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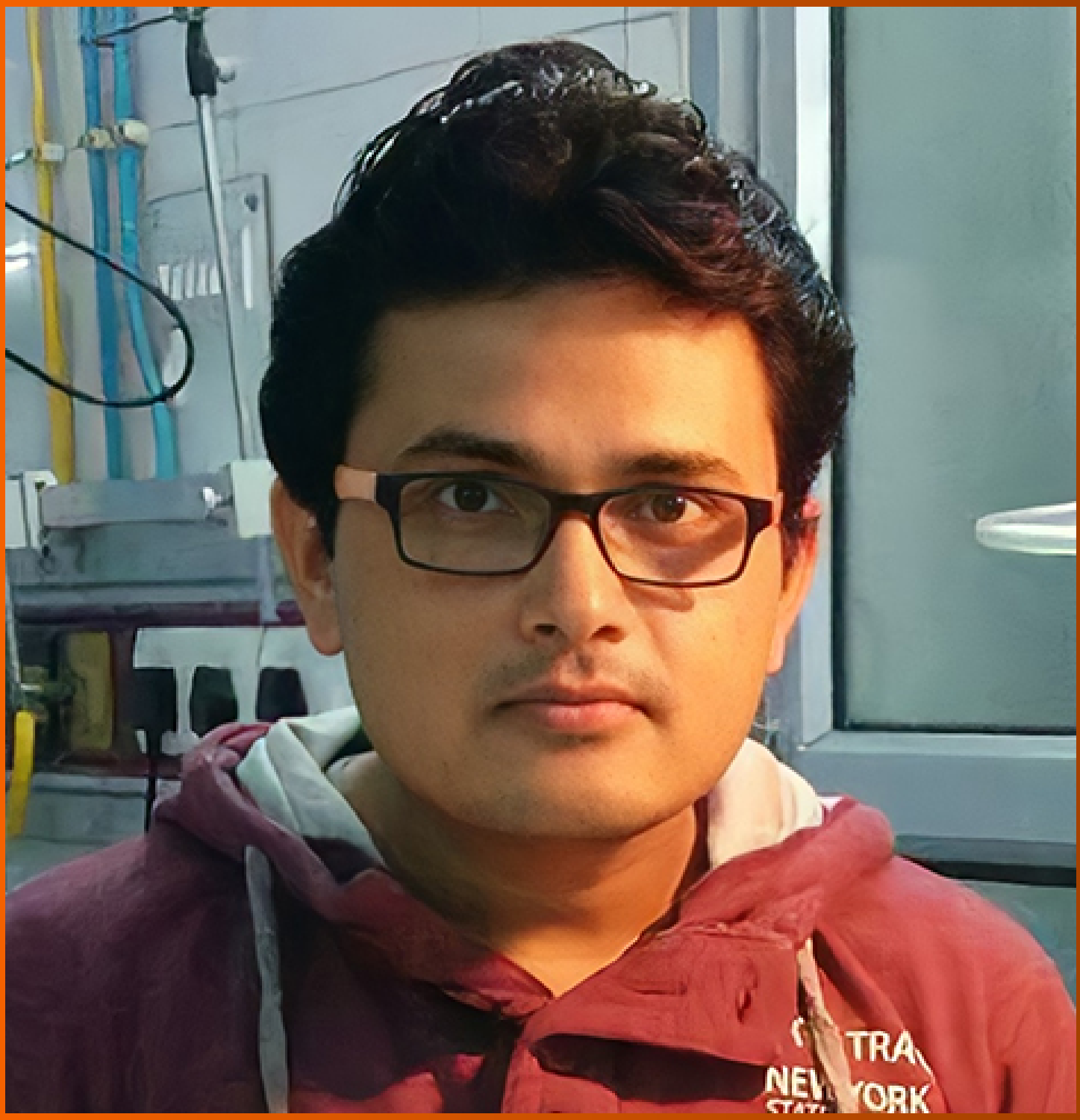

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MINIREVIEWS

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

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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.

