recipient. In cases of long-term transplant dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza	Standard immunosuppression protocols should be followed in post-transplant period
Post-transplant management with COVID-19	Consider lowering immunosuppression levels especially antimetabolite drugs (*e.g.*, azathioprine or MMF). Dose adjustment of immunosuppression should be based on severity of COVID-19. Monitor kidney function and calcineurin inhibitor levels	Dose adjustment of calcineurin- and/or mTOR- inhibitors may be required to avoid drug interactions with anti-viral therapy	Consider lowering immunosuppression levels in patients with moderate COVID-19 infection. Immunosuppression should be reduced in recipients with lymphopenia, fever or worsening pneumonia. Severe COVID-19 should be treated as per local protocol. Drug-to-drug interaction should be considered with anti-viral therapy	

AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on chronic liver failure; ALF: Acute liver failure; APASL: Asian Pacific Association for the Study of the Liver; COVID-19: Coronavirus disease 2019; CT: Computed tomography; EASL: European Association for the Study of the Liver; MELD: Model For End-Stage Liver Disease; HCC: Hepatocellular carcinoma; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

with moderate to severe disease. It is mostly asymptomatic or mild in nature. Conversely, patients with pre-existing liver disease are prone to serious COVID-19. Data on the impact of COVID-19 infection on patients with pre-existing diseases or liver transplants is either conflicting or scarce. Hence, large collaborative studies with prolonged follow-up are needed to fully comprehend the impact of this challenging infection on patients with liver diseases.

FOOTNOTES

Author contributions: Mubarak M and Luck NL conceived the study; Mubarak M, Majid Z and Hanif FM designed the study; Hanif FM, Ahmed S and Majid Z performed the research; All authors participated in primary and final drafting; All authors read and approved the final manuscript.

Conflict-of-interest statement: None of the authors have any conflicts of interest related to this research.

Country/Territory of origin: Pakistan

ORCID number: Farina M Hanif 0000-0002-2011-4721; Zain Majid 0000-0002-6961-3011; Shoaib Ahmed 0000-0003-2536-8197; Nasir H Luck 0000-0002-4752-4157; Muhammed Mubarak 0000-0001-6120-5884.

S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

REFERENCES

1 **Perisetti A**, Gajendran M, Mann R, Elhanafi S, Goyal H. COVID-19 extrapulmonary illness-special gastrointestinal and hepatic considerations. *Dis Mon* 2020; **66**: 101064 [PMID: 32807535 DOI: 10.1016/j.disamonth.2020.101064]
2 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
3 **APASL Covid-19 Task Force**. , Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int* 2020; **14**: 415-428 [PMID: 32447721 DOI: 10.1007/s12072-020-10054-w]
4 **Napodano C**, Pocino K, Stefanile A, Marino M, Miele L, Gulli F, Basile V, Pandolfi F, Gasbarrini A, Rapaccini GL, Basile U. COVID-19 and hepatic involvement: The liver as a main actor of the pandemic novel. *Scand J Immunol* 2021; **93**: e12977 [PMID: 32931622 DOI: 10.1111/sji.12977]
5 **Xiaoqiang Chai**, Longfei Hu, Yan Zhang, Weiyu Han, Zhou Lu, Aiwu Ke, Jian Zhou, Guoming Shi, Nan Fang, Jia Fan, Jiabin Cai, Jue Fan, Fei Lan. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. BioRxiv, 2020 [DOI: 10.1101/2020.02.03.931766]
6 **Ye Q**, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *Am J Physiol Gastrointest Liver Physiol* 2020; **319**: G245-G252 [PMID: 32639848 DOI: 10.1152/ajpgi.00148.2020]
7 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]
8 **Zhan K**, Liao S, Li J, Bai Y, Lv L, Yu K, Qiu L, Li C, Yuan G, Zhang A, Mei Z. Risk factors in patients with COVID-19 developing severe liver injury during hospitalisation. *Gut* 2021; **70**: 628-629 [PMID: 32571973 DOI: 10.1136/gutjnl-2020-321913]
9 **Li D**, Ding X, Xie M, Tian D, Xia L. COVID-19-associated liver injury: from bedside to bench. *J Gastroenterol* 2021; **56**: 218-230 [PMID: 33527211 DOI: 10.1007/s00535-021-01760-9]
10 **Licata A**, Minissale MG, Distefano M, Montalto G. Liver injury, SARS-COV-2 infection and COVID-19: What physicians should really know? *GastroHep* 2021; **3**: 121-130 [PMID: 34149320 DOI: 10.1002/ygh2.455]
11 **Sodeifian F**, Seyedalhosseini ZS, Kian N, Eftekhari M, Najari S, Mirsaeidi M, Farsi Y, Nasiri MJ. Drug-Induced Liver Injury in COVID-19 Patients: A Systematic Review. *Front Med (Lausanne)* 2021; **8**: 731436 [PMID: 34616757 DOI: 10.3389/fmed.2021.731436]
12 **Hundt MA**, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology* 2020; **72**: 1169-1176 [PMID: 32725890 DOI: 10.1002/hep.31487]
13 **Cai Q**, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: 32298767 DOI: 10.1016/j.jhep.2020.04.006]
14 **Muhović D**, Bojović J, Bulatović A, Vukčević B, Ratković M, Lazović R, Smolović B. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver Int* 2020; **40**: 1901-1905 [PMID: 32478465 DOI: 10.1111/Liv.14516]
15 **Schmidt-Arras D**, Rose-John S. IL-6 pathway in the liver: From physiopathology to therapy. *J Hepatol* 2016; **64**: 1403-1415 [PMID: 26867490 DOI: 10.1016/j.jhep.2016.02.004]
16 **Saviano A**, Wrensch F, Ghany MG, Baumert TF. Liver Disease and Coronavirus Disease 2019: From Pathogenesis to Clinical Care. *Hepatology* 2021; **74**: 1088-1100 [PMID: 33332624 DOI: 10.1002/hep.31684]
17 **Tian D**, Ye Q. Hepatic complications of COVID-19 and its treatment. *J Med Virol* 2020; **92**: 1818-1824 [PMID: 32437004 DOI: 10.1002/jmv.26036]
18 **Gurala D**, Al Moussawi H, Philipose J, Abergel JR. Acute Liver Failure in a COVID-19 Patient Without any Preexisting Liver Disease. *Cureus* 2020; **12**: e10045 [PMID: 32983735 DOI: 10.7759/cureus.10045]
19 **Zarifian A**, Zamiri Bidary M, Arekhi S, Rafiee M, Gholamalizadeh H, Amiriani A, Ghaderi MS, Khadem-Rezaiyan M, Amini M, Ganji A. Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis. *J Med Virol* 2021; **93**: 336-350 [PMID: 32681674 DOI: 10.1002/jmv.26314]
20 **Musa S**. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab J Gastroenterol* 2020; **21**: 3-8 [PMID: 32253172 DOI: 10.1016/j.ajg.2020.03.002]
21 **Wang X**, Lei J, Li Z, Yan L. Potential Effects of Coronaviruses on the Liver: An Update. *Front Med (Lausanne)* 2021; **8**: 651658 [PMID: 34646834 DOI: 10.3389/fmed.2021.651658]
22 **Parohan M**, Yaghoubi S, Seraji A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies. *Hepatol Res* 2020; **50**: 924-935 [PMID: 32386449 DOI:

10.1111/hepr.13510]
23 **Marjot T**, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 348-364 [PMID: 33692570 DOI: 10.1038/s41575-021-00426-4]
24 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
25 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
26 **Ding ZY**, Li GX, Chen L, Shu C, Song J, Wang W, Wang YW, Chen Q, Jin GN, Liu TT, Liang JN, Zhu P, Zhu W, Li Y, Zhang BH, Feng H, Zhang WG, Yin ZY, Yu WK, Yang Y, Zhang HQ, Tang ZP, Wang H, Hu JB, Liu JH, Yin P, Chen XP, Zhang B; Tongji Multidisciplinary Team for Treating COVID-19 (TTTC). Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol* 2021; **74**: 1295-1302 [PMID: 33347952 DOI: 10.1016/j.jhep.2020.12.012]
27 **Hajifathalian K**, Krisko T, Mehta A, Kumar S, Schwartz R, Fortune B, Sharaiha RZ; WCM-GI research group*. Gastrointestinal and Hepatic Manifestations of 2019 Novel Coronavirus Disease in a Large Cohort of Infected Patients From New York: Clinical Implications. *Gastroenterology* 2020; **159**: 1137-1140.e2 [PMID: 32389667 DOI: 10.1053/j.gastro.2020.05.010]
28 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: 32473607 DOI: 10.1002/hep.31404]
29 **Weber S**, Mayerle J, Irlbeck M, Gerbes AL. Severe liver failure during SARS-CoV-2 infection. *Gut* 2020; **69**: 1365-1367 [PMID: 32327526 DOI: 10.1136/gutjnl-2020-321350]
30 **Orandi BJ**, Li G, Dhall D, Bajpai P, Manne U, Arora N, Lu A, Coronado AC, Kassel R, Pinninti S, Lewis CE, Chapleau C, Locke JE, Gutierrez S, Luz H. Acute Liver Failure in a Healthy Young Female With COVID-19. *JPGN Reports* 2021; **2**: e108 [DOI: 10.1097/PG9.0000000000000108]
31 **Busani S**, Bedini A, Biagioni E, Serio L, Tonelli R, Meschiari M, Franceschini E, Guaraldi G, Cossarizza A, Clini E, Maiorana A, Gennari W, De Maria N, Luppi M, Mussini C, Girardis M; Modena Covid-19 Working Group (MoCo19). Two Fatal Cases of Acute Liver Failure Due to HSV-1 Infection in COVID-19 Patients Following Immunomodulatory Therapies. *Clin Infect Dis* 2021; **73**: e252-e255 [PMID: 32840571 DOI: 10.1093/cid/ciaa1246]
32 **Marjot T**, Eberhardt CS, Boettler T, Belli LS, Berenguer M, Buti M, Jalan R, Mondelli MU, Moreau R, Shouval D, Berg T, Cornberg M. Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: An updated EASL position paper. *J Hepatol* 2022; **77**: 1161-1197 [PMID: 35868584 DOI: 10.1016/j.jhep.2022.07.008]
33 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]
34 **Moon AM**, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, Genescà J, Gill US, James TW, Jones PD, Marshall A, Mells G, Perumalswami PV, Qi X, Su F, Ufere NN, Barnes E, Barritt AS, Marjot T. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. *J Hepatol* 2020; **73**: 705-708 [PMID: 32446714 DOI: 10.1016/j.jhep.2020.05.013]
35 **Ge J**, Pletcher MJ, Lai JC; N3C Consortium. Outcomes of SARS-CoV-2 Infection in Patients With Chronic Liver Disease and Cirrhosis: A National COVID Cohort Collaborative Study. *Gastroenterology* 2021; **161**: 1487-1501.e5 [PMID: 34284037 DOI: 10.1053/j.gastro.2021.07.010]
36 **Lippi G**, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: 114-115 [PMID: 32282549 DOI: 10.1097/MEG.0000000000001742]
37 **Simon TG**, Hagström H, Sharma R, Söderling J, Roelstraete B, Larsson E, Ludvigsson JF. Risk of severe COVID-19 and mortality in patients with established chronic liver disease: a nationwide matched cohort study. *BMC Gastroenterol* 2021; **21**: 439 [PMID: 34814851 DOI: 10.1186/s12876-021-02017-8]
38 **Sarin SK**, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, Hwang J, Qi X, Cua IH, Suh JI, Park JG, Putcharoen O, Kaewdech A, Piratvisuth T, Treeprasertsuk S, Park S, Wejnaruemarn S, Payawal DA, Baatarkhuu O, Ahn SH, Yeo CD, Alonzo UR, Chinbayar T, Loho IM, Yokosuka O, Jafri W, Tan S, Soo LI, Tanwandee T, Gani R, Anand L, Esmail ES, Khalaf M, Alam S, Lin CY, Chuang WL, Soin AS, Garg HK, Kalista K, Batsukh B, Purnomo HD, Dara VP, Rathi P, Al Mahtab M, Shukla A, Sharma MK, Omata M; APASL COVID Task Force, APASL COVID Liver Injury Spectrum Study (APCOLIS Study-NCT 04345640). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int* 2020; **14**: 690-700 [PMID: 32623632 DOI: 10.1007/s12072-020-10072-8]
39 **Kim D**, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, Perumalswami P, Roytman M, Li M, Vogel AS, Catana AM, Wegermann K, Carr RM, Aloman C, Chen VL, Rabiee A, Sadowski B, Nguyen V, Dunn W, Chavin KD, Zhou K, Lizaola-Mayo B, Moghe A, Debes J, Lee TH, Branch AD, Viveiros K, Chan W, Chascsa DM, Kwo P, Dhanasekaran R. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2021; **19**: 1469-1479.e19 [PMID: 32950749 DOI: 10.1016/j.cgh.2020.09.027]
40 **Moon AM**, Curtis B, Mandrekar P, Singal AK, Verna EC, Fix OK. Alcohol-Associated Liver Disease Before and After

COVID-19-An Overview and Call for Ongoing Investigation. *Hepatol Commun* 2021; **5**: 1616-1621 [PMID: 34510833 DOI: 10.1002/hep4.1747]

41 **Wang Q**, Davis PB, Xu R. COVID-19 risk, disparities and outcomes in patients with chronic liver disease in the United States. *EClinicalMedicine* 2021; **31**: 100688 [PMID: 33521611 DOI: 10.1016/j.eclinm.2020.100688]

42 **Yip TC**, Gill M, Wong GL, Liu K. Management of hepatitis B virus reactivation due to treatment of COVID-19. *Hepatol Int* 2022; **16**: 257-268 [PMID: 35235148 DOI: 10.1007/s12072-022-10306-x]

43 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

44 **Zhang B**, Huang W, Zhang S. Clinical Features and Outcomes of Coronavirus Disease 2019 (COVID-19) Patients With Chronic Hepatitis B Virus Infection. *Clin Gastroenterol Hepatol* 2020; **18**: 2633-2637 [PMID: 32553905 DOI: 10.1016/j.cgh.2020.06.011]

45 **Chen L**, Huang S, Yang J, Cheng X, Shang Z, Lu H, Cheng J. Clinical characteristics in patients with SARS-CoV-2/HBV co-infection. *J Viral Hepat* 2020; **27**: 1504-1507 [PMID: 32668494 DOI: 10.1111/jvh.13362]

46 **Yip TC**, Wong VW, Lui GC, Chow VC, Tse YK, Hui VW, Liang LY, Chan HL, Hui DS, Wong GL. Current and Past Infections of HBV Do Not Increase Mortality in Patients With COVID-19. *Hepatology* 2021; **74**: 1750-1765 [PMID: 33961298 DOI: 10.1002/hep.31890]

47 **Chen X**, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, Mo P, Yao L, Yang R, Gao S, Gui X, Hou W, Xiong Y, Li J, Zhang Y. Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 and Hepatitis B Virus Co-infection. *Virol Sin* 2020; **35**: 842-845 [PMID: 32839868 DOI: 10.1007/s12250-020-00276-5]

48 **Zou X**, Fang M, Li S, Wu L, Gao B, Gao H, Ran X, Bian Y, Li R, ShanshanYu, Ling J, Li D, Tian D, Huang J. Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection. *Clin Gastroenterol Hepatol* 2021; **19**: 597-603 [PMID: 32553907 DOI: 10.1016/j.cgh.2020.06.017]

49 **Myint A**, Tong MJ, Beaven SW. Reactivation of Hepatitis B Virus: A Review of Clinical Guidelines. *Clin Liver Dis (Hoboken)* 2020; **15**: 162-167 [PMID: 32395244 DOI: 10.1002/cld.883]

50 **Aldhaleei WA**, Alnuaimi A, Bhagavathula AS. COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case From the United Arab Emirates. *Cureus* 2020; **12**: e8645 [PMID: 32550096 DOI: 10.7759/cureus.8645]

51 **Lau G**, Yu ML, Wong G, Thompson A, Ghazinian H, Hou JL, Piratvisuth T, Jia JD, Mizokami M, Cheng G, Chen GF, Liu ZW, Baatarkhuu O, Cheng AL, Ng WL, Lau P, Mok T, Chang JM, Hamid S, Dokmeci AK, Gani RA, Payawal DA, Chow P, Park JW, Strasser SI, Mohamed R, Win KM, Tawesak T, Sarin SK, Omata M. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. *Hepatol Int* 2021; **15**: 1031-1048 [PMID: 34427860 DOI: 10.1007/s12072-021-10239-x]

52 **Sagnelli C**, Montella L, Grimaldi P, Pisaturo M, Alessio L, De Pascalis S, Sagnelli E, Coppola N. COVID-19 as Another Trigger for HBV Reactivation: Clinical Case and Review of Literature. *Pathogens* 2022; **11** [PMID: 35890060 DOI: 10.3390/pathogens11070816]

53 **Wu YF**, Yu WJ, Jiang YH, Chen Y, Zhang B, Zhen RB, Zhang JT, Wang YP, Li Q, Xu F, Shi YJ, Li XP. COVID-19 or treatment associated immunosuppression may trigger hepatitis B virus reactivation: A case report. *World J Clin Cases* 2021; **9**: 5266-5269 [PMID: 34307577 DOI: 10.12998/wjcc.v9.i19.5266]

54 **Dufour JF**, Marjot T, Becchetti C, Tilg H. COVID-19 and liver disease. *Gut* 2022; **71**: 2350-2362 [PMID: 35701093 DOI: 10.1136/gutjnl-2021-326792]

55 **Ronderos D**, Omar AMS, Abbas H, Makker J, Baiomi A, Sun H, Mantri N, Choi Y, Fortuzi K, Shin D, Patel H, Chilimuri S. Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality. *World J Clin Cases* 2021; **9**: 8749-8762 [PMID: 34734053 DOI: 10.12998/wjcc.v9.i29.8749]

56 **Lensen R**, Netea MG, Rosendaal FR. Hepatitis C Virus Reactivation Following COVID-19 Vaccination-A Case Report. *Int Med Case Rep J* 2021; **14**: 573-576 [PMID: 34512037 DOI: 10.2147/IMCRJ.S328482]

57 **Butt AA**, Yan P, Chotani RA, Shaikh OS. Mortality is not increased in SARS-CoV-2 infected persons with hepatitis C virus infection. *Liver Int* 2021; **41**: 1824-1831 [PMID: 33534931 DOI: 10.1111/Liv.14804]

58 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]

59 **Vrsaljko N**, Samadan L, Viskovic K, Mehmedović A, Budimir J, Vince A, Papic N. Association of Nonalcoholic Fatty Liver Disease With COVID-19 Severity and Pulmonary Thrombosis: CovidFAT, a Prospective, Observational Cohort Study. *Open Forum Infect Dis* 2022; **9**: ofac073 [PMID: 35287335 DOI: 10.1093/ofid/ofac073]

60 **Asemota J**, Aduli F. The Impact of Nonalcoholic Fatty Liver Disease on the Outcomes of Coronavirus Disease 2019 Infection. *Clin Liver Dis (Hoboken)* 2022; **19**: 29-31 [PMID: 35106147 DOI: 10.1002/cld.1169]

61 **Singh A**, Hussain S, Antony B. Non-alcoholic fatty liver disease and clinical outcomes in patients with COVID-19: A comprehensive systematic review and meta-analysis. *Diabetes Metab Syndr* 2021; **15**: 813-822 [PMID: 33862417 DOI: 10.1016/j.dsx.2021.03.019]

62 **Targher G**, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, Pan KH, Zheng KI, Chen YP, Eslam M, George J, Zheng MH. Detrimental effects of metabolic dysfunction-associated fatty liver disease and increased neutrophil-to-lymphocyte ratio on severity of COVID-19. *Diabetes Metab* 2020; **46**: 505-507 [PMID: 32505652 DOI: 10.1016/j.diabet.2020.06.001]

63 **Ghoneim S**, Butt MU, Hamid O, Shah A, Asaad I. The incidence of COVID-19 in patients with metabolic syndrome and non-alcoholic steatohepatitis: A population-based study. *Metabol Open* 2020; **8**: 100057 [PMID: 32924000 DOI: 10.1016/j.metop.2020.100057]

64 **Nath P**, Kumar R, Mallick B, Das S, Anand A, Panigrahi SC, Duseja A, Acharya SK, Chawla YK, Praharaj DL. Effect of Nonalcoholic Fatty Liver Disease (NAFLD) on COVID-19: A Single-Center Study of 3983 Patients With Review of Literature. *Cureus* 2022; **14**: e26683 [PMID: 35949776 DOI: 10.7759/cureus.26683]

65 **Madan K**, Rastogi R, Bhargava R, Dagar V, Singla V, Sahu A, Singh P, Garg P, Aggarwal B, Singh RK. Is Fatty Liver Associated with Increased Mortality and Morbidity in Coronavirus Disease 2019 (COVID-19) Pneumonia? *J Clin Exp Hepatol* 2022; **12**: 1320-1327 [PMID: 35469129 DOI: 10.1016/j.jceh.2022.04.013]

66 **Malas MB**, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine* 2020; **29**: 100639 [PMID: 33251499 DOI: 10.1016/j.eclinm.2020.100639]

67 **Targher G**, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, Pan KH, Zheng KI, Chen YP, Eslam M, George J, Zheng MH. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut* 2020; **69**: 1545-1547 [PMID: 32414813 DOI: 10.1136/gutjnl-2020-321611]

68 **Marjot T**, Buescher G, Sebode M, Barnes E, Barritt AS 4th, Armstrong MJ, Baldelli L, Kennedy J, Mercer C, Ozga AK, Casar C, Schramm C; contributing Members and Collaborators of ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis, Moon AM, Webb GJ, Lohse AW. SARS-CoV-2 infection in patients with autoimmune hepatitis. *J Hepatol* 2021; **74**: 1335-1343 [PMID: 33508378 DOI: 10.1016/j.jhep.2021.01.021]

69 **Gerussi A**, Rigamonti C, Elia C, Cazzagon N, Floreani A, Pozzi R, Pozzoni P, Claar E, Pasulo L, Fagiuoli S, Cristoferi L, Carbone M, Invernizzi P. Coronavirus Disease 2019 in Autoimmune Hepatitis: A Lesson From Immunosuppressed Patients. *Hepatol Commun* 2020; **4**: 1257-1262 [PMID: 32838102 DOI: 10.1002/hep4.1557]

70 **Ekpanyapong S**, Bunchorntavakul C, Reddy KR. COVID-19 and the Liver: Lessons Learnt from the EAST and the WEST, A Year Later. *J Viral Hepat* 2022; **29**: 4-20 [PMID: 34352133 DOI: 10.1111/jvh.13590]

71 **Chan SL**, Kudo M. Impacts of COVID-19 on Liver Cancers: During and after the Pandemic. *Liver Cancer* 2020; **9**: 491-502 [PMID: 33078127 DOI: 10.1159/000510765]

72 **Pomej K**, Scheiner B, Hartl L, Balcar L, Meischl T, Mandorfer M, Reiberger T, Müller C, Trauner M, Pinter M. COVID-19 pandemic: Impact on the management of patients with hepatocellular carcinoma at a tertiary care hospital. *PLoS One* 2021; **16**: e0256544 [PMID: 34437610 DOI: 10.1371/journal.pone.0256544]

73 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]

74 **Gupta T**. COVID-19 and liver disease: Are we missing something? *World J Hepatol* 2022; **14**: 479-481 [PMID: 35317182 DOI: 10.4254/wjh.v14.i2.479]

75 **Kukla M**, Skonieczna-Żydecka K, Kotfis K, Maciejewska D, Łoniewski I, Lara LF, Pazgan-Simon M, Stachowska E, Kaczmarczyk M, Koulaouzidis A, Marlicz W. COVID-19, MERS and SARS with Concomitant Liver Injury-Systematic Review of the Existing Literature. *J Clin Med* 2020; **9**: 1420 [PMID: 32403255 DOI: 10.3390/jcm9051420]