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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

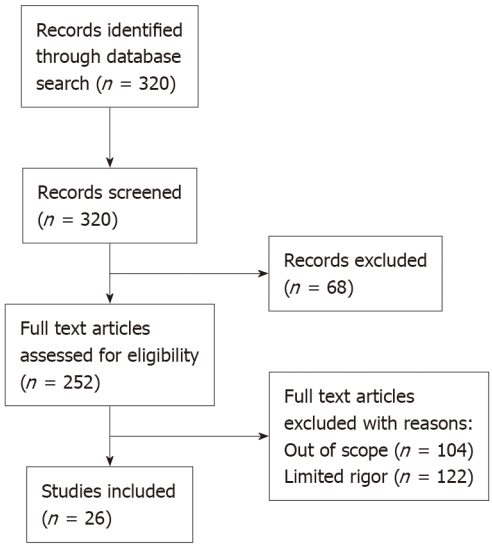

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Figure 1 PRISMA flow diagram.

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

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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

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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.

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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.

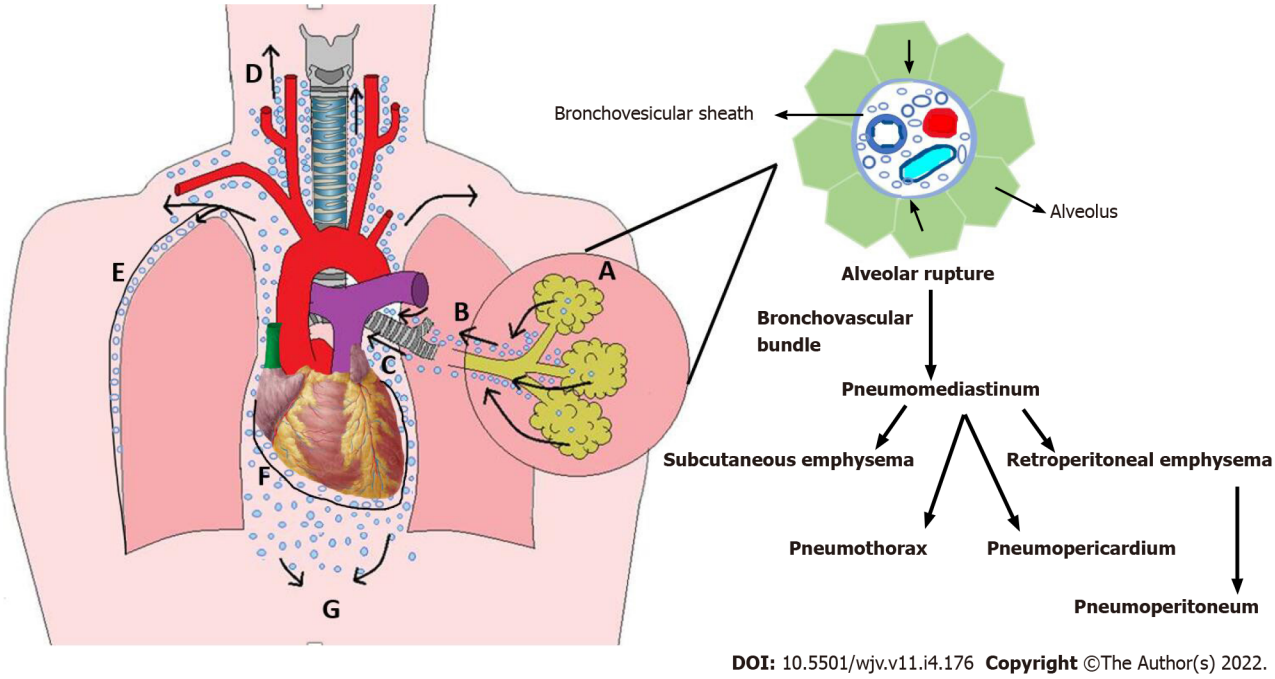

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Figure 1 Macklin effect. A: Macklin effect - Increase in pressure gradient between the damaged marginal alveoli and lung interstitium due to increase in intrathoracic pressure and or decrease pulmonary intravascular pressure, leads to alveoli rupture 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].