76 **Nathani P**, Gopal P, Rich N, Yopp A, Yokoo T, John B, Marrero J, Parikh N, Singal AG. Hepatocellular carcinoma tumour volume doubling time: a systematic review and meta-analysis. *Gut* 2021; **70**: 401-407 [PMID: 32398224 DOI: 10.1136/gutjnl-2020-321040]

77 **Shiina S**, Gani RA, Yokosuka O, Maruyama H, Nagamatsu H, Payawal DA, Dokmeci AK, Lesmana LA, Tanwandee T, Lau G, Sarin SK, Omata M. APASL practical recommendations for the management of hepatocellular carcinoma in the era of COVID-19. *Hepatol Int* 2020; **14**: 920-929 [PMID: 33174159 DOI: 10.1007/s12072-020-10103-4]

78 **Inchingolo R**, Acquafredda F, Tedeschi M, Laera L, Surico G, Surgo A, Fiorentino A, Spiliopoulos S, de'Angelis N, Memeo R. Worldwide management of hepatocellular carcinoma during the COVID-19 pandemic. *World J Gastroenterol* 2021; **27**: 3780-3789 [PMID: 34321843 DOI: 10.3748/wjg.v27.i25.3780]

79 **Boettler T**, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2**: 100113 [PMID: 32289115 DOI: 10.1016/j.jhepr.2020.100113]

80 **Pereira MR**, Arcasoy S, Farr MA, Mohan S, Emond JC, Tsapepas DS, Shi Q, Purpura L, Uhlemann AC, Zucker J, Verna EC. Outcomes of COVID-19 in solid organ transplant recipients: A matched cohort study. *Transpl Infect Dis* 2021; **23**: e13637 [PMID: 33993630 DOI: 10.1111/tid.13637]

81 **Bhatti ABH**, Nazish M, Khan NY, Manan F, Zia HH, Ilyas A, Ishtiaq W, Khan NA. Living Donor Liver Transplantation During the COVID-19 Pandemic: an Evolving Challenge. *J Gastrointest Surg* 2021; **25**: 3092-3098 [PMID: 34131867 DOI: 10.1007/s11605-021-05057-3]

82 **El Kassas M**, Alboraie M, Al Balakosy A, Abdeen N, Afify S, Abdalgaber M, Sherief AF, Madkour A, Abdellah Ahmed M, Eltabbakh M, Salaheldin M, Wifi MN. Liver transplantation in the era of COVID-19. *Arab J Gastroenterol* 2020; **21**: 69-75 [PMID: 32439237 DOI: 10.1016/j.ajg.2020.04.019]

83 **Chaudhry ZS**, Williams JD, Vahia A, Fadel R, Parraga Acosta T, Prashar R, Shrivastava P, Khoury N, Pinto Corrales J, Williams C, Nagai S, Abouljoud M, Samaniego-Picota M, Abreu-Lanfranco O, Del Busto R, Ramesh MS, Patel A, Alangaden GJ. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: A cohort study. *Am J Transplant* 2020; **20**: 3051-3060 [PMID: 32654332 DOI: 10.1111/ajt.16188]

84 **Molnar MZ**, Bhalla A, Azhar A, Tsujita M, Talwar M, Balaraman V, Sodhi A, Kadaria D, Eason JD, Hayek SS, Coca SG, Shaefi S, Neyra JA, Gupta S, Leaf DE, Kovesdy CP; STOP-COVID Investigators. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. *Am J Transplant* 2020; **20**: 3061-3071 [PMID: 32844546 DOI: 10.1111/ajt.16280]

85 **CMS Adult Elective Surgery and Procedures Recommendations**. [cited 20 September 2022]. Available from: https://www.cms.gov/files/document/covid-elective-surgery-recommendations.pdf

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 467-476

DOI: 10.5501/wjv.v11.i6.467

ISSN 2220-3249 (online)

MINIREVIEWS

Potential risk of liver injury in epileptic patients during COVID-19 pandemic

Nasim Tabrizi, Athena Sharifi-Razavi

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kar SK, India; Parvizpour F, Iran

Received: September 13, 2022
Peer-review started: September 13, 2022
First decision: September 29, 2022
Revised: October 8, 2022
Accepted: October 27, 2022
Article in press: October 27, 2022
Published online: November 25, 2022

Nasim Tabrizi, Athena Sharifi-Razavi, Department of Neurology, Mazandaran University of Medical Sciences, Sari 4815838477, Iran

Corresponding author: Athena Sharifi-Razavi, MD, Assistant Professor, Department of Neurology, Mazandaran University of Medical Sciences, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari 4815838477, Iran. athena.sharifi@yahoo.com

Abstract

Most of the antiseizure medications (ASMs) are metabolized in liver and many of them particularly first-generation ASMs have the potential to increase liver enzymes or induce liver injury. Hence, treatment of new onset seizures or epilepsy by ASMs during the course of coronavirus disease 2019 (COVID-19), which could potentially be complicated by hepatic dysfunction, is a challenging clinical issue. Intravenous form of levetiracetam which has no significant hepatic metabolism or drug-drug interaction is often a favorable option to control seizures in acute phase of COVID-19. Administration of enzyme inducer ASMs and valproate with the well-known hepatotoxicity and common drug interactions is not generally recommended. In patients with epilepsy who are under control with potentially hepatotoxic ASMs, close observation and cautious dose reduction or drug switch should be considered if any evidence of hepatic impairment exists. However, risks of possible breakthrough seizures should be weighed against benefits of lowering the hazard of liver injury. In patients with epilepsy who receive polytherapy with ASMs, transient dose modification with the tendency to increase the dose of ASMs with more favorable safety profile and less drug interaction and decrease the dose of drugs with main hepatic metabolism, high protein binding, potential to cause liver injury and known drug-drug reaction should be considered. Finally, decision making should be individualized based on patients' conditions and course of illness.

Key Words: COVID-19; Epilepsy; Seizure; Drug induced liver injury; Corona virus; Hepatic failure

Core Tip: Most of antiseizure medications (ASMs) are metabolized in liver and many of them particularly first-generation ASMs have the potential to increase liver enzymes or induce liver injury. Hence, treatment of new onset seizures or epilepsy by ASMs during the course of coronavirus disease 2019 (COVID-19), which could potentially be complicated by hepatic dysfunction, is a challenging clinical issue. In this review, we aimed to discuss the potential risks of liver injury in patients with COVID-19 who are under treatment for epilepsy or need to receive ASMs to subside acute symptomatic seizures.

Citation: Tabrizi N, Sharifi-Razavi A. Potential risk of liver injury in epileptic patients during COVID-19 pandemic. *World J Virol* 2022; 11(6): 467-476
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/467.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.467

INTRODUCTION

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the globe, creating the coronavirus disease 2019 (COVID-19) pandemic[1]. Despite the advent of COVID-19 vaccines, the global pandemic continues[2,3]. Although, the lungs are the main target organs infected during COVID-19[4,5] and the initial reported symptoms of disease focused on the respiratory system[6]; this coronavirus can also invade multiple systems (immune and nervous systems) and target several organs and tissues (brain, liver, heart, lung, intestine, muscle, kidney, and gastrointestinal tract[3,7,8]). Liver is one of the most frequently impaired organs and elevation of serum aminotransferases has been recorded in some patients with COVID-19[9-11]. Most COVID-19 patients with liver dysfunction present elevations in one or more aminotransferases, with less than a three-fold increase from the normal values[12,13]. In most patients, liver injury seems to be self-limiting, neither requiring any specific intervention, nor is associated with acute liver failure[14,15]. Chen *et al*[4], in a retrospective study on 830 cases, reported 27.3% of the COVID-19 patients presented with mild abnormalities in the liver function and approximately 3.9% eventually developed liver insufficiency[4]. Yip *et al*[16], reported 23% elevation of liver enzymes and 2% acute liver injury in a cohort study of 1040 patients[16]. In another meta-analysis, approximately 25% of COVID-19 patients experienced elevation of liver enzymes which was directly correlated to the severity of COVID-19 disease[17]. Liver dysfunction could also increase the mortality rate in these patients[18].

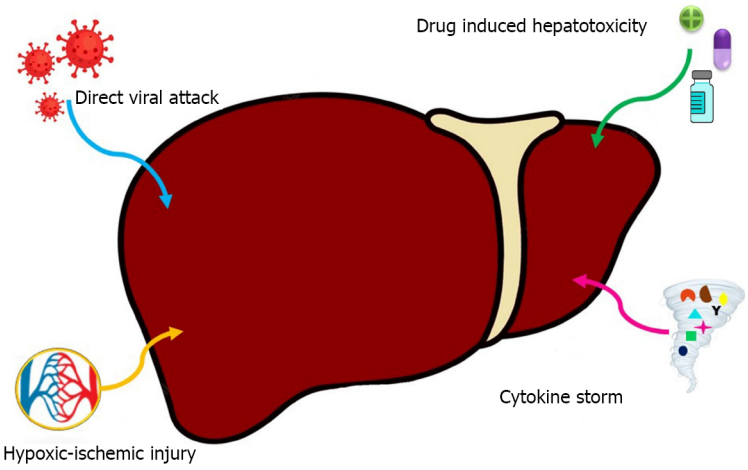
Possible mechanisms of liver injury are complex and include direct viral attack, hypoxic/ischemic injury, COVID-19 hyperinflammatory response and potential hepatotoxicity from therapeutic drugs[19,20] (Figure 1).

With the advent of the COVID-19, another health burden involved around 50 million people with epilepsy worldwide[21]. Epilepsy does not make patients more vulnerable to COVID-19 or its severe manifestations[22]. But, management of COVID-19 in patients with epilepsy needs special considerations. Many antiseizure medications (ASMs) have interactions with drugs commonly used for treatment of COVID-19[23]. Many patients with autoimmune epilepsy are under treatment with corticosteroids and other immunosuppressive drugs which might affect the defense ability of immune system[24]. On the other hand, seizure and status epilepticus as neurological manifestations of COVID-19 have been reported in patients with and without epilepsy[25-29]. In certain types of epilepsy particularly Dravet syndrome, fever might trigger seizures. Meanwhile, usual antipyretic and antihistaminic medications might lower seizure threshold in patients with epilepsy[24].

Most of the ASMs have hepatic metabolism and many of them especially older ASMs have the potential to increase hepatic enzymes or cause severe liver injury[30]. Treatment with these ASMs in patients with COVID-19 who have a potential predisposition to hepatic dysfunction, should proceed cautiously considering certain characteristics of medications and disease course. In this review, we aimed to discuss the potential risks of liver injury in patients with COVID-19 who are under treatment for epilepsy or need to receive ASMs to subside acute symptomatic seizures.

ACUTE SYMPTOMATIC SEIZURE DURING THE COURSE OF COVID-19

Several mechanisms might be involved in occurrence of acute symptomatic seizures during COVID-19 infection. SARS-CoV-2 could directly invade central nervous system by targeting angiotensin-converting-enzyme-2 (ACE-2) receptor and consequent meningoencephalitis could be a potential etiology of seizure[31-34]. Also, three indirect mechanisms including down-regulation of ACE-2 expression, cytokine storm and hypoxia could precipitate seizures[31]. Metabolic derangement and organ failure are among the other possible causes of seizure in patients with COVID-19. Detection and management of etiology often need serum metabolic and electrolyte investigation, cerebrospinal fluid



DOI: 10.5501/wjv.v11.i6.467

Figure 1 Hepatic injury mechanism in coronavirus disease 2019.

analysis and brain imaging[28]. Short-term use of ASMs is often recommended to manage seizures in acute phase of COVID-19[35]. However, judicious selection of the ASMs is necessary to prevent exacerbation of organ failure, particularly liver dysfunction and also to decrease the possible drug interactions.

Moreover, new-onset refractory status epilepticus with a mortality rate of 10% to 20% has been reported secondary to COVID-19. Considering the undesirable response to ASMs, plasma exchange, intravenous immunoglobulin, steroids and immunosuppressives have been used for management of these patients with different success rates. There is no definite approach to manage these patients and the suggested treatment algorithm should be modified individually based on patient's conditions[29].

EPILEPSY AND COVID-19

The COVID-19 pandemic has had several negative impacts on patients with epilepsy, which are beyond the scope of this paper. In patients with epilepsy who experience COVID-19 infection, breakthrough seizures might occur for at least three reasons. Firstly, predisposing factors such as sepsis, sleep deprivation, metabolic derangement and electrolyte imbalance along with previously mentioned direct and indirect mechanisms of acute phase seizures, could precipitate breakthrough seizures in patients with epilepsy[31]. Secondly, fever can trigger seizures in certain types of epilepsy particularly Dravet syndrome[24]. Finally, common medications used for treatment of COVID-19 could induce seizure *via* lowering seizure threshold or decreasing the efficacy of ASMs through drug-drug interaction[36]. Thus, recognition and addressing all possible causes are necessary to control the seizures and prevent the consequent morbidity and mortality. This point is of the greatest importance in patients with drug-resistant epilepsy.

Furthermore, previously used ASMs in patients with epilepsy, might need modifications when COVID-19 complications such as cardiac, hepatic or renal dysfunction occur. Dose adjustment of ASMs should be considered in patients with hepatic or renal impairment. On the other hand, drug switch or dose reduction might be necessary if ASMs have the potential to aggravate organ failure. However, the possible risk of uncontrolled seizures induced by changes in type and dose of ASMs, should be weighed against the benefits of modifications and it might be injudicious for some ASMs with a high risk of withdrawal seizure and status epilepticus such as barbiturates.

ASMS WITH THE HIGH POTENTIAL OF LIVER INJURY

Valproic acid

Valproate is a broad-spectrum ASM with a high bioavailability (90%) and high protein binding (74%-93%). It has several mechanisms of action including increase in gamma amino butyric acid (GABA) activity and blockage of voltage-gated Na+, Ca2+ and K+ channels. Valproate extensively metabolized in the liver *via* glucuronidation, β-oxidation and oxidation by cytochrome P450[37]. Valproate inhibits CYP2C9, uridine glucoronate-glucuronsyl transferase (UGT), and epoxide hydrolase[22]. Protease inhibitors, such as lopinavir/ritonavir could increase metabolism of valproate by induction of valproate glucuronidation[37]. In contrast, valproate decreases the plasma concentrations of darunavir/cobicistat and increases the concentrations of lopinavir/ritonavir[36]. Valproate has no significant interaction with

the other anti-COVID-19 drugs. However, there is a red flag for using this ASM in patients with abnormal liver function. Hepatotoxicity is a well-known adverse event of valproate[38]. It might occur through different mechanisms such as formation of valproate reactive metabolites, inhibition of fatty acid β-oxidation and excessive oxidative stress[39,40]. Valproate-induced liver injury has different degrees. The most common type is asymptomatic increase in liver enzymes. More than 3 times increase in liver function tests makes drug discontinuation necessary. The known risk factors for valproate hepatotoxicity are young age, polytherapy, developmental delay, metabolic disorders, febrile illness and polymerase gamma 1 related disorders[38]. Furthermore, valproate can cause hyperammonemic encephalopathy which presents as progressive confusional state leading to coma[41,42]. This condition could easily be neglected in a critically ill patient with COVID-19.

In conclusion, despite the high efficacy in treatment of various type of seizures, factors including possible drug interaction, potential to cause liver injury, exacerbation of underlying liver dysfunction and induction of hyperammonemia, have limited the use of valproate as the first line treatment in patients with COVID-19 and new onset seizures. However, in patients with epilepsy and COVID-19 who were under control by valproate, decision making is more challenging. The clinician might choose not to switch the medication at the first step; but the possibility of interaction with mentioned anti-COVID drugs should be closely observed by therapeutic drug monitoring. In addition, in case of any evidence of liver dysfunction, there should be a low threshold to lower the dose or switch the drug.

Cytochrome p450 inducers

Phenytoin, carbamazepine, phenobarbital and primidone are among the first generation of ASMs. Their strong potential to induce various cytochrome p450 enzymes often causes several drug-drug interactions[43-46].

Phenytoin

Phenytoin is one of the oldest ASMs which plays its antiseizure role by enhancing rapid inactivation of voltage-gated sodium channels[47]. Phenytoin has a high protein binding (> 90%) and 70%-100% bioavailability. It is metabolized by CYP2C9 and CYP2C19 hepatic isoenzymes.

It induces CYP1A2, CYP2B, CYP2C, CYP3A4, and UGT[22]. Phenytoin significantly decreases the serum concentration of atazanavir, darunavir/cobicistat, remdesivir, chloroquine and hydroxychloroquine and has a potential to decrease serum level of lopinavir/ritonavir. Nitazoxanide partially increases and tocilizumab weakly decreases the serum concentration of phenytoin. Phosphenytoin, the water-soluble prodrug of phenytoin has the same drug-drug interactions[36].

Hepatotoxicity is a well-known adverse effect of phenytoin which probably occurs through increase in reactive oxygen species formation and cellular oxidized glutathione, decrease in intracellular reduced glutathione, enhancement of lipid peroxidation and mitochondrial damage[48,49]. Phenytoin-induced liver injury could have a broad spectrum from mild asymptomatic elevation in liver function tests to severe hepatotoxicity which is often associated with hypersensitivity reactions[37,48,50,51]. Although the cosmetic and systemic adverse events have limited its use in chronic epilepsy, phenytoin is commonly used to abort focal and generalized seizures and also status epilepticus in emergency department[52,53]. However, it is not a good option to control seizures in patients with COVID-19. Phenytoin might cause cardiorespiratory depression which is potentially harmful in critically ill patients, elderly and underlying cardiac disease[54]. The potential for hepatotoxicity and increase in free drug level in hepatic and renal impairment[55] also limited its use in COVID-19. Moreover, significant dug-drug reaction with anti-COVID-19 agents could be challenging.

Carbamazepine

Carbamazepine is an effective ASM with a high bioavailability (75%-85%) and high protein binding (70%-80%). Its mechanism of action is similar to phenytoin. Carbamazepine is metabolized in liver by CYP3A4 and CYP2C8 enzymes[37]. It induces CYP1A2, CYP2C, CYP3A4 and UGT[22] and so, has multiple drug-drug interactions with anti-COVID medications. It significantly decreases the serum concentration of atazanavir, darunavir/cobicistat, remdesivir, chloroquine and hydroxychloroquine. Co-administration of carbamazepine with lopinavir/ritonavir also might lead to decrease in serum level of anti-COVID agent. Atazanavir, darunavir/cobicistat and lopinavir/ritonavir could increase serum concentration of carbamazepine and cause toxicity. In addition, tocilizumab has the potential to decrease carbamazepine concentration[36].

In a report of ASM-induced liver injury by FDA, carbamazepine had the highest odds ratio (2.92) among the other ASMs of first generation[30] and hepatotoxicity is a well-known adverse effect of this potent ASM[56]. Metabolic activation and following immune responses are reported as possible mechanisms of carbamazepine-induced liver injury[57].

Carbamazepine has no parenteral formulation and needs about 3 to 5 wk to reach the steady state. So, it is not commonly used for treatment of seizures in acute phase. However, many of patients with epilepsy are under treatment with this ASM. When comorbidity with COVID-19 occurs in these patients, higher doses of antiviral agents might be needed to compensate the decrement of serum concentration caused by carbamazepine. On the other hand, patients should be closely observed for sign

and symptoms of carbamazepine toxicity in co-administration of atazanavir, darunavir/cobicistat and lopinavir/ritonavir. In critical patients with increased liver enzymes, reduction of carbamazepine dosage is generally recommended to prevent harmful increase in carbamazepine concentration and also further liver damage.

Phenobarbital and primidone

Phenobarbital, one of the first ASMs used to manage epilepsy, is of limited use currently. But it is still recommended as an alternative therapy in first and second line management of status epilepticus. Phenobarbital is also prescribed in some patients with epilepsy especially in countries with limited resources[58]. It plays its antiseizure role by affecting GABA-A receptors which leads to increase in chloride ions and consequently reduction of neuronal excitability. Phenobarbital has a high bioavailability (> 90%) and moderate protein binding (55%)[59].

Primidone is another old ASM which affects synaptic and extrasynaptic GABA receptors[42]. It is metabolized to phenobarbital and phenylethylmalonamide by CYP2C9, CYP2C19, and CYP2E1 enzymes[22]. Primidone is still prescribed for patients with epilepsy; but it has some other certain indications such as essential tremor as well[60]. It has a high bioavailability (> 90%) with a low plasma protein binding (10%)[59]. Phenobarbital and primidone induce CYP1A2, CYP2A6, CYP2B, CYP2C, CYP3A4, and UGT. Similar to other enzyme inducer ASMs, these two drugs considerably decrease the serum concentration of atazanavir, darunavir/cobicistat, remdesivir, chloroquine and hydroxychloroquine and could possibly decrease serum level of lopinavir/ritonavir. Darunavir/cobicistat significantly decreases the serum concentration of phenobarbital, but has no effect on primidone. Lopinavir/ritonavir might decrease primidone level[36].

Phenobarbital can cause large spectrum of hepatic adverse effects which could be various from asymptomatic increase in liver enzymes, to devastating hepatitis and acute liver failure. A possible mechanism of liver injury by phenobarbital is oxidative stress in hepatic mitochondria[38,61,62]. Due to availability of newer effective ASMs with more favorable safety profile in recent decade, phenobarbital has been less frequently administered in acute phase seizures. IV phenobarbital has the potential to cause cardiorespiratory depression[63] and elevation of liver enzymes[38] in critically ill patients with COVID-19 who are potentially in a compromised respiratory and hepatic state. Hence, phenobarbital is an inappropriate choice for treatment of seizures in COVID-19. In patients with epilepsy who are under treatment with phenobarbital and primidone, serious drug-drug interaction with anti-COVID-19 agents should be considered. Since, rapid taper and switch of these 2 drugs are impossible due to high risk of withdrawal seizure and status epilepticus, they should be continued cautiously with slight dose reduction in hepatic impairment and therapeutic drug monitoring. According dose modification of anti-COVID agents is also indispensable.

TREATMENT OF SEIZURES IN PATIENTS WITH LIVER INJURY

Several factors should be considered in treatment of seizures in acute phase of COVID-19. The selected ASM/ASMs should have the parenteral formulation to achieve a rapid appropriate serum level. The safety profile and low risk for systemic adverse effects are also very important; particularly if the disease course is already complicated with organ failure. Most of ASMs have hepatic metabolism and many of them could potentially cause hepatotoxicity which makes judicious selection and dose modification necessary. Moreover, several drug-drug interactions are expected between ASMs and anti-COVID drugs which could form a more complicated clinical scenario. The possible drug-drug interactions of common ASMs and anti-COVID-19 agents have been summarized in Table 1.

Levetiracetam, lorazepam, gabapentin, vigabatrin and pregabalin are ASMs which have no interaction with anti-COVID drugs[36]. Among these ASMs, only levetiracetam and lorazepam have the parenteral form. IV lorazepam is the first line treatment to abort generalized convulsive seizure[64]. Benzodiazepines predominantly have hepatic metabolism. Metabolism of lorazepam is not significantly affected by liver dysfunction and the possibility of liver injury is very low with its administration[65]. However, it might cause transient respiratory depression and exacerbation of hepatic encephalopathy [22]. So, cautious use of lorazepam is acceptable for first-line treatment of seizure; but it could not be used as maintenance therapy to prevent further seizures.

Levetiracetam is an efficient broad spectrum ASM which is commonly used in treatment of epilepsy, acute phase seizures and status epilepticus[66-69]. It has a high bioavailability (> 95%) and a very low protein binding (< 10%). Less than 2% of levetiracetam is metabolized in liver which makes it a safe drug with no significant pharmacokinetic interaction[22]. It is postulated that levetiracetam mainly presents its antiseizure effect by targeting the synaptic vesicle glycoprotein SV2A[70]. Levetiracetam is a safe ASM for patients with liver dysfunction. There are very rare reports of levetiracetam-induced liver injury and elevation of liver enzymes[30]. No significant difference in pharmacokinetic of levetiracetam is expected in patients with mild to moderate hepatic impairment. But 50% reduction in total dose is recommended due to decreased drug clearance in patients with severe hepatic failure (Child-Pugh Class C)[65]. Overall, IV formulation of levetiracetam is a safe and efficient choice for treatment of acute onset

Table 1 Drug-drug interaction between antiseizure medications and anti-coronavirus disease 2019 agents

	ATV	DRV/c	LPV/r	RDV	FAV	HCLQ/CLQ	TCZ	IFN-β-1α
Brivaracetam	Mi	-	Mi	-	-	Mo	-	-
Carbamazepine	S	S	Mo	S	-	S	Mi	Mo
Clobazam	Mo	Mo	Mo	-	-	-	-	-
Diazepam	Mo	Mo	Mo	-	-	-	-	-
Eslicarbazepine	Mo	Mo	Mo	Mo	-	Mo	-	-
Ethosuximide	Mo	Mo	Mo	-	-	-	-	-
Gabapentin	-	-	-	-	-	-	-	-
Lacosamide	Mi	Mo	Mi	-	-	-	-	-
Lamotrigine	-	Mo	Mo	-	-	-	-	-
Levetiracetam	-	-	-	-	-	-	-	-
Lorazepam	-	-	-	-	-	-	-	-
Oxcarbazepine	Mo	Mo	Mo	Mo	-	Mo	-	Mo
Perampanel	Mo	Mo	Mo	-	-	-	-	-
Phenytoin	S	S	Mo	S	-	S	Mi	Mo
Phenobarbital	S	S	Mo	S	-	S	Mi	Mo
Pregabalin	-	-	-	-	-	-	-	-
Primidone	S	S	Mo	S	-	S	Mi	-
Rufinamide	Mo	Mo	Mo	Mo	-	Mo	-	-
Topiramate	-	Mo	-	-	-	-	-	-
Valproic acid	-	Mo	Mo	-	-	-	-	Mo
Vigabatrin	-	-	-	-	-	-	-	-
Zonisamide	-	Mo	-	-	-	-	-	-

ATV: Atazanavir; DRV/c: Darunavir/cobicistat; LPV/r: Lopinavir/ritonavir; RDV: Remdesivir; FAV: Favipiravir; HCLQ/CLQ: Hydroxychloroquine/chloroquine; TCZ: Tocilizumab; IFN-β-1α: Interferon β-1α; S: Severe interaction, medications should not be co-administered; Mo: Moderate interaction, dose adjustment or close monitoring is required; Mi: Mild interaction, the need for dose adjustment or monitoring is unlikely.

seizures in COVID-19.

Eslicarbazepine acetate, oxcarbazepine, lacosamide, lamotrigine, clobazam, perampanel, rufinamide, tiagabine, topiramate, and zonisamide have mild to moderate interaction with anti-COVID drugs[22]. Among these ASMs, lacosamide is available in IV form and commonly has been used in treatment of seizure and status epilepticus[71,72]. Lacosamide has an almost complete bioavailability and a very low (< 15%) protein binding. It is metabolized to inactive O-desmethyl derivatives by CYP2C19 in liver[37]. Lacosamide enhances the slow inactivation of voltage-gated sodium channels[73]. In patients with mild to moderate hepatic impairment, reduction to 75% of maximum dose is recommended. But, lacosamide should not be administered in patients with severe hepatic dysfunction. Lacosamide-induced liver injury has not been reported in the literature[30]. So, IV lacosamide is an appropriate choice for aborting seizure in patients with epilepsy and COVID-19; but dose adjustment in hepatic dysfunction, interaction with darunavir/cobicistat and potential PR prolongation in coadministration with atazanavir and lopinavir/ritonavir should be cautiously considered[22].

Among previously mentioned ASMs with the higher probability of liver injury, IV formulations of valproate, phenytoin and phenobarbital are available. However, use of these ASMs should be limited to special conditions such as unavailability of new generation ASMs and refractoriness of seizures.

TREATMENT OF EPILEPSY IN PATIENTS WITH LIVER INJURY

Many patients with epilepsy need long-term treatment with ASMs and drug withdrawal or switch might lead to breakthrough seizures or status epilepticus for them. Since, anti-COVID drugs-which have the most interaction with ASMs-are generally administered for a short course, mild to moderate drug-

drug interactions could be cautiously managed by close observation, therapeutic drug monitoring and dose modifications. However, concurrent administration of drugs with severe interactions is not recommended. In these cases, the medical team should evaluate the risk and benefits of choosing a safer anti-COVID drug over switching the ASM.

In patients with controlled epilepsy who suffer from liver dysfunction during COVID-19 infection, appropriate dose adjustment of ASMs is the first step[22]. This approach could prevent serum concentration of drugs to reach the toxic level and also could protect liver from further injury. In this stage, there should be a low threshold to reduce the dose or switch ASMs with a high potential of hepatotoxicity. In patients with drug-resistant epilepsy or those who are on polytherapy with ASMs, transient dose reduction of hepatotoxic drugs and increase in dose of ASMs with more favorable profile might help the patients to pass the critical course without experiencing breakthrough seizures.

However, if severe liver injury occurs, some ASMs should be inevitably discontinued. Appropriate replacement of these drugs by safer ASMs such as levetiracetam could prevent seizure recurrence and subsequent complications.

CONCLUSION

COVID-19 pandemic has affected many people all over the world. Liver injury is a well-known complication of this infection and have an impact on management of patients with comorbidities. Particularly, management of seizure and epilepsy in patients with COVID-19 and liver injury could be challenging. Certain considerations should be taken in account in selection of ASMs for patients with new-onset seizures. Avoidance of ASMs with potential of hepatotoxicity, reasonable dose adjustment and monitoring of drug interactions with anti-COVID-19 drugs are necessary. Furthermore, in patients with epilepsy, cautious changes in dose and type of previously used ASMs are sometimes necessary. The possibility of drug-drug interactions along with the other comorbidities of patients should also be considered. Decision making by a medical team consists of different related specialties is often necessary to choose the best treatment method for the patients.

FOOTNOTES

Author contributions: Sharifi-Razavi A designed the outline, coordinated the writing of the paper and wrote first draft of manuscript; Tabrizi N searched the literature, revised first draft and wrote final manuscript.

Conflict-of-interest statement: Nasim Tabrizi and Athena Sharifi-Razavi are faculty member of Mazandaran University of Medical Sciences.

Country/Territory of origin: Iran

ORCID number: Nasim Tabrizi 0000-0001-7978-2014; Athena Sharifi-Razavi 0000-0003-3861-9741.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Sasanejad P**, Afshar Hezarkhani L, Arsang-Jang S, Tsivgoulis G, Ghoreishi A, Barlinn K, Rahmig J, Farhoudi M, Sadeghi Hokmabadi E, Borhani-Haghighi A, Sariaslani P, Sharifi-Razavi A, Ghandehari K, Khosravi A, Smith C, Nilanont Y, Akbari Y, Nguyen TN, Bersano A, Yassi N, Yoshimoto T, Lattanzi S, Gupta A, Zand R, Rafie S, Pourandokht Mousavian S, Reza Shahsavaripour M, Amini S, Kamenova SU, Kondybayeva A, Zhanuzakov M, Macri EM, Nobleza COS, Ruland S, Cervantes-Arslanian AM, Desai MJ, Ranta A, Moghadam Ahmadi A, Rostamihosseinkhani M, Foroughi R, Hooshmandi E, Akhoundi FH, Shuaib A, Liebeskind DS, Siegler J, Romano JG, Mayer SA, Bavarsad Shahripour R, Zamani B, Woolsey A, Fazli Y, Mojtaba K, Isaac CF, Biller J, Di Napoli M, Azarpazhooh MR. Safety and Outcomes of Intravenous Thrombolytic Therapy in Ischemic Stroke Patients with COVID-19: CASCADE Initiative. *J Stroke Cerebrovasc Dis* 2021; **30**: 106121 [PMID: 34601242 DOI: 10.1016/j.jstrokecerebrovasdis.2021.106121]

2 **Jiang SX**, Schwab K, Enns R, Ko HH. Survey of the Impact of COVID-19 on Chronic Liver Disease Patient Care

Experiences and Outcomes. *J Can Assoc Gastroenterol* 2022; **18**: gwac022 [DOI: 10.1093/jcag/gwac022]
3 **Bouare N**, Minta DK, Dabo A, Gerard C. COVID-19: A pluralistic and integrated approach for efficient management of the pandemic. *World J Virol* 2022; **11**: 20-39 [PMID: 35117969 DOI: 10.5501/wjv.v11.i1.20]
4 **Chen F**, Chen W, Chen J, Xu D, Xie W, Wang X, Xie Y. Clinical features and risk factors of COVID-19-associated liver injury and function: A retrospective analysis of 830 cases. *Ann Hepatol* 2021; **21**: 100267 [PMID: 33053426 DOI: 10.1016/j.aohep.2020.09.011]
5 **Sharifi-Razavi A**, Karimi N, Zarvani A, Cheraghmakani H, Baghbanian SM. Ischemic stroke associated with novel coronavirus 2019: a report of three cases. *Int J Neurosci* 2021; **131**: 1243-1247 [PMID: 32543260 DOI: 10.1080/00207454.2020.1782902]
6 **Amiri HA**, Razavi AS, Tabrizi N, Cheraghmakani H, Baghbanian SM, Sedaghat-Chaijan M, Zarvani A, Ghazaeian M, Hosseinnataj A. The Effects of COVID-19 on Patients with Acute Ischemic and Hemorrhagic Stroke. *J Stroke Cerebrovasc Dis* 2022; **31**: 106512 [PMID: 35489184 DOI: 10.1016/j.jstrokecerebrovasdis.2022.106512]
7 **Sharifi-Razavi A**, Sedaghat Z, Baziboroun M, Karimi N. COVID-19 accompanied with intracerebral hemorrhage: A case series. *Arch Clin Infect Dis* 2020; **15**: e104877 [DOI: 10.5812/archcid.104877]
8 **John KJ**, Mishra AK, Ramasamy C, George AA, Selvaraj V, Lal A. Heart failure in COVID-19 patients: Critical care experience. *World J Virol* 2022; **11**: 1-19 [PMID: 35117968 DOI: 10.5501/wjv.v11.i1.1]
9 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]
10 **Mohammed SA**, Eid KM, Anyiam FE, Wadaaallah H, Muhamed MAM, Morsi MH, Dahman NBH. Liver injury with COVID-19: laboratory and histopathological outcome-systematic review and meta-analysis. *Egypt Liver J* 2022; **12**: 9 [PMID: 35096428 DOI: 10.1186/s43066-022-00171-6]
11 **Kumar R**, Kumar V, Arya R, Anand U, Priyadarshi RN. Association of COVID-19 with hepatic metabolic dysfunction. *World J Virol* 2022; **11**: 237-251 [PMID: 36188741 DOI: 10.5501/wjv.v11.i5.237]
12 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
13 **Yu D**, Du Q, Yan S, Guo XG, He Y, Zhu G, Zhao K, Ouyang S. Liver injury in COVID-19: clinical features and treatment management. *Virol J* 2021; **18**: 121 [PMID: 34108015 DOI: 10.1186/s12985-021-01593-1]
14 **Ghoda A**, Ghoda M. Liver Injury in COVID-19 Infection: A Systematic Review. *Cureus* 2020; **12**: e9487 [PMID: 32879813 DOI: 10.7759/cureus.9487]
15 **Jothimani D**, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol* 2020; **73**: 1231-1240 [PMID: 32553666 DOI: 10.1016/j.jhep.2020.06.006]
16 **Yip TC**, Lui GC, Wong VW, Chow VC, Ho TH, Li TC, Tse YK, Hui DS, Chan HL, Wong GL. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. *Gut* 2021; **70**: 733-742 [PMID: 32641471 DOI: 10.1136/gutjnl-2020-321726]
17 **Wijarnpreecha K**, Ungprasert P, Panjawatanan P, Harnois DM, Zaver HB, Ahmed A, Kim D. COVID-19 and liver injury: a meta-analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: 990-995 [PMID: 32639420 DOI: 10.1097/MEG.0000000000001817]
18 **Macías-Rodríguez RU**, Solís-Ortega AA, Ornelas-Arroyo VJ, Ruiz-Margáin A, González-Huezo MS, Urdiales-Morán NA, Román-Calleja BM, Mayorquín-Aguilar JM, González-Regueiro JA, Campos-Murguía A, Toledo-Coronado IV, Chapa-Ibargüengoitia M, Valencia-Peña B, Martínez-Cabrera CF, Flores-García NC. Prognostic performance of an index based on lactic dehydrogenase and transaminases for patients with liver steatosis and COVID-19. *World J Gastroenterol* 2022; **28**: 5444-5456 [DOI: 10.3748/wjg.v28.i37.5444]
19 **Zghal M**, Bouhamed M, Mellouli M, Triki M, Kallel R, Ayedi L, Boudawara TS, Makni S. Liver injury in COVID-19: pathological findings. *Pan Afr Med J* 2022; **41**: 56 [PMID: 35317475 DOI: 10.11604/pamj.2022.41.56.31114]
20 **McConnell MJ**, Kondo R, Kawaguchi N, Iwakiri Y. Covid-19 and Liver Injury: Role of Inflammatory Endotheliopathy, Platelet Dysfunction, and Thrombosis. *Hepatol Commun* 2022; **6**: 255-269 [PMID: 34658172 DOI: 10.1002/hep4.1843]
21 **GBD 2016 Epilepsy Collaborators**. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18**: 357-375 [PMID: 30773428 DOI: 10.1016/S1474-4422(18)30454-X]
22 **Asadi-Pooya AA**, Attar A, Moghadami M, Karimzadeh I. Management of COVID-19 in people with epilepsy: drug considerations. *Neurol Sci* 2020; **41**: 2005-2011 [PMID: 32594268 DOI: 10.1007/s10072-020-04549-5]
23 **Kuroda N**. Epilepsy and COVID-19: Updated evidence and narrative review. *Epilepsy Behav* 2021; **116**: 107785 [PMID: 33515934 DOI: 10.1016/j.yebeh.2021.107785]
24 **French JA**, Brodie MJ, Caraballo R, Devinsky O, Ding D, Jehi L, Jette N, Kanner A, Modi AC, Newton CR, Patel AA, Pennell PB, Perucca E, Sander JW, Scheffer IE, Singh G, Williams E, Wilmshurst J, Cross JH. Keeping people with epilepsy safe during the COVID-19 pandemic. *Neurology* 2020; **94**: 1032-1037 [PMID: 32327490 DOI: 10.1212/WNL.0000000000009632]
25 **Moriguchi T**, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N, Nakao A, Takeda M, Haro H, Inoue O, Suzuki-Inoue K, Kubokawa K, Ogihara S, Sasaki T, Kinouchi H, Kojin H, Ito M, Onishi H, Shimizu T, Sasaki Y, Enomoto N, Ishihara H, Furuya S, Yamamoto T, Shimada S. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020; **94**: 55-58 [PMID: 32251791 DOI: 10.1016/j.ijid.2020.03.062]
26 **Lu L**, Xiong W, Liu D, Liu J, Yang D, Li N, Mu J, Guo J, Li W, Wang G, Gao H, Zhang Y, Lin M, Chen L, Shen S, Zhang H, Sander JW, Luo J, Chen S, Zhou D. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. *Epilepsia* 2020; **61**: e49-e53 [PMID: 32304092 DOI: 10.1111/epi.16524]
27 **Dono F**, Nucera B, Lanzone J, Evangelista G, Rinaldi F, Speranza R, Troisi S, Tinti L, Russo M, Di Pietro M, Onofrj M,

Bonanni L, Assenza G, Vollono C, Anzellotti F, Brigo F. Status epilepticus and COVID-19: A systematic review. *Epilepsy Behav* 2021; **118**: 107887 [PMID: 33743344 DOI: 10.1016/j.yebeh.2021.107887]

28 **Asadi-Pooya AA**, Simani L, Shahisavandi M, Barzegar Z. COVID-19, de novo seizures, and epilepsy: a systematic review. *Neurol Sci* 2021; **42**: 415-431 [PMID: 33237493 DOI: 10.1007/s10072-020-04932-2]

29 **Arif A**, Chavarria Y, Qamar MA, Tebha SS, Butt M, Qamar K, Yosufi A. New-Onset Refractory Status Epilepticus Secondary to COVID-19 Infection in Adults: A Systematic Review. *Neuropsychiatr Dis Treat* 2022; **18**: 1951-1961 [PMID: 36065386 DOI: 10.2147/NDT.S381018]

30 **Kamitaki BK**, Minacapelli CD, Zhang P, Wachuku C, Gupta K, Catalano C, Rustgi V. Drug-induced liver injury associated with antiseizure medications from the FDA Adverse Event Reporting System (FAERS). *Epilepsy Behav* 2021; **117**: 107832 [PMID: 33626490 DOI: 10.1016/j.yebeh.2021.107832]

31 **Narula N**, Joseph R, Katyal N, Daouk A, Acharya S, Avula A, Maroun R. Seizure and COVID-19: association and review of potential mechanism. *Neurol Psychiatry Brain Res* 2020; **38**: 49-53 [PMID: 33071468 DOI: 10.1016/j.npbr.2020.10.001]

32 **Desforges M**, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, Talbot PJ. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses* 2020; **12**: 14 [PMID: 31861926 DOI: 10.3390/v12010014]

33 **Fotuhi M**, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimers Dis* 2020; **76**: 3-19 [PMID: 32538857 DOI: 10.3233/JAD-200581]

34 **Iroegbu JD**, Ifenatuoha CW, Ijomone OM. Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2. *Neurol Sci* 2020; **41**: 1329-1337 [PMID: 32424503 DOI: 10.1007/s10072-020-04469-4]

35 **Asadi-Pooya AA**. Seizures associated with coronavirus infections. *Seizure* 2020; **79**: 49-52 [PMID: 32416567 DOI: 10.1016/j.seizure.2020.05.005]

36 **Russo E**, Iannone L. 2020. Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19 patients. [cited 20 August 2022]. Available from: ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19.pdf

37 **Karaźniewicz-Łada M**, Główka AK, Mikulska AA, Główka FK. Pharmacokinetic Drug-Drug Interactions among Antiepileptic Drugs, Including CBD, Drugs Used to Treat COVID-19 and Nutrients. *Int J Mol Sci* 2021; **22** [PMID: 34502487 DOI: 10.3390/ijms22179582]

38 **Vidaurre J**, Gedela S, Yarosz S. Antiepileptic Drugs and Liver Disease. *Pediatr Neurol* 2017; **77**: 23-36 [PMID: 29097018 DOI: 10.1016/j.pediatrneurol.2017.09.013]

39 **Guo HL**, Jing X, Sun JY, Hu YH, Xu ZJ, Ni MM, Chen F, Lu XP, Qiu JC, Wang T. Valproic Acid and the Liver Injury in Patients with Epilepsy: An Update. *Curr Pharm Des* 2019; **25**: 343-351 [PMID: 30931853 DOI: 10.2174/1381612825666190329145428]

40 **Fu D**, Cardona P, Ho H, Watkins PB, Brouwer KLR. Novel Mechanisms of Valproate Hepatotoxicity: Impaired Mrp2 Trafficking and Hepatocyte Depolarization. *Toxicol Sci* 2019 [PMID: 31368504 DOI: 10.1093/toxsci/kfz154]

41 **Habhab SF**, Ulvin LB, Taubøll E, Svalheim S, Olsen KB, Horn MA, Heuser K. Influence of valproate-induced hyperammonemia on treatment decision in an adult status epilepticus cohort. *Epilepsy Behav* 2020; **111**: 107193 [PMID: 32759060 DOI: 10.1016/j.yebeh.2020.107193]

42 **Smith KM**, Britton JW, Hocker SE, Toledano M. Hyperammonemia in Patients With Status Epilepticus Treated With or Without Valproic Acid. *Neurologist* 2021; **26**: 80-82 [PMID: 33942787 DOI: 10.1097/NRL.0000000000000335]

43 **Kanner AM**, Bicchi MM. Antiseizure Medications for Adults With Epilepsy: A Review. *JAMA* 2022; **327**: 1269-1281 [PMID: 35380580 DOI: 10.1001/jama.2022.3880]

44 **Zaccara G**, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord* 2014; **16**: 409-431 [PMID: 25515681 DOI: 10.1684/epd.2014.0714]

45 **Brodie MJ**. Sodium Channel Blockers in the Treatment of Epilepsy. *CNS Drugs* 2017; **31**: 527-534 [PMID: 28523600 DOI: 10.1007/s40263-017-0441-0]

46 **Lee-Lane E**, Torabi F, Lacey A, Fonferko-Shadrach B, Harris D, Akbari A, Lyons RA, Rees MI, Sawhney I, Halcox J, Powell R, Pickrell WO. Epilepsy, antiepileptic drugs, and the risk of major cardiovascular events. *Epilepsia* 2021; **62**: 1604-1616 [PMID: 34046890 DOI: 10.1111/epi.16930]

47 **Patocka J**, Wu Q, Nepovimova E, Kuca K. Phenytoin - An anti-seizure drug: Overview of its chemistry, pharmacology and toxicology. *Food Chem Toxicol* 2020; **142**: 111393 [PMID: 32376339 DOI: 10.1016/j.fct.2020.111393]

48 **Björnsson E**. Hepatotoxicity associated with antiepileptic drugs. *Acta Neurol Scand* 2008; **118**: 281-290 [PMID: 18341684 DOI: 10.1111/j.1600-0404.2008.01009.x]

49 **Eghbal MA**, Taziki S, Sattari MR. Mechanisms of phenytoin-induced toxicity in freshly isolated rat hepatocytes and the protective effects of taurine and/or melatonin. *J Biochem Mol Toxicol* 2014; **28**: 111-118 [PMID: 24493665 DOI: 10.1002/jbt.21542]

50 **Wall M**, Baird-Lambert J, Buchanan N, Farrell G. Liver function tests in persons receiving anticonvulsant medications. *Seizure* 1992; **1**: 187-190 [PMID: 1344766 DOI: 10.1016/1059-1311(92)90024-u]

51 **Sasaki E**, Matsuo K, Iida A, Tsuneyama K, Fukami T, Nakajima M, Yokoi T. A novel mouse model for phenytoin-induced liver injury: involvement of immune-related factors and P450-mediated metabolism. *Toxicol Sci* 2013; **136**: 250-263 [PMID: 23986454 DOI: 10.1093/toxsci/kft184]

52 **Crawshaw AA**, Cock HR. Medical management of status epilepticus: Emergency room to intensive care unit. *Seizure* 2020; **75**: 145-152 [PMID: 31722820 DOI: 10.1016/j.seizure.2019.10.006]

53 **Nevitt SJ**, Marson AG, Tudur Smith C. Carbamazepine versus phenytoin monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev* 2019; **7**: CD001911 [PMID: 31318037 DOI: 10.1002/14651858.CD001911.pub4]

54 **Mathews SR**, Badyal DK, Mathew R. Phenytoin-induced bradycardia and hypotension. *Indian J Pharmacol* 2019; **51**: 120-122 [PMID: 31142948 DOI: 10.4103/ijp.IJP_254_17]

55 **Patsalos PN**, Spencer EP, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update.