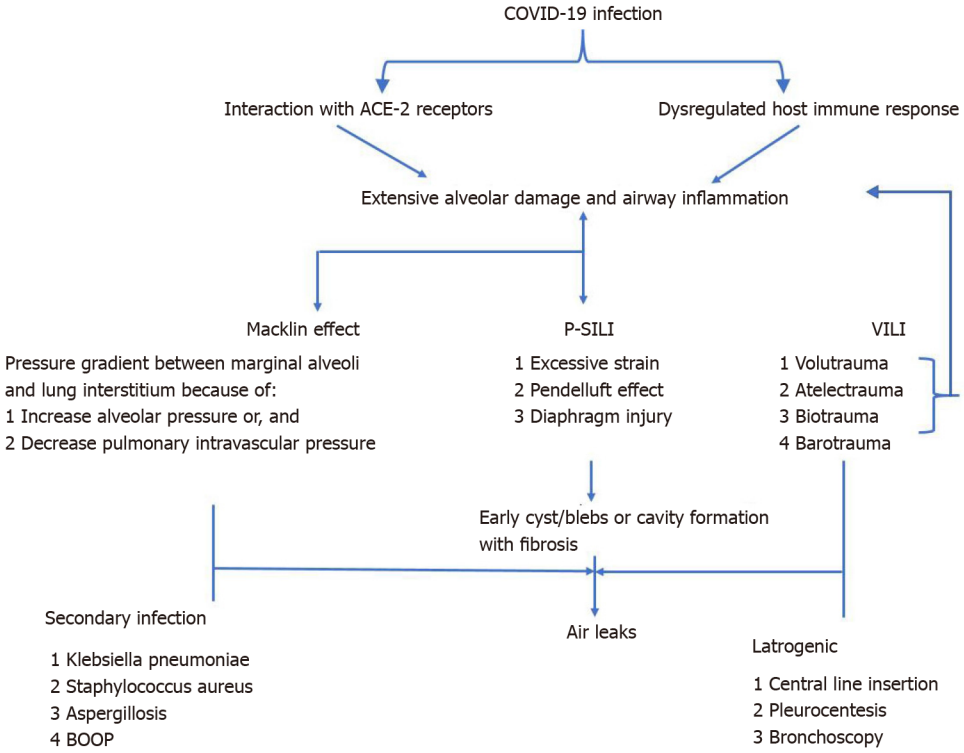

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Figure 2 Pathogenesis of air leaks in coronavirus disease 2019. COVID-19: Coronavirus disease 2019; ACE-2: Angiotensin-converting enzyme-2; P-SILI: Patient self-inflicted lung injury; VILI: Ventilator-induced lung injury.

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.

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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]

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SYSTEMATIC REVIEWS

COVID-19 pandemic effects on the distribution of healthcare services in India: A systematic review

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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.

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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