Ther Drug Monit 2018; **40**: 526-548 [PMID: 29957667 DOI: 10.1097/FTD.0000000000000546]

56 **Pal R**, Singh K, Khan SA, Chawla P, Kumar B, Akhtar MJ. Reactive metabolites of the anticonvulsant drugs and approaches to minimize the adverse drug reaction. *Eur J Med Chem* 2021; **226**: 113890 [PMID: 34628237 DOI: 10.1016/j.ejmech.2021.113890]

57 **Higuchi S**, Yano A, Takai S, Tsuneyama K, Fukami T, Nakajima M, Yokoi T. Metabolic activation and inflammation reactions involved in carbamazepine-induced liver injury. *Toxicol Sci* 2012; **130**: 4-16 [PMID: 22790970 DOI: 10.1093/toxsci/kfs222]

58 **Farhat S**, Nasreddine W, Alsaadi T, Beydoun AA, Arabi M, Beydoun A. Treatment of generalized convulsive status epilepticus: An international survey in the East Mediterranean Countries. *Seizure* 2020; **78**: 96-101 [PMID: 32315955 DOI: 10.1016/j.seizure.2020.03.016]

59 **Hakami T**. Neuropharmacology of Antiseizure Drugs. *Neuropsychopharmacol Rep* 2021; **41**: 336-351 [PMID: 34296824 DOI: 10.1002/npr2.12196]

60 **Delgado N**, Berry DS, Hernandez DI, Louis ED. Prospective, longitudinal analysis of medication use in a cohort of elderly essential tremor cases. *J Neurol Sci* 2022; **442**: 120387 [PMID: 36041330 DOI: 10.1016/j.jns.2022.120387]

61 **Di Mizio G**, Gambardella A, Labate A, Perna A, Ricci P, Quattrone A. Hepatonecrosis and cholangitis related to long-term phenobarbital therapy: an autopsy report of two patients. *Seizure* 2007; **16**: 653-656 [PMID: 17574447 DOI: 10.1016/j.seizure.2007.05.008]

62 **Santos NA**, Medina WS, Martins NM, Rodrigues MA, Curti C, Santos AC. Involvement of oxidative stress in the hepatotoxicity induced by aromatic antiepileptic drugs. *Toxicol In Vitro* 2008; **22**: 1820-1824 [PMID: 18783732 DOI: 10.1016/j.tiv.2008.08.004]

63 **Byun JI**, Chu K, Sunwoo JS, Moon J, Kim TJ, Lim JA, Jun JS, Lee HS, Lee WJ, Lee DY, Jeon D, Lee ST, Jung KH, Jung KY, Lee SK. Mega-dose phenobarbital therapy for super-refractory status epilepticus. *Epileptic Disord* 2015; **17**: 444-452 [PMID: 26575689 DOI: 10.1684/epd.2015.0778]

64 **Kamdar HA**, Hamed M, Smetana KS, Shanmugam K, Peters E, Yasin R, Thakur G, Gopal M, Sawalha K, Greene-Chandos D, Hussein O. Lorazepam timing for acute convulsive seizure control (LoTASC). *Seizure* 2020; **83**: 41-47 [PMID: 33080484 DOI: 10.1016/j.seizure.2020.09.024]

65 **Ahmed SN**, Siddiqi ZA. Antiepileptic drugs and liver disease. *Seizure* 2006; **15**: 156-164 [PMID: 16442314 DOI: 10.1016/j.seizure.2005.12.009]

66 **Smith PEM**. Initial Management of Seizure in Adults. *N Engl J Med* 2021; **385**: 251-263 [PMID: 34260837 DOI: 10.1056/NEJMcp2024526]

67 **Haller JT**, Bonnin S, Radosevich J. Rapid administration of undiluted intravenous levetiracetam. *Epilepsia* 2021; **62**: 1865-1870 [PMID: 34164804 DOI: 10.1111/epi.16961]

68 **Chamberlain JM**, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, Barsan W, Cloyd J, Lowenstein D, Bleck TP, Conwit R, Meinzer C, Cock H, Fountain NB, Underwood E, Connor JT, Silbergleit R; Neurological Emergencies Treatment Trials; Pediatric Emergency Care Applied Research Network investigators. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet* 2020; **395**: 1217-1224 [PMID: 32203691 DOI: 10.1016/S0140-6736(20)30611-5]

69 **Kapur J**, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, Shinnar S, Conwit R, Meinzer C, Cock H, Fountain N, Connor JT, Silbergleit R; NETT and PECARN Investigators. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. *N Engl J Med* 2019; **381**: 2103-2113 [PMID: 31774955 DOI: 10.1056/NEJMoa1905795]

70 **Löscher W**, Gillard M, Sands ZA, Kaminski RM, Klitgaard H. Synaptic Vesicle Glycoprotein 2A Ligands in the Treatment of Epilepsy and Beyond. *CNS Drugs* 2016; **30**: 1055-1077 [PMID: 27752944 DOI: 10.1007/s40263-016-0384-x]

71 **Strzelczyk A**, Zöllner JP, Willems LM, Jost J, Paule E, Schubert-Bast S, Rosenow F, Bauer S. Lacosamide in status epilepticus: Systematic review of current evidence. *Epilepsia* 2017; **58**: 933-950 [PMID: 28295226 DOI: 10.1111/epi.13716]

72 **Eilam A**, Khmeliov N, Penker D, Gilad R. Intravenous Lacosamide in Seizure Clusters: Dose and Efficacy. *Clin Neuropharmacol* 2021; **44**: 85-88 [PMID: 33811195 DOI: 10.1097/WNF.0000000000000445]

73 **Rogawski MA**, Tofighy A, White HS, Matagne A, Wolff C. Current understanding of the mechanism of action of the antiepileptic drug lacosamide. *Epilepsy Res* 2015; **110**: 189-205 [PMID: 25616473 DOI: 10.1016/j.eplepsyres.2014.11.021]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 477-484

DOI: 10.5501/wjv.v11.i6.477

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical characteristics of COVID-19 patients who underwent tracheostomy and its effect on outcome: A retrospective observational study

Yudhyavir Singh, Kapil Dev Soni, Abhishek Singh, Nikita Choudhary, Fahina Perveen, Richa Aggarwal, Nishant Patel, Shailendra Kumar, Anjan Trikha

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lelisho ME; Neagu TP

Received: April 20, 2022
Peer-review started: April 20, 2022
First decision: May 31, 2022
Revised: June 12, 2022
Accepted: September 21, 2022
Article in press: September 21, 2022
Published online: November 25, 2022

Yudhyavir Singh, Abhishek Singh, Nikita Choudhary, Fahina Perveen, Nishant Patel, Shailendra Kumar, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi 110029, India

Kapil Dev Soni, Richa Aggarwal, Department of Critical and Intensive Care, Jai Prakash Narayan Apex Trauma Center, All India Institute of Medical Sciences, New Delhi 110029, India

Anjan Trikha, Department of Anesthesia, All India Institute of Medical Sciences, New Delhi 110029, India

Corresponding author: Abhishek Singh, MD, Assistant Professor, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, 5th floor, Teaching block All India Institute of Medical Sciences, New Delhi 110029, India. bikunrs77@gmail.com

Abstract

BACKGROUND

The exponential rise in Coronavirus disease 2019 (COVID-19) cases has resulted in an increased number of patients requiring prolonged ventilatory support and subsequent tracheostomy. With the limited availability of literature regarding the outcomes of COVID-19 patients with tracheostomy, we attempted to study the clinical characteristics and multiple parameters affecting the outcomes in these patients.

AIM

To determine all-cause mortality following tracheostomy and its association with various risk factors in COVID-19 patients.

METHODS

This retrospective study included 73 adult COVID-19 patients admitted to the ICU between 1 April, 2020 and 30 September, 2021 who underwent tracheostomy as a result of acute respiratory failure due to COVID-19. The data collected included demographics (age, sex), comorbidities, type of oxygen support at admission, severity of COVID-19, complications, and other parameters such as admission to tracheostomy, intubation to tracheostomy, ICU stay, hospital stay,

and outcome.

RESULTS

This study included 73 adult patients with an average age of 52 ± 16.67 years, of which 52% were men. The average time for admission to tracheostomy was 18.12 ± 12.98 days while intubation to tracheostomy was 11.97 ± 9 days. The mortality rate was 71.2% and 28.8% of patients were discharged alive. The mean duration of ICU and hospital stay was 25 ± 11 days and 28.21 ± 11.60 days, respectively. Greater age, severe COVID-19, mechanical ventilation, shock and acute kidney injury were associated with poor prognosis; however, early tracheostomy in intubated patients resulted in better outcomes.

CONCLUSION

Patients with severe COVID-19 requiring mechanical ventilation have a poor prognosis but patients with early tracheostomy may benefit with no added risk. We recommend that the timing of tracheostomy be decided on a case-by-case basis and a well-designed randomised controlled trial should be performed to elucidate the potential benefit of early tracheostomy in such patients.

Key Words: COVID-19; Intubation; Mechanical ventilation; ICU; Tracheostomy; Oxygen therapy

Core Tip: Tracheostomies are commonly performed in critically ill patients who require mechanical ventilation for a prolonged duration. Various recommendations and guidelines have been published regarding the safety of tracheostomy in Coronavirus disease 2019 (COVID-19) patients but literature with respect to indication, timing and outcome of tracheostomy in COVID-19 patients is still lacking. Therefore, in this study we aimed to describe the clinical characteristics of patients who underwent elective tracheostomies and multiple parameters affecting the outcomes in these patients. We found that patients with severe COVID-19 requiring mechanical ventilation had a poor prognosis but patients with early tracheostomy may benefit from this procedure.

Citation: Singh Y, Soni KD, Singh A, Choudhary N, Perveen F, Aggarwal R, Patel N, Kumar S, Trikha A. Clinical characteristics of COVID-19 patients who underwent tracheostomy and its effect on outcome: A retrospective observational study. *World J Virol* 2022; 11(6): 477-484

URL: https://www.wjgnet.com/2220-3249/full/v11/i6/477.htm

DOI: https://dx.doi.org/10.5501/wjv.v11.i6.477

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has resulted in extreme stress in healthcare establishments worldwide. Various studies have shown that 5%-15% of the patients with COVID-19 will develop severe disease requiring endotracheal intubation and mechanical ventilation[1,2]. Some patients may require prolonged ventilatory support. Tracheostomies are commonly performed in critically ill patients who require prolonged mechanical ventilation[3]. Compared with the orotracheal tube, the tracheostomy tube bypasses the mouth and pharynx resulting in better patient comfort and sedation requirement[4]. Other benefits of tracheostomy include a reduced incidence of ventilator-associated pneumonia, reduction in anatomical dead space leading to less work of breathing, easy airway suctioning and toileting, and facilitation of weaning from mechanical ventilation[5]. During the pandemic, tracheostomy will help in early transition of the patients from ICU care to ward care, thus helping to create a much-needed ICU bed that is always scarce in resource-limited countries with limited manpower. Tracheostomy will also help reduce the generation of highly infectious aerosols that are associated with the use of high flow oxygen devices or non-invasive ventilation[6].

Various guidelines have been published regarding the safety of tracheostomy in COVID-19 patients; however, literature regarding the indications, timing, and outcomes of tracheostomy in COVID-19 patients is lacking[7,8]. Some authors suggest that tracheostomy should be delayed for at least 14 days after endotracheal intubation to obtain better information regarding patient prognosis along with reduced viral load[9-13]. Early tracheostomy is advised so that patients can be weaned from the ventilator and transferred to ward care sparing the ICU bed[14]. However, these recommendations are based on expert opinions and a well-designed study is needed to provide a high level of evidence. In this study, we aimed to describe the clinical characteristics of patients who underwent elective tracheostomies and to study multiple parameters affecting the outcomes of these patients.

MATERIALS AND METHODS

Study overview

This study was conducted by the Department of Anaesthesiology, Pain Medicine, and Critical Care in a tertiary care centre. The retrospective data presented in this study is part of the project titled-Post discharge outcomes of COVID-19 patients following admission to the intensive care unit, which was approved by the institute ethics committee (IEC-291/17.04.2020). As the study is retrospective in nature, informed written consent from individual patients was waived. Major databases such as PubMed, Embase, Scopus, Web of Science and Google Scholar were searched to identify the latest literature. The search was strengthened using a new tool called Reference Citation Analysis (https://www.referencecitationanalysis.com/).

Inclusion criteria

The study included all confirmed COVID-19 adult patients admitted to the ICU who underwent tracheostomy between April 1, 2020 and September 30, 2021.

Exclusion criteria

All patients with missing data or polytrauma cases who were incidentally COVID-19 positive were excluded from the study.

Data collection

Data were retrospectively collected using medical records and a computerized patient record system. Data collected included demographics (age, sex), comorbidities, type of oxygen support at admission, the severity of COVID-19, complications, and tracheostomy-related parameters such as admission to tracheostomy, intubation to tracheostomy, ICU stay, hospital stay, and outcome. The timing of tracheostomy was classified as early (within 10 days of intubation) and late (more than 10 days of intubation).

Statistical analysis

The primary outcome of the study was to measure all-cause mortality following tracheostomy and its association with various risk factors. The secondary outcome included various tracheostomy-related parameters such as the timing of tracheostomy, admission to tracheostomy, intubation to tracheostomy, ICU stay, and hospital stay. Continuous variables were expressed as mean ± SD and categorical variables as number (percentage). Group comparison was performed using independent *t*-tests or Fisher's exact test. *P* values less than 0.05 were considered statistically significant.

RESULTS

During the study period, 113 mechanically ventilated patients with confirmed COVID-19 who underwent tracheostomy were screened for possible inclusion in the study. Seventy-three patients satisfied the inclusion criteria. They were further subdivided into survivors and non-survivors.

Table 1 shows the patient's demographics, comorbidities, COVID-19 severity, initial respiratory support, and tracheostomy-related parameters. The average age of the patients was 52 years (SD 16.67) and 52% were male. Hypertension was the most common comorbidity (35.6%) followed by chronic kidney disease with superimposed acute kidney injury (34.3%), diabetes (24.6%), cerebrovascular accident (15.1%), and coronary artery disease (5.44%). The most common oxygen therapy modality used at the time of ICU admission was mechanical ventilation (42.5%), followed by a non-rebreathing mask (19.2%), high flow nasal canula (10.9%), room air (12.3%), face mask (8.2%) and non-invasive ventilation (6.8%). Most of the patients who were admitted to the ICU were suffering from severe COVID-19 (50.6%) followed by moderate (30.2%) and mild (19.2%) disease. The mortality rate was 71.2% and 28.2% were discharged alive. The mean duration of ICU and hospital stay was 25 ± 11 days and 28.21 ± 11.60 days, respectively.

The average time for admission to tracheostomy was 18.12 ± 12.98 days while intubation to tracheostomy was 11.97 ± 9 days. In 35 (47.9%) patients, tracheostomies were performed early *i.e.*, within 10 days of intubation. Subgroup analysis among survivors and non-survivors showed that patients in the non-survivor group were older ($P = 0.02$), had severe COVID-19 ($P = 0.001$), and had a late tracheostomy ($P = 0.03$) as compared to survivors. However, the number of days from admission to tracheostomy, duration of ICU, and hospital stay were not significantly different between survivors and non-survivors (Table 2).

Table 1 Clinical-demographic parameters of COVID-19 patients who underwent tracheostomy

Characteristics	*n* = 73
Age (yr)	52 ± 16.67
Male	38 (52%)
Female	35 (48%)
Comorbities & COVID related complications *n* (%)	
HTN	26 (35.6%)
DM	18 (24.66%)
CAD	04 (5.44%)
CKD with AKI	25 (34.3%)
CVA	11 (15.1%)
TBI	02 (2.74%)
Stroke	05 (6.8%)
Pneumothorax	10 (13.7%)
Mucormycosis	06 (8.22%)
Shock	44 (60.2%)
COVID severity *n* (%)	
Mild	14 (19.2%)
Moderate	22 (30.2%)
Severe	37 (50.6%)
Initial respiratory support *n* (%)	
RA	9 (12.3%)
FM	6 (8.2%)
NRBM	14 (19.2%)
HFNC	8 (10.9%)
NIV	5 (6.8%)
MV	31 (42.5%)
Tracheostomy related events (mean ± SD)	
Admission to tracheostomy (d)	18.12 ± 12.98
Intubation to tracheostomy (d)	11.97 ± 9
ICU stay (d)	25 ± 11
Hospital stay (d)	28.21 ± 11.60
Death (*n*, %)	52 (71.2%)
Discharge (*n*, %)	21 (28.8%)

HTN: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; CKD with AKI: Chronic kidney disease with acute kidney injury; CVA: Cerebrovascular accident; TBI: Traumatic brain injury; RA: Room air; FM: Face mask; NRBM: Non-rebreathing mask; HFNC: High-flow nasal cannula; NIV: Non-invasive ventilation; MV: Mechanical ventilation.

DISCUSSION

This retrospective study describes the effect of tracheostomy in COVID-19 patients suffering from acute respiratory failure in a tertiary care centre in northern India. In our cohort of tracheotomized patients with COVID-19 pneumonia, we found that the average time from intubation to tracheostomy was 12 days; tracheostomy was performed in 6.4% of the patients admitted to the ICU. This rate is slightly lower than the French COVID-ICU study which reported a rate of 9%[15]. The patients in the non-survivor group were older and had severe COVID-19 and late tracheostomy.

Table 2 Comparison of tracheostomy-related events between survivors and non-survivors

Parameters		Survivors	Non-survivors	*P* value
Age (yr)		44.95 ± 4.19	54.84 ± 2.05	0.02
Gender male		12 (57.2%)	26 (50%)	0.38
Female		9 (42.8%)	26 (50%)	
Comorbidities	Present	06 (28.6%)	16 (30.77%)	0.54
	Absent	15 (71.4%)	36 (69.23%)	
COVID severity	Mild	10 (71.4%)	04 (28.6%)	0.001
	Moderate	03 (13.6%)	19 (86.4%)	
	Severe	08 (21.6%)	29 (78.4%)	
Admission to tracheostomy (d)		17.09 ± 2.54	18.53 ± 1.88	0.67
Intubation to tracheostomy (d)		9.19 ± 8.57	13.09 ± 9.02	0.01
Early tracheostomy (< 10 d)		14 (66.6%)	21 (40.3%)	
Late tracheostomy (> 10 d)		7 (33.4%)	31 (59.6%)	0.03
ICU stay (d)		26.19 ± 3.50	24.55 ± 1.41	0.6
Hospital stay (d)		30.85 ± 3.15	27.15 ± 1.41	0.21

The timing of tracheostomy in COVID-19 has been a matter of debate as published studies have presented heterogeneous results[8,16-19] and this debate is not going to be settled as most of the studies on tracheostomy are retrospective in nature. Various researchers have demonstrated that early tracheostomy has the advantage of rapid weaning from mechanical ventilation, decreased need for sedation, and shorter length of ICU stay[20]. Other proposed advantages include reduced risk of oropharyngeal and laryngeal damage as well as facilitation of oral feeding and oral care[21].

Before the COVID-19 pandemic, a systematic review by Adly *et al*[20] suggested that early tracheostomy *i.e.*, within 7 days, was associated with a reduced duration of mechanical ventilation, decreased mortality rate, and shorter length of ICU stay. A Cochrane review by Andriolo *et al*[22] found that early tracheostomy was associated with lower mortality rates and a higher probability of discharge from the ICU at day 28. However, a meta-analysis by Griffiths *et al*[23] and Siempos *et al*[24] demonstrated that there was no survival benefit following early tracheostomy as compared to late tracheostomy. The TracMan randomized controlled[25] trial comparing early (within 4 days) *vs* late tracheostomy (after 10 days), demonstrated that there were no differences in 30-day mortality and 1- and 2-year survival or length of ICU stay between them.

During the COVID-19 pandemic, various studies have described different timing of tracheostomy. Kwak *et al*[26], the Queen Elizabeth Hospital Birmingham COVID-19 airway team[27], Angel *et al*[28], Chao *et al*[10], Martin-Villares *et al*[18], Hernandez-Gracia *et al*[29] and Mario *et al*[30] have reported a mean time from intubation to tracheostomy of 12.2, 13.9, 10.6, 19.7, 12, 17 and 15 days, respectively. In our study, the mean intubation to open tracheostomy time was 11.97 days and in 47.9% (n = 35) of COVID-19 patients tracheotomies were performed within 10 days of intubation.

The subgroup analysis of tracheostomy among non-survivors and survivors showed that the mean age of non-survivors was higher than survivors. This poor outcome in older patients with tracheostomies is consistent with many studies published on COVID-19[1,18]. Similarly, non-survivors with tracheostomies were suffering from severe COVID-19, which was also consistent with previously published research. Furthermore, most of the non-survivors in our study had late tracheostomy demonstrating poor outcome in patients with late tracheostomy (beyond 10 days), which may be due to worsening of the disease at later stages. However, Tang *et al*[16] suggested better outcomes in tracheostomies done after 14 days whereas Aviles-Jurado *et al*[31] in their prospective study on the safety of tracheostomy reported that early tracheostomy (< 10 days) had no association with mortality. Other parameters such as the number of days from admission to tracheostomy, duration of ICU, and hospital stay were not significantly different between survivors and non-survivors. The overall mortality in our study was 71.2%, which was consistent with other studies reporting > 50% mortality in COVID-19 patients on mechanical ventilation[32,33].

Limitations

Our study had several limitations. First, it was a retrospective observational study with a relatively small sample size. Therefore, a well-designed multicentre randomized controlled trial with adequate sample size is needed to validate the findings in our study. Second, due to its retrospective nature, some

key statistical tests could not be performed. Thirdly, the various scores used in the ICU in predicting the outcome were not analysed. Lastly, we were unable to retrieve and calculate the incidence of complications associated with a tracheostomy. The present study may help other clinicians in designing a clinical trial for future research to identify the best time of tracheostomy in critically ill mechanically ventilated patients.

CONCLUSION

Our study describes the clinical characteristics and outcome of a cohort of patients who underwent tracheostomy after intubation due to COVID-19. The results showed that early tracheostomy (less than 10 days) was associated with reduced mortality. However, a well-designed randomized multicentre trial is needed to elucidate the potential benefit of early tracheostomy in mechanically ventilated COVID-19 patients. We also suggest that the timing of tracheostomy be decided on a case-by-case basis rather than following a strict rule.

ARTICLE HIGHLIGHTS

Research background

The rapid increase in Coronavirus disease 2019 (COVID-19) patients has resulted in an increased number of patients with severe disease requiring prolonged ventilatory support and subsequently tracheostomy. Details regarding the timing, and safety of tracheostomy in the management of COVID-19 patients continue to evolve.

Research motivation

With the limited availability of literature regarding the outcomes of COVID-19 patients with tracheostomy, we attempted to study the clinical characteristics and multiple parameters affecting the outcomes in these patients.

Research objectives

Our research objective was to determine the all-cause mortality after tracheostomy and its relation with various risk factors in COVID-19 patients.

Research methods

We conducted a retrospective observational study at a tertiary care hospital. The study included 73 adult COVID-19 patients admitted to the ICU between 1 April, 2020 and 30 September, 2021 who underwent tracheostomy as a result of acute respiratory failure due to COVID-19.

Research results

Seventy-three adult patients were included in the study with an average age of 52 ± 16.67 years, of which 52% were male. The average time for admission to tracheostomy was 18.12 ± 12.98 days while intubation to tracheostomy was 11.97 ± 9 days. The mortality rate was 71.2% and only 28.8% of patients were discharged alive. Greater age, severe COVID-19, mechanical ventilation, presence of shock and acute kidney injury were associated with a poor prognosis; however, early tracheostomy in intubated patients resulted in a better outcome.

Research conclusions

The study showed that early tracheostomy (less than 10 days) was associated with reduced mortality with no added risk to the patient. Furthermore, the timing of tracheostomy should be decided on a case-by-case basis rather than following a strict rule.

Research perspectives

A well designed randomised controlled trial should be performed to elucidate the potential benefit of early tracheostomy in COVID-19 patients.

FOOTNOTES

Author contributions: Singh A, Soni KD, Aggarwal R, Singh Y, Patel N, Kumar K, Chaudhary N, Perveen F, and Trikha A contributed to conception, study design, as well as data collection and evaluation; Singh A and Soni KD contributed to statistical analysis, and interpretation of data; Singh A, Singh Y, and Trikha A drafted the manuscript, which was revised by Soni KD; all authors have read and approved the final manuscript.

Institutional review board statement: The retrospective data presented in this study is the part of the project titled–Post discharge outcomes of COVID-19 patients following admission to the intensive care unit, which was approved by the institute ethics committee (Reference No. IEC-291/17.04.2020).

Informed consent statement: As the study was retrospective in nature, informed written consent from individual patients was waived.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript.

Data sharing statement: Data can be made available at proper request by writing to the authors at bikunrs77@gmail.com.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: India

ORCID number: Abhishek Singh 0000-0002-4690-5118.

S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

REFERENCES

1 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]
2 **Möhlenkamp S**, Thiele H. Ventilation of COVID-19 patients in intensive care units. *Herz* 2020; **45**: 329-331 [PMID: 32313971 DOI: 10.1007/s00059-020-04923-1]
3 **Scales DC**, Ferguson ND. Tracheostomy: it's time to move from art to science. *Crit Care Med* 2006; **34**: 3039-3040 [PMID: 17130697 DOI: 10.1097/01.CCM.0000242924.24342.9D]
4 **Bösel J**, Schiller P, Hook Y, Andes M, Neumann JO, Poli S, Amiri H, Schönenberger S, Peng Z, Unterberg A, Hacke W, Steiner T. Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT): a randomized pilot trial. *Stroke* 2013; **44**: 21-28 [PMID: 23204058 DOI: 10.1161/STROKEAHA.112.669895]
5 **Robba C**, Galimberti S, Graziano F, Wiegers EJA, Lingsma HF, Iaquaniello C, Stocchetti N, Menon D, Citerio G; CENTER-TBI ICU Participants and Investigators. Tracheostomy practice and timing in traumatic brain-injured patients: a CENTER-TBI study. *Intensive Care Med* 2020; **46**: 983-994 [PMID: 32025780 DOI: 10.1007/s00134-020-05935-5]
6 **Tran K**, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012; **7**: e35797 [PMID: 22563403 DOI: 10.1371/journal.pone.0035797]
7 **Khanna P**, Garg H, Singh Y. Tracheostomy in Patients with Coronavirus Disease 2019: An Overview. *Turk J Anaesthesiol Reanim* 2021; **49**: 273-277 [PMID: 35110007 DOI: 10.5152/TJAR.2020.950]
8 **McGrath BA**, Brenner MJ, Warrillow SJ, Pandian V, Arora A, Cameron TS, Añon JM, Hernández Martínez G, Truog RD, Block SD, Lui GCY, McDonald C, Rassekh CH, Atkins J, Qiang L, Vergez S, Dulguerov P, Zenk J, Antonelli M, Pelosi P, Walsh BK, Ward E, Shang Y, Gasparini S, Donati A, Singer M, Openshaw PJM, Tolley N, Markel H, Feller-Kopman DJ. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. *Lancet Respir Med* 2020; **8**: 717-725 [PMID: 32422180 DOI: 10.1016/S2213-2600(20)30230-7]
9 **Miles BA**, Schiff B, Ganly I, Ow T, Cohen E, Genden E, Culliney B, Mehrotra B, Savona S, Wong RJ, Haigentz M, Caruana S, Givi B, Patel K, Hu K. Tracheostomy during SARS-CoV-2 pandemic: Recommendations from the New York Head and Neck Society. *Head Neck* 2020; **42**: 1282-1290 [PMID: 32304119 DOI: 10.1002/hed.26166]
10 **Chao TN**, Braslow BM, Martin ND, Chalian AA, Atkins J, Haas AR, Rassekh CH; Guidelines from the COVID-19 Tracheotomy Task Force, a Working Group of the Airway Safety Committee of the University of Pennsylvania Health System. Tracheotomy in Ventilated Patients With COVID-19. *Ann Surg* 2020; **272**: e30-e32 [PMID: 32379079 DOI: 10.1097/SLA.0000000000003956]
11 **David AP**, Russell MD, El-Sayed IH, Russell MS. Tracheostomy guidelines developed at a large academic medical center during the COVID-19 pandemic. *Head Neck* 2020; **42**: 1291-1296 [PMID: 32329926 DOI: 10.1002/hed.26191]
12 **Givi B**, Schiff BA, Chinn SB, Clayburgh D, Iyer NG, Jalisi S, Moore MG, Nathan CA, Orloff LA, O'Neill JP, Parker N,

Zender C, Morris LGT, Davies L. Safety Recommendations for Evaluation and Surgery of the Head and Neck During the COVID-19 Pandemic. *JAMA Otolaryngol Head Neck Surg* 2020; **146**: 579-584 [PMID: 32232423 DOI: 10.1001/jamaoto.2020.0780]

13 **Takhar A**, Walker A, Tricklebank S, Wyncoll D, Hart N, Jacob T, Arora A, Skilbeck C, Simo R, Surda P. Recommendation of a practical guideline for safe tracheostomy during the COVID-19 pandemic. *Eur Arch Otorhinolaryngol* 2020; **277**: 2173-2184 [PMID: 32314050 DOI: 10.1007/s00405-020-05993-x]

14 **Schultz MJ**, Pattnaik R, Dondorp AM. Walking the line between benefit and harm from tracheostomy in COVID-19. *Lancet Respir Med* 2020; **8**: 656-657 [PMID: 32422179 DOI: 10.1016/S2213-2600(20)30231-9]

15 **COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators**. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2021; **47**: 60-73 [PMID: 33211135 DOI: 10.1007/s00134-020-06294-x]

16 **Tang Y**, Wu Y, Zhu F, Yang X, Huang C, Hou G, Xu W, Hu M, Zhang L, Cheng A, Xu Z, Liu B, Hu S, Zhu G, Fan X, Zhang X, Yang Y, Feng H, Yu L, Wang B, Li Z, Peng Y, Shen Z, Fu S, Ouyang Y, Xu J, Zou X, Fang M, Yu Z, Hu B, Shang Y. Tracheostomy in 80 COVID-19 Patients: A Multicenter, Retrospective, Observational Study. *Front Med (Lausanne)* 2020; **7**: 615845 [PMID: 33425960 DOI: 10.3389/fmed.2020.615845]

17 **Volo T**, Stritoni P, Battel I, Zennaro B, Lazzari F, Bellin M, Michieletto L, Spinato G, Busatto C, Politi D, Spinato R. Elective tracheostomy during COVID-19 outbreak: to whom, when, how? *Eur Arch Otorhinolaryngol* 2021; **278**: 781-789 [PMID: 32656673 DOI: 10.1007/s00405-020-06190-6]

18 **Martin-Villares C**, Perez Molina-Ramirez C, Bartolome-Benito M, Bernal-Sprekelsen M; COVID ORL ESP Collaborative Group (*). Outcome of 1890 tracheostomies for critical COVID-19 patients: a national cohort study in Spain. *Eur Arch Otorhinolaryngol* 2021; **278**: 1605-1612 [PMID: 32749607 DOI: 10.1007/s00405-020-06220-3]

19 **Rosano A**, Martinelli E, Fusina F, Albani F, Caserta R, Morandi A, Dell'Agnolo P, Dicembrini A, Mansouri L, Marchini A, Schivalocchi V, Natalini G. Early Percutaneous Tracheostomy in Coronavirus Disease 2019: Association With Hospital Mortality and Factors Associated With Removal of Tracheostomy Tube at ICU Discharge. A Cohort Study on 121 Patients. *Crit Care Med* 2021; **49**: 261-270 [PMID: 33201005 DOI: 10.1097/CCM.0000000000004752]

20 **Adly A**, Youssef TA, El-Begermy MM, Younis HM. Timing of tracheostomy in patients with prolonged endotracheal intubation: a systematic review. *Eur Arch Otorhinolaryngol* 2018; **275**: 679-690 [PMID: 29255970 DOI: 10.1007/s00405-017-4838-7]

21 **Whited RE**. A prospective study of laryngotracheal sequelae in long-term intubation. *Laryngoscope* 1984; **94**: 367-377 [PMID: 6700353 DOI: 10.1288/00005537-198403000-00014]

22 **Andriolo BN**, Andriolo RB, Saconato H, Atallah ÁN, Valente O. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev* 2015; **1**: CD007271 [PMID: 25581416 DOI: 10.1002/14651858.CD007271.pub3]

23 **Griffiths J**, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ* 2005; **330**: 1243 [PMID: 15901643 DOI: 10.1136/bmj.38467.485671.E0]

24 **Siempos II**, Ntaidou TK, Filippidis FT, Choi A. Effect of early vs late or no tracheostomy on mortality and pneumonia of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med 2015; 3:150-8 [DOI: 10.1016/S2213-2600(15)00007-7]

25 **Young D**, Harrison DA, Cuthbertson BH, Rowan K; TracMan Collaborators. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *JAMA* 2013; **309**: 2121-2129 [PMID: 23695482 DOI: 10.1001/jama.2013.5154]

26 **Kwak PE**, Connors JR, Benedict PA, Timen MR, Wang B, Zhang Y, Youlios S, Sureau K, Persky MJ, Rafeq S, Angel L, Amin MR. Early Outcomes From Early Tracheostomy for Patients With COVID-19. *JAMA Otolaryngol Head Neck Surg* 2021; **147**: 239-244 [PMID: 33331855 DOI: 10.1001/jamaoto.2020.4837]

27 **Queen Elizabeth Hospital Birmingham COVID-19 airway team**. Safety and 30-day outcomes of tracheostomy for COVID-19: a prospective observational cohort study. *Br J Anaesth* 2020; **125**: 872-879 [PMID: 32988602 DOI: 10.1016/j.bja.2020.08.023]

28 **Angel L**, Kon ZN, Chang SH, Rafeq S, Palasamudram Shekar S, Mitzman B, Amoroso N, Goldenberg R, Sureau K, Smith DE, Cerfolio RJ. Novel Percutaneous Tracheostomy for Critically Ill Patients With COVID-19. *Ann Thorac Surg* 2020; **110**: 1006-1011 [PMID: 32339508 DOI: 10.1016/j.athoracsur.2020.04.010]

29 **Hernández-García E**, Martínez-RuizCoello M, Navarro Mediano A, Pérez-Martín N, García-Peces V, Velayos C, Rodríguez-Campoo B, Plaza G. Open Tracheostomy for Critically Ill Patients with COVID-19. *Int J Otolaryngol* 2020; **2020**: 8861013 [PMID: 34966431 DOI: 10.1155/2020/8861013]

30 **Turri-Zanoni M**, Battaglia P, Czaczkes C, Pelosi P, Castelnuovo P, Cabrini L. Elective Tracheostomy During Mechanical Ventilation in Patients Affected by COVID-19: Preliminary Case Series From Lombardy, Italy. *Otolaryngol Head Neck Surg* 2020; **163**: 135-137 [PMID: 32396455 DOI: 10.1177/0194599820928963]

31 **Avilés-Jurado FX**, Prieto-Alhambra D, González-Sánchez N, de Ossó J, Arancibia C, Rojas-Lechuga MJ, Ruiz-Sevilla L, Remacha J, Sánchez I, Lehrer-Coriat E, López-Chacón M, Langdon C, Guilemany JM, Larrosa F, Alobid I, Bernal-Sprekelsen M, Castro P, Vilaseca I. Timing, Complications, and Safety of Tracheotomy in Critically Ill Patients With COVID-19. *JAMA Otolaryngol Head Neck Surg* 2020 [PMID: 33034625 DOI: 10.1001/jamaoto.2020.3641]

32 **Godeau D**, Petit A, Richard I, Roquelaure Y, Descatha A. Return-to-work, disabilities and occupational health in the age of COVID-19. *Scand J Work Environ Health* 2021; **47**: 408-409 [PMID: 34003294 DOI: 10.1016/S0140-6736(20)30566-3]

33 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 485-495

DOI: 10.5501/wjv.v11.i6.485

ISSN 2220-3249 (online)

SYSTEMATIC REVIEWS

Musculoskeletal complications in long COVID-19: A systematic review

Raktim Swarnakar, Shoibam Jenifa, Sanjay Wadhwa

Specialty type: Virology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mahmoud MZ, Saudi Arabia; Mehri-Ghahfarrokhi A, Iran

Received: July 28, 2022
Peer-review started: July 28, 2022
First decision: August 22, 2022
Revised: September 1, 2022
Accepted: October 14, 2022
Article in press: October 14, 2022
Published online: November 25, 2022

Raktim Swarnakar, Shoibam Jenifa, Sanjay Wadhwa, Department of Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, New Delhi 110029, Delhi, India

Corresponding author: Sanjay Wadhwa, DNB, Professor & Head, Department of Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, Delhi, India. wadhwadr@gmail.com

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has crippled humanity since early 2020. Various sequelae of COVID-19 have been reported in different body systems. Musculoskeletal symptoms are widely reported during COVID-19 infection, but musculoskeletal complications in long COVID-19 are underreported. However, post-COVID-19 survivors have reported complaints of persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness, *etc* in clinical practice. The well-known detrimental effects of steroids on the musculoskeletal system coupled with their over-the-counter availability can also be anticipated since they were the cornerstone of life-saving management in this pandemic.

AIM

To determine the musculoskeletal complications in long COVID.

METHODS

We performed a systematic review of 'systematic reviews and meta-analyses'.

RESULTS

Of the 63 articles screened, 24 articles were included. Two articles specifically discussed children and adolescents. One article discussed rehabilitation intervention. No article addressed rehabilitation of musculoskeletal issues in long COVID-19 in particular. Fatigue was the most common musculoskeletal complication.

CONCLUSION

Fatigue is found to be very common along with myalgia and arthralgia. There were no studies on rehabilitation intervention in musculoskeletal complications specifically. Considering the lacuna in literature and the needs of the current situation, further studies are warranted to standardize effective rehabilitation interventions in musculoskeletal complications. More homogenous studies are needed. Studies on functional impairment due to musculoskeletal involvement

are essential.

Key Words: Musculoskeletal complications; COVID-19; Long COVID-19; Post-COVID-19 syndrome; Rehabilitation; SARS-CoV-2

Core Tip: Though musculoskeletal involvement is reported in severe acute respiratory syndrome coronavirus 2 infection, the literature is limited for musculoskeletal symptoms in long coronavirus disease 2019 (COVID-19). Moreover, rehabilitation of each musculoskeletal complaint is not addressed in most reviews. We highlighted those keys areas through our review article. Fatigue is the most common musculoskeletal issue in long COVID-19. Considering the gaps in literature and current needs, future studies are warranted to standardize effective rehabilitation interventions in musculoskeletal complications.

Citation: Swarnakar R, Jenifa S, Wadhwa S. Musculoskeletal complications in long COVID-19: A systematic review. *World J Virol* 2022; 11(6): 485-495
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/485.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.485

INTRODUCTION

Since 2020 the world has witnessed multiple waves of the coronavirus disease 2019 (COVID-19) pandemic caused by different variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at different times and places. As of September 1, 2022, 599 million confirmed cases and more than 6 million deaths have been reported[1]. The loss of lives, superimposed by the deterioration of the quality of life of a significant number of survivors, made this pandemic a huge hurdle for the whole world. A range of long-term effects or complications involving different body systems have been reported. The respiratory sequelae of COVID-19 have been widely investigated, but musculoskeletal complications are underreported. Here we performed a systematic review of systematic reviews and meta-analyses to find musculoskeletal complications caused by long COVID-19 conditions.

MATERIALS AND METHODS

Here a systematic review of systematic reviews and meta-analyses was conducted (Figure 1). We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Eligibility criteria

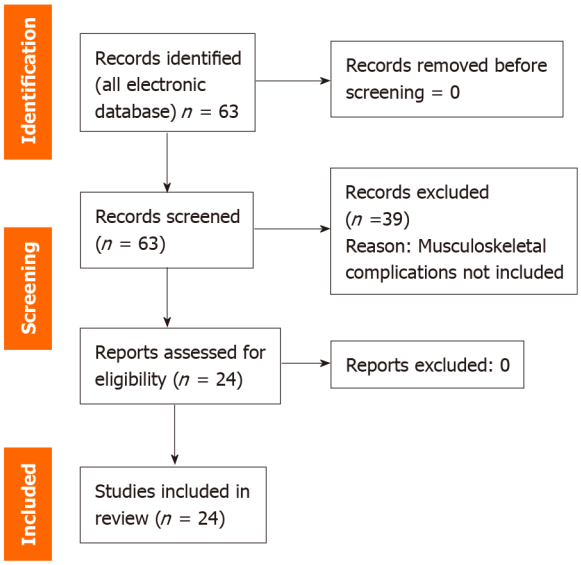
PICOS model: (1) Studies that considered patients with long-term COVID-19 symptoms at least > 4 wk of COVID-19 infections (population); (2) Studies where the primary aim was to evaluate long-term COVID-19 symptoms in mild, moderate, severe, and critical patients that have a follow-up of at least 14 d (interventions); (3) Studies with or without a control group (comparisons); (4) Studies that reported the long COVID-19 symptoms (outcomes); and (5) Systematic review and meta-analyses (study designs). From January 2020 to mid-July 2022, any relevant studies that followed the above mentioned PICOS model and that reported musculoskeletal complications in long COVID-19 were eligible for inclusion.

Search strategy

The search was carried out by two independent researchers in all electronic databases, mainly MEDLINE, EMBASE, Web of Science, and Google Scholar with this time period. We combined search terms and key words related to the population (*e.g.*, "COVID-19", "SARS-CoV-2", "long Covid-19", "long Covid", "long haulers") and outcomes (*e.g.*, "fatigue", "pain", "musculoskeletal", "myalgia", "myopathy", "arthralgia", "arthritis", "rheumatic", "joint"). We additionally filtered study designs "systemic review" and "meta-analyses" in humans.

Inclusion and exclusion

All the systematic reviews and meta-analyses on long COVID-19 following our above-mentioned PICOS model were included. After the preliminary search, we extracted the musculoskeletal complications that



DOI: 10.5501/wjv.v11.i6.485

Figure 1 Flow diagram of the study.

were reported in long COVID-19 studies or in post COVID-19 studies (at least 4 wk after COVID-19 active infection). We excluded any musculoskeletal issues that occurred after any neurological sequelae of long COVID-19 and excluded any myocarditis or issues related to smooth muscle dysfunction.

Study selection and data extraction

Titles and abstracts were screened for potentially eligible studies. Following an initial screening, full texts of potentially eligible studies were acquired for detailed evaluation eliminating all duplicates. Manual scanning of key articles and review papers was conducted to identify additional articles missed by the search strategy. Two reviewers assessed the articles independently and in case of any disagreements, the opinion of the third reviewer was consulted.

Analysis

We performed a descriptive analysis of the included reviews.

RESULTS

Of the 63 articles screened; 24 articles were included[2-25]. Two articles specifically discussed children and adolescents. One article discussed rehabilitation intervention. No article addressed rehabilitation on musculoskeletal issues in long COVID-19 in particular. Details of the selected articles are listed in Table 1.

DISCUSSION

According to the National Institute of Health and Care Excellence guidelines, post-acute COVID-19 and post-COVID-19 syndrome are included in long COVID. Post-acute-COVID-19 means ongoing symptomatic COVID-19 for people who still have symptoms 4 wk and 12 wk after acute COVID-19. On the other hand, post-COVID-19 syndrome means that patients are having persisting symptoms for > 12 wk after acute symptoms[26]. According to the World Health Organization, post-COVID-19 conditions generally occur 3 mo from the onset of COVID-19 with symptoms lasting for at least 2 mo and should be unexplained by any alternative diagnosis[27].

Another definition consists of "not recovering several weeks or months following the start of symptoms that were suggestive of COVID-19, regardless individuals were tested or not"[28]. Common symptoms reported are fatigue, shortness of breath, cognitive dysfunction/attention disorder, hair loss, and dyspnea[29,30]. Musculoskeletal symptoms of skeletal muscle, neurological, bone, and joint disorders have also been reported. The proinflammatory responses can impact nearly every organ system, including the musculoskeletal system. Myalgias, arthralgias, fatigue, exercise, and intolerance are some of the common musculoskeletal sequelae.

Table 1 Included systematic reviews and meta-analyses in this systematic review

Serial no.	Ref.	Reported musculoskeletal complications	Type of study	Types of patients	Rehabilitation intervention
1	Ludvigsson[2], 2021	Fatigue, muscle weakness	Systematic review	Children	No
2	Akbarialiabad *et al*[3], 2021	Fatigue (63%), muscle weakness	Systematic scoping review	All age groups	No
3	Michelen *et al*[4], 2021	Weakness (41%; 95%CI: 25%-59%), general malaise (33%; 95%CI: 15%-57%), fatigue (31%; 95%CI: 24%-39%)	Living systematic review	All age groups	No
4	Iqbal *et al*[5], 2021	48% fatigue in >12 wk	Systematic review and meta-analysis	All age groups	No
5	Vollbracht and Kraft[6], 2021	Vitamin C improved in post-COVID-19 fatigue; the IV vitamin C doses administered ranged from 3.5 g to > 75 g/d	A systematic review on intervention	All age groups	No
6	Jennings *et al*[7], 2021	Arthralgia 13% (6%-29%), myalgia 34% (2%-86%), fatigue 44% (10%-71%)	Systematic review	All age groups	No
7	Fernández-de-Las-Peñas *et al*[8], 2021	Fatigue (58%), headache (44%), joint pain (15%-20%)	Systematic review	All age groups	No
8	Malik *et al*[9], 2022	Fatigue (64, 54-73), arthralgia (24.3, 14.0-36.0), headache (21, 3-47)	Systematic review and meta-analysis	All age groups	No
9	Ceban *et al*[10], 2022	Fatigue in 30% of cases	Systematic review and meta-analysis	All age groups	No
10	Chen *et al*[11], 2022	Fatigue prevalence 0.23 (95%CI: 0.17-0.30)	Systematic review and meta-analysis	All age groups	No
11	van Kessel *et al*[12], 2022	Fatigue most common	Systematic review	All age groups	No
12	Alkodaymi *et al*[13], 2022	Fatigue 3-6 mo follow-up 32%, 36% 6-9 mo, 37% 9-12 mo, > 12 mo, 41%	Systematic review	All age groups	No
13	Fernández-de-Las-Peñas *et al*[14], 2022	Prevalence of post-COVID-19 myalgia, joint pain, and chest pain ranged from 5.65% to 18.15%, 4.6% to 12.1%, and 7.8% to 23.6%, respectively, at different follow-up periods during the 1st yr postinfection. Almost 10% of individuals infected by SARS-CoV-2 will suffer from musculoskeletal post-COVID-19 pain symptomatology at some time during the 1st yr after the infection	Systematic review	All age groups	No
14	Han *et al*[15], 2022	Fatigue/weakness (28%, 95%CI: 18%-39%), arthromyalgia (26%, 95%CI: 8%-44%)	Systematic review	All age groups	No
15	d'Ettorre *et al*[16], 2022	63% of fatigue reported	Systematic review	All age groups	No
16	Behnood *et al*[17], 2022	47% fatigue, 25% myalgia, 35% headache, females with higher pain symptoms	Systematic review	In children and young people	No
17	Nguyen *et al*[18], 2022	Fatigue (16%-64%), arthralgia (8%-55%), thoracic pain (5%-62%), myalgia (1%-22%), headache (9%-15%)	Systematic review	All age groups	No
18	Lopez-Leon *et al*[19], 2022	Fatigue (9.66%)	Systematic review	Children and adolescents	No
19	Abdel-Gawad *et al*[20], 2022	Fatigue (72.8%) and joint pain (31.4%)	Systematic review	All age groups	No
20	Almas *et al*[21], 2022	Fatigue (54.11%), arthralgia (16.35%), myalgia (5.78%), chest pain (10.37%)	Systematic review	All age groups	No
21	Maglietta *et al*[22], 2022	Fatigue and female sex association statistically significant, with OR = 1.54, 95%CI: 1.32-1.79	Systematic review	All age groups	No
22	Healey *et al*[23], 2022	fatigue (37%; 95%CI: 23%-55%), myalgia (12%; 95%CI: 5%-25%), headache (7%; 95%CI: 3%-16%), chest pain (3%; 95%CI: 1%-8%)	Systematic review	All age groups	No
23	de Oliveira Almeida *et al*[24], 2022	Fatigue. COVID-19 survivors can have a reduction in physical function, ability to perform activities of daily living and their health-related quality of life 1-6 mo post-infection	Systematic review	All age groups	No
24	Fugazzaro *et al*	Muscle strength, walking capacity, sit-to-stand performance	Systematic review	All age	Yes

[25], 2022	improvements		of rehabilitation interventions	groups

CI: Confidence interval; COVID-19: Coronavirus disease 2019; IV: Intravenous; OR: Odds ratio; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Why musculoskeletal system affected?