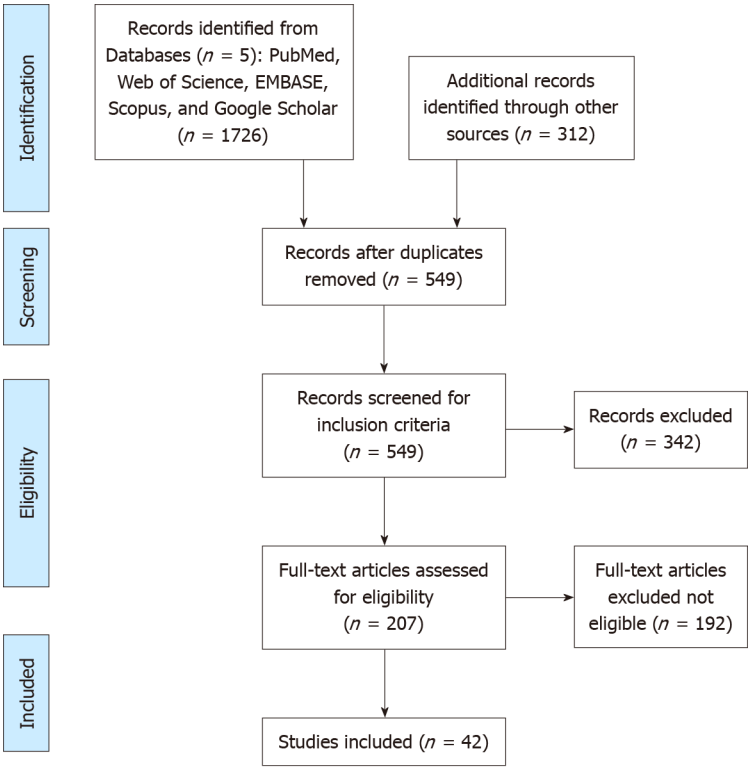

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Figure 1 PRISMA flowchart.

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

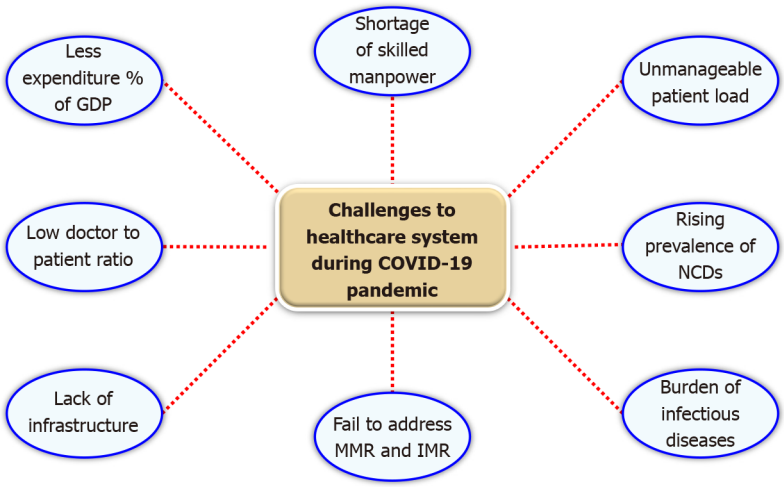

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Figure 2 Challenges faced by healthcare system during coronavirus disease 2019 pandemic. COVID-19: Coronavirus disease 2019; GDP: Gross domestic product; NCDs: Non-communicable diseases; IMR: Infant mortality rate; MMR: Maternal mortality ratio.

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

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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/

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CASE REPORT

COVID-19 presenting with persistent hiccup and myocardial infarction in a peritoneal dialysis patient: A case report

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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.

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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%.

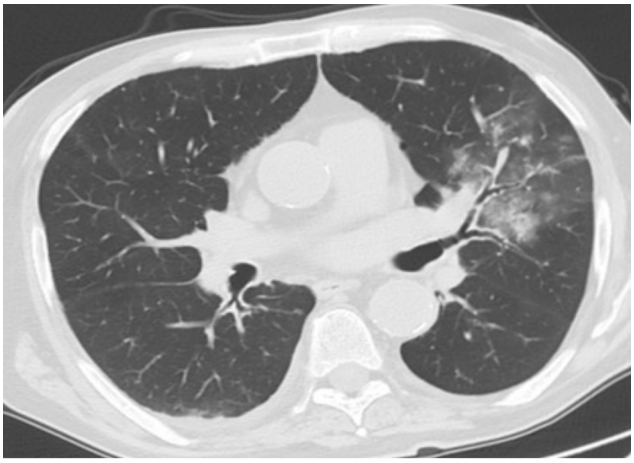

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Figure 1 Chest computed tomography at admission.

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.

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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.

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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]

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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

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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.

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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.

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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]

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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

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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.

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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.

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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]

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LETTER TO THE EDITOR

Cautious optimism in anticipation of hepatitis B curative therapies

Alla Turshudzhyan, Micheal Tadros

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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.

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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

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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]

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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

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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.

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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

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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]

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