SARS-CoV-2 has three structural proteins (membrane protein, spike protein, and envelope protein). Spike glycoprotein through its subunits S1 and S2 helps in entering the host cells[31]. The angiotensin-converting enzyme 2 (ACE2) receptor acts as the entry receptor using the serine protease transmembrane protease, serine 2 (TMPRSS2) for spike protein priming[32]. Following the binding of the receptor, viral spike protein is broken down by TMPRSS2 proteolytically, which exposes a fusion peptide signal that helps in the fusion of viral and human membranes. It leads to the cytoplasmic release of viral RNA. Interestingly, ACE2 is found in the lung, heart, kidney, liver, gastrointestinal, and musculoskeletal systems.

In humans, endothelial cells, smooth muscle cells, pericytes, muscle stem cells, macrophages, B cells, T cells, natural killer cells, and myonuclei express TMPRSS2. Furthermore, several cells in the synovium including fibroblasts, monocytes, B cells, and T cells express ACE2 and TMPRSS2. However, only smooth muscle cells and pericytes express ACE2. Articular cartilage (proliferative, hypertrophic, and effector chondrocytes) express ACE2, and only homeostatic chondrocytes (which control circadian rhythm in cartilage) express TMPRSS2. In the meniscus, a few cartilage progenitors and regulatory fibrochondrocytes express ACE2 (no TMPRSS2 is detected). ACE2 is also found to be present in composite unenriched cortical and trabecular bone and osteoblast enriched tissues. TMPRSS2 was almost absent in composite bone tissue, and TMPRSS2 was detected in all osteoblast-enriched samples.

The presence of these receptors implies that skeletal muscle, synovium, and cortical bone may serve as potential areas of direct SARS-CoV-2 infection and its probable long-term sequelae[33]. The cytokines and signaling molecules are induced by the infection [C-X-C motif chemokine 10, interferon-gamma, interleukin (IL)-1β, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α)]. They play a crucial role in the pathogenesis of clinical signs and symptoms and long-term sequelae of COVID-19. Interferon-gamma, IL-1β, IL-6, IL-17, and TNF-α show a negative impact on skeletal muscle (fiber proteolysis and decreasing protein synthesis). IL-1β and IL-6 may lead to fibrosis after inducing increased muscle fibroblast activity. IL-1β and TNF-α induce muscle fiber growth by inhibiting the differentiation and proliferation of satellite cells, the progenitor cells[34].

COVID-19 therapy sequelae in the musculoskeletal system

Corticosteroids, a lifesaving medication in the management of COVID-19, has been overused in many cases. Additionally, long-term corticosteroid use has been known to cause a variety of effects on the bone, including osteonecrosis, reduced bone mineral density (BMD), avascular necrosis of the hip joint, and osteoporosis with or without fracture. It implies that steroids might be an important cause of multiple musculoskeletal complications.

Skeletal muscle and fatigue

Many studies have reported fatigue myalgia and generalized weakness as some of the common persisting complaints in symptomatic infections of the disease[35]. In the previous epidemics of SARS, extensive myalgias and muscle dysfunction were also reported. Direct viral infection and/or the cytokine storm could lead to pathological changes in skeletal muscle tissue in addition to deconditioning due to prolonged disuse during the hospitalization or disease period.

Mayer *et al*[36] showed that a long intensive care unit stay is linked with a rapid and significant reduction in the volume of the rectus femoris muscle (average: 18.5%), until the 7th d of hospitalization. Carfì *et al*[37], in a study to follow up the post-COVID-19 patients in a hospital in Italy, found that in recovered patients, 87.4% responded with at least one persistent symptom, especially fatigue. Paneroni *et al*[38] evaluated the muscle strength of the quadriceps and biceps femoris of patients in post-discharge recovered COVID-19 cases. They found that 86% of cases had quadriceps weakness and 73% had biceps femoris weakness. These findings proved muscle dysfunction in individuals with long COVID-19. Jacobs *et al*[39] in their study to assess the persistence of symptoms and quality of life at 35 d after hospitalization of COVID-19 infection found fatigue as the most common persisting symptom.

Fatigue was found to be the most common symptom followed by shortness of breath (31%), loss of smell (22%), and muscle ache (21%) by the Office for the National Statistics, census 2021, in the estimates of the prevalence of self-reported long COVID-19 and associated activity limitation using United Kingdom Coronavirus (COVID-19) Infection Survey data[40]. Compared with age-matched healthy controls, approximately 2-3 mo after discharge, moderate to severe cases had a 32% reduction in grip strength and a 13% reduction in the distance walked in 6 min[41].

Aiyegbusi *et al*[42] did a review on symptoms, complications, and management of long COVID-19 and found that 47% reporting fatigue as the most common, myalgia (muscle pain) in 25%, and joint pain in 20%. Varghese *et al*[43] found that 54% of the patients reported fatigue as one of the persisting symptoms. Huang *et al*[44] did a follow-up study from June 16, 2020 to September 3, 2020 to assess 6 mo consequences of COVID-19 in patients discharged from the hospital, and they reported fatigue (63%) and sleep difficulties (26%) as the most common symptoms. Miyazato *et al*[45] also reported fatigue as one of the prolonged and late-onset symptoms conducted in patients admitted for COVID-19 to the Disease Control and Prevention Center and National Center for Global Health and Medicine from February to June 2020. Daher *et al*[46] conducted a follow-up study on 33 confirmed COVID-19 positive patients 6 wk post-discharge to assess the pulmonary and extrapulmonary disease sequelae and found a significant tendency among the patients to suffer from fatigue symptoms with significant limitations of their mobility, which was reflected by reduced 6-min walking test distance among the extrapulmonary sequelae. In their study, characterizing long COVID-19 in an international cohort over 7 mo of symptoms and their impact, Davis *et al*[47] also reported the patients who have had or were suspicious of COVID-19 reported fatigue as the most common persisting symptom even after 6 mo.

Multiple etiologies of fatigue (physical, mental, emotional) could be present. Therefore, fatigue should be researched according to the accompanying symptoms or more specific features[48]. Another sequelae is intolerance to physical activities associated with a chronic fatigue condition and difficulty in returning to normal daily life[49]. Eighteen people living with long COVID-19 in the United Kingdom were interviewed with a semi-structured questionnaire in a qualitative study by Humphrey *et al*[50] showing people faced reduced physical function, compounded by the cognitive and psychological effects of long COVID-19.

Arthralgia and myalgia

Arthralgia is pain localized to the joints, while myalgia is pain localized to muscle. They are typically present in the early course of the disease and in patients experiencing long-term effects of COVID-19 or a prolonged disease course. Studies have described how SARS-CoV-2 infection induces systemic elevations of cytokines and signaling molecules. This 'cytokine storm' is thought to be implicated in musculoskeletal manifestations, among many others. Myalgia and arthralgia are reported as one of the most common persistent symptoms in patients with post-acute sequelae of COVID-19 and are more notable in patients who were prone to being positioned during intensive care unit admission[51].

In a study of 294 patients hospitalized with COVID-19, Hoong *et al*[52] observed that 30% of patients reported musculoskeletal complaints; 37.5% had myalgia, 5.7% had arthralgia, 6.8% had new-onset backache, and 50% had generalized body aches. Elhiny *et al*[53] reported that physical decline was the most common symptom reported in musculoskeletal complications. Patients who also had mild to moderate forms of the infection can experience exacerbated muscle and joint pain. Petersen *et al*[54] in their study of long COVID-19 in a longitudinal study in the Faroe Islands found out arthralgia is one of the most persistent symptoms following fatigue and loss of smell and taste.

Follow-up of adults with non-critical COVID-19 after symptom onset in a study by Carvalho-Schneider *et al*[55] found that 13% of the patients who never had arthralgia at the onset of the disease reported arthralgia 30 d after discharge and 21% after 60 d. The study by Chopra *et al*[56] on clinical predictors of long COVID-19 symptoms in patients with mild COVID-19 at 30 d post-discharge (long COVID-19) found myalgia as one of the most common persistent symptoms following fatigue and cough. Stavem *et al*[57] also reported myalgia as one of the most common persisting symptoms 1.5-6.0 mo after infection in non-hospitalized patients. Ghosn *et al*[58] in a large prospective cohort study in France among the post-discharge patients at 3 mo and 6 mo observed mostly fatigue, dyspnea, joint pain, and myalgia. COVID-19 has also been found to cause reactive arthritis and new-onset inflammatory arthritis typically occurring within a month after its diagnosis[59].

There were reported cases of reactive arthritis post discharge from COVID-19[60]. Derksen *et al*[61] in a Dutch study of 5 patients who presented with inflammatory arthritis 6.6 wk post COVID-19 infection, found that 2 patients had strongly positive and another patient had weakly positive anti-CCP antibodies, suggesting post-COVID-19 rheumatoid arthritis development.

BMD

C-X-C motif chemokine 10, IL-17, and TNF-α induce osteoclastogenesis and inhibit osteoblast proliferation and differentiation causing increased bone fragility[34]. Berktaş *et al*[62] assessed the BMD of hospitalized COVID-19 patients at diagnosis and follow-up visits using chest computed tomography. BMD was retrospectively measured by quantitative computed tomography. BMD decreased by a mean of 8.6% (± 10.5%) from diagnosis to follow-up. The osteoporosis ratio increased two-fold after hospitalization for COVID-19 because of this substantial bone loss.

An animal experimental study characterized the effects of SARS-CoV-2 infections on bone metabolism in an established golden Syrian hamster model for COVID-19. SARS-CoV-2 caused significant multifocal loss of bone trabeculae in the long bones and lumbar vertebrae of all infected hamsters implicating the same could happen in humans post-COVID-19. A multicenter study by Kottlor *et al*[63] showed that COVID-19 patients requiring intensive care had significantly lower BMD than those who were managed in non-intensive care settings.

Researchers at Indiana University School of Medicine discovered that the mouse models infected with the novel coronavirus lost nearly 25% of their bone mass within 2 wk of infection. They also found mouse models with a 63% increase in osteoclasts, the cells that cause the bone to break down.

Neuromuscular

Musculoskeletal manifestations can be a result of underlying neurological disturbances. The central and peripheral nervous systems control our movements *via* the spinal motor neurons, which act as the final common pathway to the muscles[64]. Many studies have reported peripheral neuropathy, most commonly Guillain-Barre and related symptoms. Guillain-Barre syndrome and critical illness-induced polyneuropathy/myopathy are two important peripheral neuropathies seen in COVID-19[65].

A follow-up study conducted for 8 mo in Denmark performed electromyography and conventional nerve conduction study of 20 patients with persistent fatigue. They found that all patients with myopathic electromyography reported physical fatigue; 8 patients reported about myalgia while 3 patients without myopathic changes complained about physical fatigue. Long-term COVID-19 does not cause large fiber neuropathy, but myopathic changes were seen[66]. Acute myopathies are reported in acute COVID-19 infection[67], which may have a detrimental effect in the muscle in the post infective stages.

Rehabilitation perspectives

COVID-19 has multisystem effects including physical as well as psychological effects. The wholesome evaluation and rehabilitation of such patients require a multifaceted and interdisciplinary approach to cover all aspects properly. Identification of the pre-existing disabling conditions contributing to the cumulative effect of long COVID-19 is also an important aspect. Reinfection, post-viral bacterial and fungal infections, baseline routine investigations along with C-reactive protein, fibrinogen, D-dimer, troponin, and ferritin can also be considered if clinically indicated. Cardiac function tests (echocardiography) should be done to check cardiopulmonary status before framing the exercise program.

Rehabilitation should be addressed holistically following the domains of the International Classification of Functioning, Disability, and Health. Studies have shown that early mobilization helps in the reduction of the harmful effects of the disease, especially on muscle and cardiopulmonary function, mobility, and function[68], implying rehabilitation of long COVID-19 should start from the beginning. Physical exercise should be individualized specifying intensity, frequency, duration, and type of exercise. Exercise should be gradually increased according to one's capacity. The patient should be educated with an emphasis on self-management. The patient should respect the pain and their own capabilities. Energy conservation techniques such as simplifying tasks, pacing the activities over time, and taking breaks should be followed. Repeated practice of functional activities and a set of specific actions according to the patient's priorities, needs, and goals may improve the functional aspects. All such activities need to be evaluated regularly to determine whether they should be continued, changed, or stopped[69].

However, no studies on rehabilitation intervention have been investigated in long COVID-19 for musculoskeletal complications in particular[70]. In our systematic reviews, we did only descriptive analysis. We did not address the individual cases or case series study or any cohort or trials, which may miss the characteristics of the individual cases in particular. However, performing a systematic review of all systematic reviews and meta-analyses provided a stronger evidence-based study.

CONCLUSION

Musculoskeletal involvement is common during active SARS-CoV-2 infection. Fatigue is very common during this phase. Here we have highlighted the musculoskeletal complications in long COVID-19 syndrome. Again, fatigue is found to be very common along with myalgia and arthralgia. There is a lack of studies on these aspects. Moreover, all the studies are heterogeneous, especially in terms of the duration of post-COVID and the definition of long COVID. There are no studies for rehabilitation intervention in musculoskeletal complications specifically. This study reinforced the gravity of the current situation. Considering the lacuna in literature and the needs of the current situation, further studies are warranted to standardize effective rehabilitation interventions in musculoskeletal complications. More homogenous studies are needed using proper case definition and duration of long COVID. Studies on functional impairment due to musculoskeletal involvement are needed.

ARTICLE HIGHLIGHTS

Research background

Research is lacking in musculoskeletal complications in long coronavirus disease 2019 (COVID-19).

Research motivation
Currently, many long COVID-19 patients are coming to outpatient departments of rehabilitation for musculoskeletal issues.

Research objectives
To find musculoskeletal complications in long COVID-19 and relevant rehabilitation interventions.

Research methods
A systematic review of systematic reviews and meta-analyses was done.

Research results
Among many musculoskeletal issues, fatigue was found to be the most common complication. Rehab intervention is severely lacking in literature.

Research conclusions
Rehabilitation need identification is of the utmost importance in musculoskeletal aspects of long COVID. Fatigue was found to be the most common complication.

Research perspectives
Identification of rehabilitation needed following identification of musculoskeletal complications is crucial in long COVID-19 cases.

FOOTNOTES

Author contributions: Swarnakar R and Wadhwa S contributed to conception and design of this study; Swarnakar R, Jenifa S and Wadhwa S contributed to literature search and writing.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: India

ORCID number: Raktim Swarnakar 0000-0002-7221-2825; Sanjay Wadhwa 0000-0003-1832-3361.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ

REFERENCES

1 **World Health Organization**. Data at WHO. [cited 1 September 2022]. Available from: https://www.who.int/data
2 **Ludvigsson JF**. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatr* 2021; **110**: 914-921 [PMID: 33205450 DOI: 10.1111/apa.15673]
3 **Akbarialiabad H**, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, Razani B, Mwangi J, Asadi-Pooya AA, Malekmakan L, Bastani B. Long COVID, a comprehensive systematic scoping review. *Infection* 2021; **49**: 1163-1186 [PMID: 34319569 DOI: 10.1007/s15010-021-01666-x]
4 **Michelen M**, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, O'Hara M, Suett J, Dahmash D, Bugaeva P, Rigby I, Munblit D, Harriss E, Burls A, Foote C, Scott J, Carson G, Olliaro P, Sigfrid L, Stavropoulou C. Characterising long COVID: a living systematic review. *BMJ Glob Health* 2021; **6** [PMID: 34580069 DOI: 10.1136/bmjgh-2021-005427]
5 **Iqbal FM**, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine* 2021; **36**: 100899 [PMID: 34036253 DOI: 10.1016/j.eclinm.2021.100899]
6 **Vollbracht C**, Kraft K. Feasibility of Vitamin C in the Treatment of Post Viral Fatigue with Focus on Long COVID, Based on a Systematic Review of IV Vitamin C on Fatigue. *Nutrients* 2021; **13** [PMID: 33807280 DOI: 10.3390/nu13041154]

7 **Jennings G**, Monaghan A, Xue F, Mockler D, Romero-Ortuño R. A Systematic Review of Persistent Symptoms and Residual Abnormal Functioning following Acute COVID-19: Ongoing Symptomatic Phase vs. Post-COVID-19 Syndrome. *J Clin Med* 2021; **10** [PMID: 34945213 DOI: 10.3390/jcm10245913]

8 **Fernández-de-Las-Peñas C**, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, Navarro-Santana M. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021; **92**: 55-70 [PMID: 34167876 DOI: 10.1016/j.ejim.2021.06.009]

9 **Malik P**, Patel K, Pinto C, Jaiswal R, Tirupathi R, Pillai S, Patel U. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* 2022; **94**: 253-262 [PMID: 34463956 DOI: 10.1002/jmv.27309]

10 **Ceban F**, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, Lin K, Mansur RB, Ho RC, Rosenblat JD, Miskowiak KW, Vinberg M, Maletic V, McIntyre RS. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun* 2022; **101**: 93-135 [PMID: 34973396 DOI: 10.1016/j.bbi.2021.12.020]

11 **Chen C**, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review. *J Infect Dis* 2022 [PMID: 35429399 DOI: 10.1093/infdis/jiac136]

12 **van Kessel SAM**, Olde Hartman TC, Lucassen PLBJ, van Jaarsveld CHM. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. *Fam Pract* 2022; **39**: 159-167 [PMID: 34268556 DOI: 10.1093/fampra/cmab076]

13 **Alkodaymi MS**, Omrani OA, Fawzy NA, Shaar BA, Almamlouk R, Riaz M, Obeidat M, Obeidat Y, Gerberi D, Taha RM, Kashour Z, Kashour T, Berbari EF, Alkattan K, Tleyjeh IM. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clin Microbiol Infect* 2022; **28**: 657-666 [PMID: 35124265 DOI: 10.1016/j.cmi.2022.01.014]

14 **Fernández-de-Las-Peñas C**, Navarro-Santana M, Plaza-Manzano G, Palacios-Ceña D, Arendt-Nielsen L. Time course prevalence of post-COVID pain symptoms of musculoskeletal origin in patients who had survived severe acute respiratory syndrome coronavirus 2 infection: a systematic review and meta-analysis. *Pain* 2022; **163**: 1220-1231 [PMID: 34561390 DOI: 10.1097/j.pain.0000000000002496]

15 **Han Q**, Zheng B, Daines L, Sheikh A. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. *Pathogens* 2022; **11** [PMID: 35215212 DOI: 10.3390/pathogens11020269]

16 **d'Ettorre G**, Gentilini Cacciola E, Santinelli L, De Girolamo G, Spagnolello O, Russo A, Tarsitani L, Ciccozzi M, Mastroianni CM, d'Ettorre G, Ceccarelli G. Covid-19 sequelae in working age patients: A systematic review. *J Med Virol* 2022; **94**: 858-868 [PMID: 34655247 DOI: 10.1002/jmv.27399]

17 **Behnood SA**, Shafran R, Bennett SD, Zhang AXD, O'Mahoney LL, Stephenson TJ, Ladhani SN, De Stavola BL, Viner RM, Swann OV. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies. *J Infect* 2022; **84**: 158-170 [PMID: 34813820 DOI: 10.1016/j.jinf.2021.11.011]

18 **Nguyen NN**, Hoang VT, Dao TL, Dudouet P, Eldin C, Gautret P. Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review. *Eur J Clin Microbiol Infect Dis* 2022; **41**: 515-545 [PMID: 35142947 DOI: 10.1007/s10096-022-04417-4]

19 **Lopez-Leon S**, Wegman-Ostrosky T, Ayuzo Del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. Long-COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep* 2022; **12**: 9950 [PMID: 35739136 DOI: 10.1038/s41598-022-13495-5]

20 **Abdel-Gawad M**, Zaghloul MS, Abd-Elsalam S, Hashem M, Lashen SA, Mahros AM, Mohammed AQ, Hassan AM, Bekhit AN, Mohammed W, Alboraie M. Post-COVID-19 Syndrome Clinical Manifestations: A Systematic Review. *Antiinflamm Antiallergy Agents Med Chem* 2022 [PMID: 35346011 DOI: 10.2174/1871523021666220328115818]

21 **Almas T**, Malik J, Alsubai AK, Jawad Zaidi SM, Iqbal R, Khan K, Ali M, Ishaq U, Alsufyani M, Hadeed S, Alsufyani R, Ahmed R, Thakur T, Huang H, Antony M, Antony I, Bhullar A, Kotait F, Al-Ani L. Post-acute COVID-19 syndrome and its prolonged effects: An updated systematic review. *Ann Med Surg (Lond)* 2022; **80**: 103995 [PMID: 35721785 DOI: 10.1016/j.amsu.2022.103995]

22 **Maglietta G**, Diodati F, Puntoni M, Lazzarelli S, Marcomini B, Patrizi L, Caminiti C. Prognostic Factors for Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis. *J Clin Med* 2022; **11** [PMID: 35329867 DOI: 10.3390/jcm11061541]

23 **Healey Q**, Sheikh A, Daines L, Vasileiou E. Symptoms and signs of long COVID: A rapid review and meta-analysis. *J Glob Health* 2022; **12**: 05014 [PMID: 35596571 DOI: 10.7189/jogh.12.05014]

24 **de Oliveira Almeida K**, Nogueira Alves IG, de Queiroz RS, de Castro MR, Gomes VA, Santos Fontoura FC, Brites C, Neto MG. A systematic review on physical function, activities of daily living and health-related quality of life in COVID-19 survivors. *Chronic Illn* 2022; 17423953221089309 [PMID: 35404175 DOI: 10.1177/17423953221089309]

25 **Fugazzaro S**, Contri A, Esseroukh O, Kaleci S, Croci S, Massari M, Facciolongo NC, Besutti G, Iori M, Salvarani C, Costi S; Reggio Emilia COVID-19 Working Group. Rehabilitation Interventions for Post-Acute COVID-19 Syndrome: A Systematic Review. *Int J Environ Res Public Health* 2022; **19** [PMID: 35564579 DOI: 10.3390/ijerph19095185]

26 **Venkatesan P**. NICE guideline on long COVID. *Lancet Respir Med* 2021; **9**: 129 [PMID: 33453162 DOI: 10.1016/S2213-2600(21)00031-X]

27 A clinical case definition of post COVID-19 condition by a Delphi consensus (6 October 2021). [cited 6 July 2022]. Available from: https://reliefweb.int/report/world/clinical-case-definition-post-covid-19-condition-delphi-consensus-6-october-2021

28 **Nabavi N**. Long covid: How to define it and how to manage it. *BMJ* 2020; **370**: m3489 [PMID: 32895219 DOI: 10.1136/bmj.m3489]

29 **Yan Z**, Yang M, Lai CL. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. *Biomedicines* 2021; **9** [PMID: 34440170 DOI: 10.3390/biomedicines9080966]

30 **Soriano JB**, Murthy S, Marshall JC, Relan P, Diaz JV; WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022; **22**: e102-e107 [PMID: 34951953 DOI: 10.1016/S1473-3099(21)00703-9]

31 **Wang MY**, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. *Front Cell Infect Microbiol* 2020; **10**: 587269 [PMID: 33324574 DOI: 10.3389/fcimb.2020.587269]

32 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

33 **Disser NP**, De Micheli AJ, Schonk MM, Konnaris MA, Piacentini AN, Edon DL, Toresdahl BG, Rodeo SA, Casey EK, Mendias CL. Musculoskeletal Consequences of COVID-19. *J Bone Joint Surg Am* 2020; **102**: 1197-1204 [PMID: 32675661 DOI: 10.2106/JBJS.20.00847]

34 **Hasan LK**, Deadwiler B, Haratian A, Bolia IK, Weber AE, Petrigliano FA. Effects of COVID-19 on the Musculoskeletal System: Clinician's Guide. *Orthop Res Rev* 2021; **13**: 141-150 [PMID: 34584465 DOI: 10.2147/ORR.S321884]

35 **Tenforde MW**, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, Gibbs KW, Erickson HL, Steingrub JS, Smithline HA, Gong MN, Aboodi MS, Exline MC, Henning DJ, Wilson JG, Khan A, Qadir N, Brown SM, Peltan ID, Rice TW, Hager DN, Ginde AA, Stubblefield WB, Patel MM, Self WH, Feldstein LR; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 993-998 [PMID: 32730238 DOI: 10.15585/mmwr.mm6930e1]

36 **Mayer KP**, Thompson Bastin ML, Montgomery-Yates AA, Pastva AM, Dupont-Versteegden EE, Parry SM, Morris PE. Acute skeletal muscle wasting and dysfunction predict physical disability at hospital discharge in patients with critical illness. *Crit Care* 2020; **24**: 637 [PMID: 33148301 DOI: 10.1186/s13054-020-03355-x]

37 **Carfì A**, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 2020; **324**: 603-605 [PMID: 32644129 DOI: 10.1001/jama.2020.12603]

38 **Paneroni M**, Simonelli C, Saleri M, Bertacchini L, Venturelli M, Troosters T, Ambrosino N, Vitacca M. Muscle Strength and Physical Performance in Patients Without Previous Disabilities Recovering From COVID-19 Pneumonia. *Am J Phys Med Rehabil* 2021; **100**: 105-109 [PMID: 33181531 DOI: 10.1097/PHM.0000000000001641]

39 **Jacobs LG**, Gourna Paleoudis E, Lesky-Di Bari D, Nyirenda T, Friedman T, Gupta A, Rasouli L, Zetkulic M, Balani B, Ogedegbe C, Bawa H, Berrol L, Qureshi N, Aschner JL. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One* 2020; **15**: e0243882 [PMID: 33306721 DOI: 10.1371/journal.pone.0243882]

40 Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics [Internet]. [cited 14 July 2022]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/7july2022

41 **Lau HM**, Lee EW, Wong CN, Ng GY, Jones AY, Hui DS. The impact of severe acute respiratory syndrome on the physical profile and quality of life. *Arch Phys Med Rehabil* 2005; **86**: 1134-1140 [PMID: 15954051 DOI: 10.1016/j.apmr.2004.09.025]

42 **Aiyegbusi OL**, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, Haroon S, Price G, Davies EH, Nirantharakumar K, Sapey E, Calvert MJ; TLC Study Group. Symptoms, complications and management of long COVID: a review. *J R Soc Med* 2021; **114**: 428-442 [PMID: 34265229 DOI: 10.1177/01410768211032850]

43 **Varghese J**, Sandmann S, Ochs K, Schrempf IM, Frömmel C, Dugas M, Schmidt HH, Vollenberg R, Tepasse PR. Persistent symptoms and lab abnormalities in patients who recovered from COVID-19. *Sci Rep* 2021; **11**: 12775 [PMID: 34140539 DOI: 10.1038/s41598-021-91270-8]

44 **Huang C**, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; **397**: 220-232 [PMID: 33428867 DOI: 10.1016/S0140-6736(20)32656-8]

45 **Miyazato Y**, Morioka S, Tsuzuki S, Akashi M, Osanai Y, Tanaka K, Terada M, Suzuki M, Kutsuna S, Saito S, Hayakawa K, Ohmagari N. Prolonged and Late-Onset Symptoms of Coronavirus Disease 2019. *Open Forum Infect Dis* 2020; **7**: ofaa507 [PMID: 33230486 DOI: 10.1093/ofid/ofaa507]

46 **Daher A**, Balfanz P, Cornelissen C, Müller A, Bergs I, Marx N, Müller-Wieland D, Hartmann B, Dreher M, Müller T. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020; **174**: 106197 [PMID: 33120193 DOI: 10.1016/j.rmed.2020.106197]

47 **Davis HE**, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Redfield S, Austin JP, Akrami A. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021; **38**: 101019 [PMID: 34308300 DOI: 10.1016/j.eclinm.2021.101019]

48 **Yelin D**, Margalit I, Nehme M, Bordas-Martínez J, Pistelli F, Yahav D, Guessous I, Durà-Miralles X, Carrozzi L, Shapira-Lichter I, Vetter P, Peleato-Catalan D, Tiseo G, Wirtheim E, Kaiser L, Gudiol C, Falcone M, Leibovici L; On Behalf Of The LongCOV Research Group. Patterns of Long COVID Symptoms: A Multi-Center Cross Sectional Study. *J Clin Med* 2022; **11** [PMID: 35207171 DOI: 10.3390/jcm11040898]

49 **Dos Santos PK**, Sigoli E, Bragança LJG, Cornachione AS. The Musculoskeletal Involvement After Mild to Moderate COVID-19 Infection. *Front Physiol* 2022; **13**: 813924 [PMID: 35492595 DOI: 10.3389/fphys.2022.813924]

50 **Humphreys H**, Kilby L, Kudiersky N, Copeland R. Long COVID and the role of physical activity: a qualitative study. *BMJ Open* 2021; **11**: e047632 [PMID: 33692189 DOI: 10.1136/bmjopen-2020-047632]

51 **Cardemil CV**, Balachandran N, Kambhampati A, Grytdal S, Dahl RM, Rodriguez-Barradas MC, Vargas B, Beenhouwer

DO, Evangelista KV, Marconi VC, Meagley KL, Brown ST, Perea A, Lucero-Obusan C, Holodniy M, Browne H, Gautam R, Bowen MD, Vinjé J, Parashar UD, Hall AJ. Incidence, Etiology, and Severity of Acute Gastroenteritis Among Prospectively Enrolled Patients in 4 Veterans Affairs Hospitals and Outpatient Centers, 2016-2018. *Clin Infect Dis* 2021; **73**: e2729-e2738 [PMID: 32584956 DOI: 10.1093/cid/ciaa806]

52 **Hoong CWS**, Amin MNME, Tan TC, Lee JE. Viral arthralgia a new manifestation of COVID-19 infection? *Int J Infect Dis* 2021; **104**: 363-369 [PMID: 33476761 DOI: 10.1016/j.ijid.2021.01.031]

53 **Elhiny R**, Al-Jumaili AA, Yawuz MJ. What might COVID-19 Patients Experience after Recovery? A Systematic Review. 2021 Preprint. Available from: PPR: PPR358497 [DOI: 10.22541/au.162392727.73465025/v1]

54 **Petersen MS**, Kristiansen MF, Hanusson KD, Danielsen ME, Á Steig B, Gaini S, Strøm M, Weihe P. Long COVID in the Faroe Islands: A Longitudinal Study Among Nonhospitalized Patients. *Clin Infect Dis* 2021; **73**: e4058-e4063 [PMID: 33252665 DOI: 10.1093/cid/ciaa1792]

55 **Carvalho-Schneider C**, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, Flament T, Ferreira-Maldent N, Bruyère F, Stefic K, Gaudy-Graffin C, Grammatico-Guillon L, Bernard L. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021; **27**: 258-263 [PMID: 33031948 DOI: 10.1016/j.cmi.2020.09.052]

56 **Chopra N**, Chowdhury M, Singh AK, Ma K, Kumar A, Ranjan P, Desai D, Wig N. Clinical predictors of long COVID-19 and phenotypes of mild COVID-19 at a tertiary care centre in India. *Drug Discov Ther* 2021; **15**: 156-161 [PMID: 34234065 DOI: 10.5582/ddt.2021.01014]

57 **Stavem K**, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax* 2021; **76**: 405-407 [PMID: 33273028 DOI: 10.1136/thoraxjnl-2020-216377]

58 **Ghosn J**, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, Laouénan C; French COVID cohort study and investigators groups. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. *Clin Microbiol Infect* 2021; **27**: 1041.e1-1041.e4 [PMID: 34125067 DOI: 10.1016/j.cmi.2021.03.012]

59 **Ono K**, Kishimoto M, Shimasaki T, Uchida H, Kurai D, Deshpande GA, Komagata Y, Kaname S. Reactive arthritis after COVID-19 infection. *RMD Open* 2020; **6** [PMID: 32763956 DOI: 10.1136/rmdopen-2020-001350]

60 **Sapkota HR**, Nune A. Long COVID from rheumatology perspective - a narrative review. *Clin Rheumatol* 2022; **41**: 337-348 [PMID: 34845562 DOI: 10.1007/s10067-021-06001-1]

61 **Derksen VFAM**, Kissel T, Lamers-Karnebeek FBG, van der Bijl AE, Venhuizen AC, Huizinga TWJ, Toes REM, Roukens AHE, van der Woude D. Onset of rheumatoid arthritis after COVID-19: coincidence or connected? *Ann Rheum Dis* 2021; **80**: 1096-1098 [PMID: 33648960 DOI: 10.1136/annrheumdis-2021-219859]

62 **Berktaş BM**, Gökçek A, Hoca NT, Koyuncu A. COVID-19 illness and treatment decrease bone mineral density of surviving hospitalized patients. *Eur Rev Med Pharmacol Sci* 2022; **26**: 3046-3056 [PMID: 35503607 DOI: 10.26355/eurrev_202204_28636]

63 **Kottlors J**, Große Hokamp N, Fervers P, Bremm J, Fichter F, Persigehl T, Safarov O, Maintz D, Tritt S, Abdullayev N. Early extrapulmonary prognostic features in chest computed tomography in COVID-19 pneumonia: Bone mineral density is a relevant predictor for the clinical outcome - A multicenter feasibility study. *Bone* 2021; **144**: 115790 [PMID: 33301962 DOI: 10.1016/j.bone.2020.115790]

64 **Kerkman JN**, Daffertshofer A, Gollo LL, Breakspear M, Boonstra TW. Network structure of the human musculoskeletal system shapes neural interactions on multiple time scales. *Sci Adv* 2018; **4**: eaat0497 [PMID: 29963631 DOI: 10.1126/sciadv.aat0497]

65 **Bahouth S**, Chuang K, Olson L, Rosenthal D. COVID-19 related muscle denervation atrophy. *Skeletal Radiol* 2021; **50**: 1717-1721 [PMID: 33517510 DOI: 10.1007/s00256-021-03721-y]

66 **Agergaard J**, Leth S, Pedersen TH, Harbo T, Blicher JU, Karlsson P, Østergaard L, Andersen H, Tankisi H. Myopathic changes in patients with long-term fatigue after COVID-19. *Clin Neurophysiol* 2021; **132**: 1974-1981 [PMID: 34020890 DOI: 10.1016/j.clinph.2021.04.009]

67 **Islam B**, Ahmed M, Islam Z, Begum SM. Severe acute myopathy following SARS-CoV-2 infection: a case report and review of recent literature. *Skelet Muscle* 2021; **11**: 10 [PMID: 33883014 DOI: 10.1186/s13395-021-00266-5]

68 **Bonorino KC**, Cani KC. Early mobilization in the time of COVID-19. *Rev Bras Ter Intensiva* 2020; **32**: 484-486 [PMID: 33470350 DOI: 10.5935/0103-507X.20200086]

69 **Wade DT**. Rehabilitation after COVID-19: an evidence-based approach. *Clin Med (Lond)* 2020; **20**: 359-365 [PMID: 32518105 DOI: 10.7861/clinmed.2020-0353]

70 **Swarnakar R**, Yadav SL. Rehabilitation in long COVID-19: A mini-review. *World J Methodol* 2022; **12**: 235-245 [PMID: 36159093 DOI: 10.5662/wjm.v12.i4.235]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 496-501

DOI: 10.5501/wjv.v11.i6.496

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Global challenge with the SARS-CoV-2 omicron BA.2 (B.1.1.529.2) subvariant: Should we be concerned?

Jalil Roohani, Masoud Keikha

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cazzato G, Italy

Received: May 19, 2022
Peer-review started: May 19, 2022
First decision: August 22, 2022
Revised: August 23, 2022
Accepted: October 4, 2022
Article in press: Octobe 4, 2022
Published online: November 25, 2022

Jalil Roohani, Department of Biotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad 13131-99137, Iran

Masoud Keikha, Department of Medical Microbiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

Corresponding author: Masoud Keikha, Doctor, MD, Pediatric Gastroenterology Fellow, Department of Medical Microbiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.
masoud.keykha90@gmail.com

Abstract

BA.2 is a novel omicron offshoot of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has gone viral. There is limited knowledge regarding this variant of concern. Current evidence suggests that this variant is more contagious but less severe than previous SARS-CoV-2 variants. However, there is concern regarding the virus mutations that could influence pathogenicity, transmissibility, and immune evasion.

Key Words: SARS-CoV-2; Omicron; BA.2; B.1.1.529.2; Subvariant

Core Tip: BA.2 is novel omicron offshoot that goes viral. There is limit knowledge regarding this variant of concern. Current evidence suggested this variant is more contagious but less severe than previous severe acute respiratory syndrome coronavirus 2 previous variants. However, there is concern regarding the virus mutations that could be influenced pathogenicity, transmissibility as well as immune evasion.

Citation: Roohani J, Keikha M. Global challenge with the SARS-CoV-2 omicron BA.2 (B.1.1.529.2) subvariant: Should we be concerned? *World J Virol* 2022; 11(6): 496-501
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/496.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.496

TO THE EDITOR

The proliferation of omicron (B.1.1.529) and its global dissemination

On November 25, 2021, 22 patients in Gauteng province, South Africa, were diagnosed with atypical pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Afterward, the Technical Advisory Group of the World Health Organization (WHO) designated the novel SARS-CoV-2 variant as B.1.1.529[1]. Omicron has been identified as the fifth variant of concern (VOCs); the B.1.1.529 genome contains over 50 mutations that increase transmissibility, infectivity, immune system evasion, and vaccine inefficacy[2].

In late November 2021, the South African National Institute of Communicable Diseases reported a 22.4% increase in infections with this variant in a single day[1]. Based on a retrospective study conducted in South Africa, the VOC omicron significantly increased the risk of reinfection (× 2.39) compared to the beta and delta variants, indicating that this variant has a higher potential to evade the immune system[3]. Belgium, Hong Kong, Israel, Germany, the Netherlands, and the United Kingdom reported the detection of the omicron variant shortly after.

On November 27, 2021 due to the omicron variant's spread to more than 50 countries, the United States and Australia banned all transportation to those countries. However, on November 29, 2021 the first omicron case in Australia was identified in a traveler who traveled to Johannesburg, South Africa (https://www.abc.net.au/news/2021-11-29/nt-covid-outbreakkatherine-traveller-positive-for-omicron/100657690). Subsequently, the VOC omicron was identified in populations that were unvaccinated, partially or fully vaccinated, and immune to previous natural infection.

The birth of omicron BA.2 (B.1.1.59.2)

According to the WHO classification, the omicron variant has three to four subvariants, namely BA.1, BA.1.1, BA.2, and BA.3; nucleotide sequencing analysis revealed that BA.1, BA.1.1, BA.2, and BA.3 subvariants possess 39, 40, 31, and 34 mutations, respectively. All three subvariants evolved simultaneously in South Africa[4] (Figure 1). According to the hypothesis of Gao *et al*[5], omicron subvariants have emerged in the unvaccinated African population with compromised immune systems. Immunocompromised individuals are unable to fight SARS-CoV-2 infection effectively, and they have the best opportunity for multiplication, mutagenesis, and the emergence of new surge variants. Furthermore, animals can act as reservoirs for the evolution of novel variants. Nonetheless, there has been an increase in cases of BA.2 in recent days, to the point where the BA.2 variant is now the most common SARS-CoV-2 variant in most European countries.

BA.2 is also known as the "stealth variant" because it lacks a deletion signature at positions 69-70 that was not detected by the spike (S) gene target failure assay; therefore, BA.2 was underestimated with the current reverse transcription polymerase chain reaction setup, and its detection is only possible *via* whole genome sequencing[6,7]. According to viral genome sequences uploaded to the global GISAID database, the United Kingdom, the United States, Denmark, Germany, and Canada are the five countries with the highest prevalence of BA.2 (https://www.gisaid.org/). By February 18, 2022, BA.2 was reported in 153 countries (https://www.gisaid.org).

The VOC BA.2 is a highly contagious subvariant

Beginning in 2022, BA.2 has been on the rise in European countries. On January 1, 2022, the prevalence of BA.2 in the United Kingdom was approximately 5%, and it has been steadily rising[8]. According to preliminary studies conducted in Denmark, the first reports of BA.1 and BA.2 occurred on November 25, 2021 and December 5, 2021, respectively. During the 52nd wk of 2021, BA.2 prevalence in Denmark was 20%, while more than 45% of circulating SARS-CoV-2 strains in Denmark during the 2nd wk of 2022 were the BA.2 subvariant[9]. To this end, BA.2 is spreading at an alarming rate across the globe (Figure 2).

Lyngse *et al*[9] demonstrated that the BA.2 subvariant was able to infect unvaccinated individuals (odds ratio = 2.19; 95% confidence interval: 1.58-3.14) and individuals vaccinated with a third booster (odds ratio = 2.99; 95% confidence interval: 2.11-4.20). According to the Danish Staten's Serum Institute, BA.2 is approximately 1.5 and 4.2 times more contagious than BA.1 and the delta variant[9,10]. Yu *et al* [11] observed that the neutralizing antibody titer against BA.1 and BA.2 is 23-fold and 27-fold lower than that of WA1/2020. According to their research, the mean neutralizing antibody titers after the third booster of the BNT162b2 mRNA vaccine were approximately 1.4-fold lower than BA.1, indicating the capacity of BA.2 to confer neutralizing antibodies and evade humoral immunity[11].

Chen and Wei[10] hypothesized that BA.2 mutations caused the ability of the immune evasion to be approximately 30% and 17-fold greater than that of BA.1 and the delta variants, respectively, and resistant to most monoclonal antibodies except for sotrovimab. Evidently, BA.2 will quickly become the next dominant global variant. In addition, the United Kingdom Health Security Agency (UKHSA) cautioned that contact tracing data from the United Kingdom estimates that BA.2 is more likely to infect household contacts than BA.1 (10.3%). UKHSA estimated that the increase in the number of BA.2 patients after a third booster dose vaccination was more significant than that of BA.1-infected population (63% for BA.1 *vs* 70% for BA.2)[12]. According to Covglobe data, the incidence of BA.2

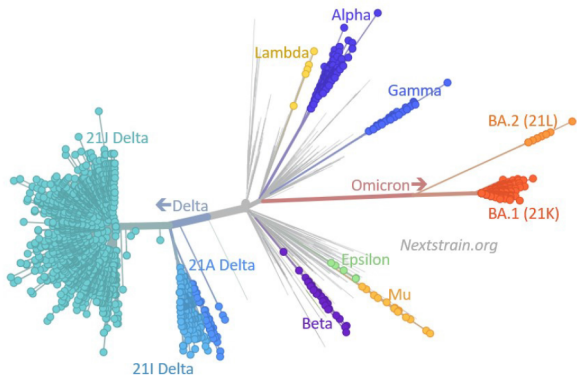


Figure 1 Severe acute respiratory syndrome coronavirus 2 genetic family tree diagram comprising omicron subvariants. Available from: https://www.npr.org/sections/goatsandsoda/2022/02/09/1047616658/take-a-look-at-sars-cov-2s-family-tree-its-full-of-surprises.

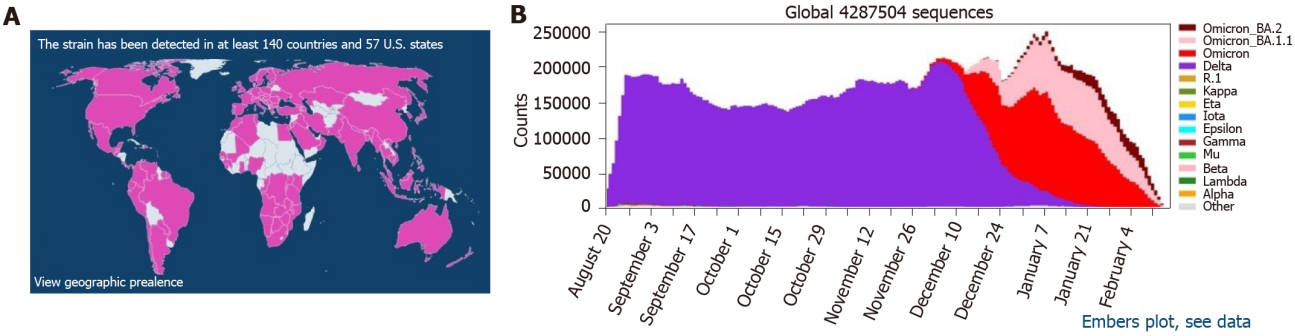


Figure 2 Global distribution of the BA.2 omicron subvariant in various countries/territories. Available from: https://gisaid.org/hcov19-variants/. A: According to GISAID databases, BA.2 is reported in more than 150 countries; B: The recent trend of BA.2 nucleotide sequence submission.

infections has been on the rise since October 2021 and has recently supplanted the VOC B.1.1.529; according to existing databases, BA.2 typically affects younger age groups (Figure 3).

BA.2 variant genome analysis

According to Nextstrain online server data, the omicron variant comprises three distinct branches: 21K (or Pangolin lineage12 BA.1), 21L (or BA.2), and BA.3 of the 21M omicron clade[4] (Figure 4). The BA.2 genome contains 20 shared and 6 unique mutations in the S protein compared to B.1.1.529 (archetypical) variant. BA.2 has significantly more mutations than BA1; most of these mutations are non-synonymous. By analyzing and comparing the genomes of BA.1 and BA.2, Wiegand *et al*[13] observed that BA.2 possesses the most genetic variation in the S protein (24-35 mutations, mean = 30.7) and that the effect of these mutations on virulence, viral transmission, and immune evasion has been identified in previous research. After the S protein, the nucleoprotein has the most genetic changes, but the majority of these changes are non-synonymous, affecting the sensitivity and specificity of diagnostic methods[13]. According to the CoronaTrend online server, the S, nsp6, and M proteins exhibited the most BA.2 mutations (Figure 5).

Kumar *et al*[4] demonstrated in a recent study that multiple alignments of four omicron subvariants revealed that BA.1 comprised 39 mutations, BA.1.1 comprised 40 mutations, BA.2 comprised 31 mutations, and BA.3 comprised 34 mutations. BA.1.1 has a single unique mutation of R346K, and BA.2 has eight mutations. Only one unique mutation exists in T19I, L24del (deletion), P25del, P26del, A27S, V213G, T376A, R408S, and BA.3 (R216del). Meanwhile, all subvariants comprise eleven shared mutations in their second receptor binding domain, including G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, and N501Y. By increasing the positive electrostatic surface, these mutations improve the interaction between the receptor binding domain motif and human angiotensin-converting enzyme 2[4]. They also observed that R400, R490, and R495 mutations in BA.2 formed new salt bridges and hydrogen, resulting in higher viral transmission than the BA.1 and BA.1.1 subvariants [4].

Desingu and Nagarajan[14] deduced that the BA.2 subvariant consisted of five distinct phylogenetically based original geographic regions, namely Sweden/Denmark, Philippines, Hong Kong, India, and China. They demonstrated that each of these clades exhibited unique mutations, such as the H78Y mutation in Denmark, the substitutions of ORF1a: A2909V and ORF3a: L140F in isolates from the

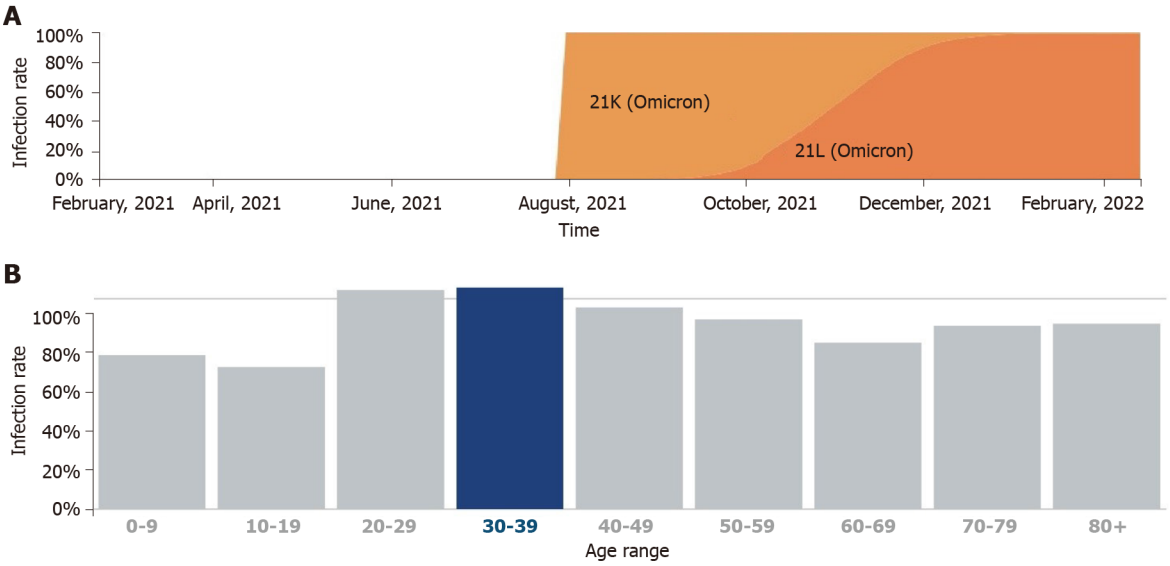


Figure 3 Global outbreak statistics for the BA.2 omicron subvariant. Available from: https://cov-spectrum.org/explore (https://covglobe.org). A: Rising trend of BA.2, available from: https://covglobe.org; B: Age distribution of individuals infected with BA.2, available from: https://cov-spectrum.org/explore.

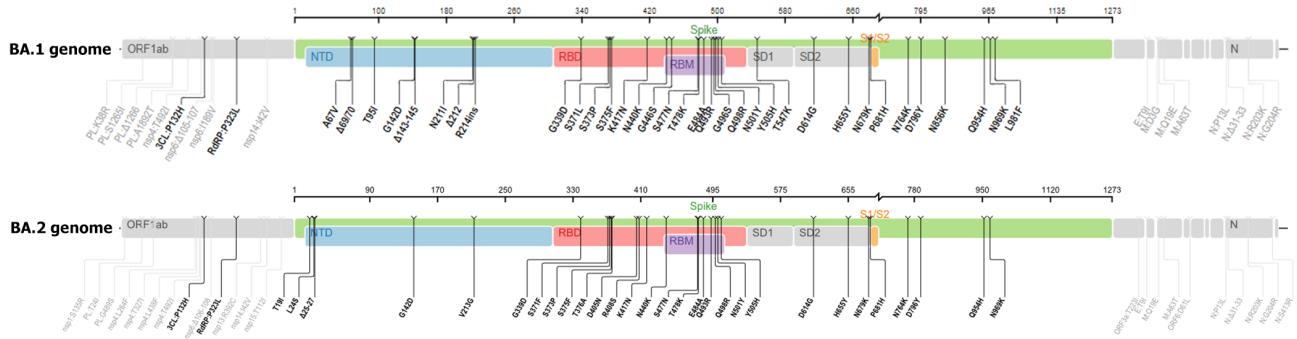


Figure 4 Comparison between the BA.1 and BA.2 omicron subvariant genomes. Available from: https://covdb.stanford.edu/page/mutation-viewer/#omicron.

Philippines and Hong Kong, and ORF1a: -3677L, ORF1b: S959P, and ORF7b: H42Y in the Indian subgroup. Each distinct mutation in the subpopulations modified the characteristics of BA.2 in terms of viral transmission, infectivity, disease severity, vaccine efficacy, and clinical outcomes in different geographic regions[14,15]. Recent studies suggest that mutations of P681H, H655Y, and N679K at the furin cleavage site increase the replication of omicron variants and as a result the transmissibility of omicron subvariants[4].

Vaccination against the BA.2 omicron subvariant

The 21L/BA.2 omicron variant has become predominant even after the third dose of the Pfizer-BioNTech vaccine, according to reports from Denmark (www.news-medical.net/news/20220214/First-survey-on-Omicron-BA2-in-France.aspx). Moreover, on January 26, 2022, Tyra Grove Krause stated, "*There is some evidence that it is more contagious, particularly among the unvaccinated, but it can also infect vaccinated individuals to a greater extent*" (https://www.gavi.org/vaccineswork/stealth-omicron-everything-you-need-know-about-new-ba2-subvariant-coronavirus).

Lyngse *et al*[9] showed that the viral load of unvaccinated individuals is significantly greater than that of fully immunized populations. Thus, non-immunized individuals can more effectively release BA.2. Initial UKHSA surveys indicated that the effectiveness of the BA.2 vaccine against symptomatic BA.2 infection was greater than that of the BA.1 vaccine (13% for BA.2 *vs* 9% for BA.1); additionally, a third booster dose may increase the effectiveness of the BA.2 vaccine (70% for BA.2 *vs* 63% for BA.1)[12,16]. However, Peiris *et al*[17] evaluated the effect of the third dose of BNT162b2 or CoronaVac vaccines against BA.2; they concluded that three doses with BNT162b2 or vaccination with two doses of CoronaVac and a third booster dose with BNT162b2 increased plaque reduction neutralization antibody titer above the threshold for protection against symptomatic BA.2 infection.

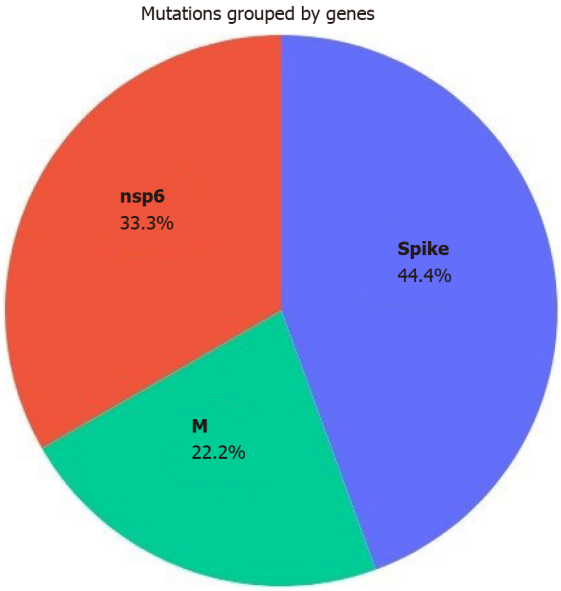


Figure 5 Significant mutation registrations of the BA.2 omicron subvariant. Available from: https://coronatrend.live/.

Although BA.2 mutations confer resistance to neutralizing antibodies, recent research shows that a third booster causes antibodies to cross-react with the omicron variant[18]. In addition, Lippi *et al*[19] revealed that the third booster vaccination increases neutralizing antibodies against the omicron variant and is a safe strategy until a new, more effective vaccine is introduced.

Further perspective

Despite the recent increase in BA.2 cases, the WHO has not yet given BA.2 a special designation. However, on January 21, 2022 the UKHSA designated BA.2 as a "variant under investigation" (https://www.gavi.org/vaccineswork/stealth-omicron-everything-you-need-know-about-new-ba2-subvariant-coronavirus). The WHO official Dr. Maria Van Kerkhove stated that BA.2 is significantly more contagious than BA.1 (https://www.cnbc.com/2022/02/08/who-says-omicron-bapoint2-subvariant-will-rise-globally.html); nonetheless, preliminary studies indicate that there is no difference between BA.2 and BA.1 in terms of hospitalization risk.

The remarkable increase in BA.2 infection cases and the rapidity with which it has spread in a short period of time is perplexing. In addition, intensive care unit admissions and mortality rates are rising, causing worldwide concern in healthcare facilities. According to the Infectious Diseases Society of America, the most effective treatments for SARS-CoV-2 B1.1.529 are monoclonal antibodies such as sotrovimab, evusheld, convalescent sera, and Oxford-AstraZeneca and Pfizer-BioNTech vaccines (https://www.idsociety.org/covid-19-real-time-learning-network/emerging-variants/emerging-covid-19-variants/#). Hand hygiene, physical distance, mask use, and mass vaccination, particularly a third booster dose, are recommended countermeasures to control the global spread of the BA.2 variant, as is the consideration of nationwide lockdowns.

FOOTNOTES

Author contributions: Rouhani J and Keikha M wrote and edited the draft; Keikha M contributed to the study design and data collection; and all authors read and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Iran

ORCID number: Masoud Keikha 0000-0003-1208-8479.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ

REFERENCES

1 **National Institute for Communicable Diseases**. Latest Confirmed Cases of COVID-19 in South Africa (2 December 2021). [cited 20 April 2022]. https://www.nicd.ac.za/Latest-confirmed-cases-of-covid-19-in-southafrica-2-december-2021/
2 **Rahimi F**, Talebi Bezmin Abadi A. The Omicron subvariant BA.2: Birth of a new challenge during the COVID-19 pandemic. *Int J Surg* 2022; **99**: 106261 [PMID: 35167986 DOI: 10.1016/j.ijsu.2022.106261]
3 **Pulliam JRC**, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, Dushoff J, Mlisana K, Moultrie H. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* 2022; **376**: eabn4947 [PMID: 35289632 DOI: 10.1126/science.abn4947]
4 **Kumar S**, Karuppanan K, Subramaniam G. Omicron (BA.1) and sub-variants (BA.1.1, BA.2, and BA.3) of SARS-CoV-2 spike infectivity and pathogenicity: A comparative sequence and structural-based computational assessment. *J Med Virol* 2022; **94**: 4780-4791 [PMID: 35680610 DOI: 10.1002/jmv.27927]
5 **Gao SJ**, Guo H, Luo G. Omicron variant (B.1.1.529) of SARS-CoV-2, a global urgent public health alert! *J Med Virol* 2022; **94**: 1255-1256 [PMID: 34850421 DOI: 10.1002/jmv.27491]
6 **Li K**, Zheng Z, Zhao X, Zeng Q, Zhou T, Guo Q, Hu Y, Xu W, Zhang Z, Li B. An Imported Case and an Infected Close Contact of the Omicron Variant of SARS-CoV-2 - Guangdong Province, China, December 13, 2021. *China CDC Wkly* 2022; **4**: 96-97 [PMID: 35186377 DOI: 10.46234/ccdcw2021.265]
7 **Carrazco-Montalvo A**, Armendáriz-Castillo I, Tello CL, Morales D, Armas-Gonzalez R, Guizado-Herrera D, León-Sosa A, Ramos-Sarmiento D, Fuertes B; USFQ-Consortium, Patino L. First detection of SARS-CoV-2 variant B.1.1.529 (Omicron) in Ecuador. *New Microbes New Infect* 2022; **45**: 100951 [PMID: 35018222 DOI: 10.1016/j.nmni.2022.100951]
8 **Leeman D**, Campos-Matos I, Dabrera G. Inequalities associated with emergence of Delta SARS-CoV-2 variant of concern (B.1.617.2) in England: awareness for future variants. *Public Health* 2022; **205**: e14-e15 [PMID: 35279303 DOI: 10.1016/j.puhe.2021.12.021]
9 **Lyngse FP**, Kirkeby CT, Denwood M, Christiansen LE, Mølbak K, Møller CH, Skov RL, Krause TG, Rasmussen M, Sieber RN, Johannesen TB, Lillebaek T, Fonager J, Fomsgaard A, Møller FT, Stegger M, Overvad M, Spiess K, Mortensen LH. Transmission of SARS-CoV-2 Omicron VOC subvariants BA. 1 and BA. 2: Evidence from Danish Households. 2022 Preprint. Available from: medRxiv:2022.01.28.22270044 [DOI: 10.1101/2022.01.28.22270044]
10 **Chen J**, Wei GW. Omicron BA.2 (B.1.1.529.2): high potential to becoming the next dominating variant. *ArXiv* 2022 [PMID: 35169598]
11 **Yu J**, Collier AY, Rowe M, Mardas F, Ventura JD, Wan H, Miller J, Powers O, Chung B, Siamatu M, Hachmann NP, Surve N, Nampanya F, Chandrashekar A, Barouch DH. Comparable Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants. *N Engl J Med* 2022 [PMID: 35169817 DOI: 10.1101/2022.02.06.22270533]
12 **Mahase E**. Omicron sub-lineage BA.2 may have "substantial growth advantage," UKHSA reports. *BMJ* 2022; **376**: o263 [PMID: 35101887 DOI: 10.1136/bmj.o263]
13 **Wiegand TR**, McVey A, Nemudraia A, Nemudryi A, Wiedenheft B. The rise and fall of SARS-CoV-2 variants and the emergence of competing Omicron lineages. 2022 Preprint. Available from: bioRxiv:2022.02.09.479842 [DOI: 10.1101/2022.02.09.479842]
14 **Desingu PA**, Nagarajan K. Omicron BA.2 Lineage spreads in clusters and is concentrated in Denmark. *J Med Virol* 2022; **94**: 2360-2364 [PMID: 35150013 DOI: 10.1002/jmv.27659]
15 **Desingu PA**, Nagarajan K, Dhama K. Emergence of Omicron third lineage BA.3 and its importance. *J Med Virol* 2022; **94**: 1808-1810 [PMID: 35043399 DOI: 10.1002/jmv.27601]
16 **Mahase E**. Covid-19: What do we know about omicron sublineages? *BMJ* 2022; **376**: o358 [PMID: 35149516 DOI: 10.1136/bmj.o358]
17 **Peiris M**, Cheng S, Chan K, Luk L, Li J, Tsang L, Poon L, Mok CKP, Ng SS, Ko F, Chen C, Yiu K, Hui D, Lam B. Virus neutralization of SARS-CoV-2 Omicron variant BA. 2 in those vaccinated with three doses of BNT162b2 or CoronaVac vaccines. 2022 Preprint. Available from: Research Square:2022.10.21203/rs.3.rs-1331606/v1 [DOI: 10.21203/rs.3.rs-1331606/v1]
18 **Garcia-Beltran WF**, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, Berrios C, Ofoman O, Chang CC, Hauser BM, Feldman J, Roederer AL, Gregory DJ, Poznansky MC, Schmidt AG, Iafrate AJ, Naranbhai V, Balazs AB. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell* 2022; **185**: 457-466.e4 [PMID: 34995482 DOI: 10.1016/j.cell.2021.12.033]
19 **Lippi G**, Mattiuzzi C, Henry BM. Neutralizing potency of COVID-19 vaccines against the SARS-CoV-2 Omicron (B.1.1.529) variant. *J Med Virol* 2022; **94**: 1799-1802 [PMID: 34988998 DOI: 10.1002/jmv.27575]

World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

World J Virol 2022 November 25; 11(6): 502-504

DOI: 10.5501/wjv.v11.i6.502

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Effect of the pandemic on rehabilitation healthcare services in India: Breaking barriers

Raktim Swarnakar, Shiv Lal Yadav

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Barve P, United States; Saeed MAM, Egypt; Seid AA, Ethiopia

Received: August 9, 2022
Peer-review started: August 9, 2022
First decision: August 22, 2022
Revised: August 24, 2022
Accepted: October 12, 2022
Article in press: October 12, 2022
Published online: November 25, 2022

Raktim Swarnakar, Shiv Lal Yadav, Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, New Delhi 110029, Delhi, India

Corresponding author: Raktim Swarnakar, MBBS, MD, Doctor, Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, Delhi, India. raktimswarnakar@hotmail.com

Abstract

We would like to highlight the rehabilitation medicine perspective from India. Difficulties are impacted by the pandemic during this time, especially for people with disabilities. Awareness building among the public regarding the need for rehabilitation along with improvement in infrastructure is the key unmet need.

Key Words: COVID-19; India; Physical medicine and rehabilitation; Rehabilitation; Healthcare service; Disability

Core Tip: Rehabilitation is a vital component of Universal Health Coverage. The coronavirus disease 2019 pandemic impacted negatively on health care delivery and rehabilitation services have been hindered severely as well. Proper awareness and health care infrastructure building are essential aspects that need to be addressed soon.

Citation: Swarnakar R, Yadav SL. Effect of the pandemic on rehabilitation healthcare services in India: Breaking barriers. *World J Virol* 2022; 11(6): 502-504
URL: https://www.wjgnet.com/2220-3249/full/v11/i6/502.htm
DOI: https://dx.doi.org/10.5501/wjv.v11.i6.502

TO THE EDITOR

We read with interest the review article by Nimavat *et al*[1] where they have shown healthcare difficulties impacted by the pandemic in India. We would like to emphasize the awareness, accessibilities and barriers of rehabilitation healthcare services in India and how coronavirus disease 2019 (COVID-19) pandemic has influenced it. Globally, 1

in 3 people is living with a health condition that would benefit from rehabilitation[2]. India, despite facing many odds, has played a distinguished role during the pandemic in terms of health care. Being the second largest populated country, it pioneered the country-wide COVID-19 vaccination drive[3]. On the other hand, though World Health Organization stated that rehabilitation should be incorporated into Universal Health Coverage as essential and indispensable health care[2], unfortunately, rehabilitation aspects are often neglected mainly due to the lack of awareness and partly due to misconception.

Physiatrists (expert doctors in rehabilitation medicine) are mainly responsible for patient care regarding rehabilitation. It is catering its service *via* the physical medicine and rehabilitation (PMR) department in Indian hospitals. The three most common misconceptions about rehabilitation are: (1) 'Rehabilitation' is often wrongly equated with 'exercise'; exercises are part of rehabilitation but not the sole part of it. Rehabilitation is far broader, from medical management to surgical rehabilitation. Such thought confinement to 'exercise'/'physiotherapy' leads to losing the scope of overall possibilities of holistic rehabilitation; (2) 'Rehabilitation'/'Rehab' is wrongly equated with 'only drug addiction/mental illness rehab'. It results in losing opportunities for rehabilitation; and (3) It is considered wrongly as only 'tertiary prevention' of the disease spectrum, forgetting its immense role in an acute rehabilitation setting. Proper rehabilitation can reduce the duration of acute illness and also prevent disability.

In India, 2.21% (26.8 million) of the population has one or another kind of disability[4]. And in cases of disability, rehabilitation plays a vital role, even PMR departments in India are involved in disability certifications in India. The COVID-19 pandemic has caused disruption of routine rehabilitation services all over the world and India was no exception. People with disabilities like spinal cord injury/paraplegia faced multiple issues like barriers in obtaining rehab services from hospitals and visiting hospitals for health complications[5]. But telemedicine facilities and telerehabilitation launched during the pandemic and opened a new arena for catering the health care service across India. Moreover, comorbidities and disabilities are risks for severe COVID-19 which led to home confinement and health service deprivation. Furthermore, stigma is another factor which causes concealment and which in turn results in avoidance of utilization of health services[6].

In this context, urgent needs are: (1) To increase the doctor population ratio; (2) To increase rehabilitation service centers at block and primary hospital levels; (3) Awareness regarding rehabilitation and its perceived benefit should be emphasized among the general population; and (4) Considering the increasing population of non-communicable diseases caused by long COVID, rehabilitation services and infrastructure should be strengthened[7]. Keeping pace with other developed countries, where much awareness of rehabilitation exists[8]; in India, developing such awareness is a key unmet need. Furthermore, there is an increasing trend or demand for the utilization of rehabilitation health services among the pediatric differently-abled population, any chronic disabling conditions like osteoarthritis, rheumatoid arthritis, stroke, traumatic brain injury, spinal cord injury/disorder *etc*, increasing geriatric population, people with cancers, amputations and many more. It is imperative that for a better post-COVID world coordinated action should be taken by all stakeholders to strengthen the health system to provide quality and timely rehabilitation (rehabilitation initiative 2030)[2].

FOOTNOTES

Author contributions: Swarnakar R designed and analyzed the manuscript; Swarnakar R and Yadav SL performed the research and wrote the letter.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: India

ORCID number: Raktim Swarnakar 0000-0002-7221-2825.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ

REFERENCES

1 **Nimavat N**, Hasan MM, Charmode S, Mandala G, Parmar GR, Bhangu R, Khan I, Singh S, Agrawal A, Shah A, Sachdeva

V. COVID-19 pandemic effects on the distribution of healthcare services in India: A systematic review. *World J Virol* 2022; **11**: 186-197 [DOI: 10.5501/wjv.v11.i4.186]

2 **World Health Organization**. Rehabilitation initiative 2030. [cited 9 August 2022]. Available from: https://www.who.int/initiatives/rehabilitation-2030

3 **Kaur H**, Kaur M, Bhattacharyya A, Prajapat M, Thota P, Sarma P, Kumar S, Kaur G, Sharma S, Prakash A, Saifuddin PK, Medhi B. Indian contribution toward biomedical research and development in COVID-19: A systematic review. *Indian J Pharmacol* 2021; **53**: 63-72 [PMID: 33976001 DOI: 10.4103/ijp.ijp_168_21]

4 **The National Handicapped Finance and Development Corporation**. Persons with Disabilities (Divyangjan) in India - A Statistical Profile: 2021. [cited 9 August 2022]. Available from: http://www.nhfdc.nic.in/upload/nhfdc/Persons_Disabilities_31mar21.pdf

5 **Swarnakar R**, Santra S. Personal hygiene care in persons with spinal cord injury during the COVID-19 pandemic and lockdown: an Indian perspective. *Spinal Cord Ser Cases* 2020; **6**: 76 [PMID: 32820154 DOI: 10.1038/s41394-020-00328-8]

6 **Swarnakar R**, Santra S. COVID-19, stigma, and people with disabilities: A mental health perspective. *World J Clin Infect Dis* 2022; **12**: 47-49 [DOI: 10.5495/wjcid.v12.i1.47]

7 **Swarnakar R**, Yadav SL. Communicable to Non-communicable Disease Pandemic in the Making: An Urgent Call for Post-COVID-19 Preparedness. *Cureus* 2022; **14**: e27453 [PMID: 36051716 DOI: 10.7759/cureus.27453]

8 **Stein J**, Visco CJ, Barbuto S. Rehabilitation Medicine Response to the COVID-19 Pandemic. *Am J Phys Med Rehabil* 2020; **99**: 573-579 [PMID: 32433243 DOI: 10.1097/PHM.0000000000001470]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com