ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 January 28; 13(1): 1-39

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 1 January 28, 2021

World Journal of Radiology

Monthly Volume 13 Number 1 January 28, 2021

Contents

ABOUT COVER

Edward Araujo Júnior, PhD, Associate Professor, Department of Obstetrics, Paulista School of Medicine - Federal University of Sao Paulo, São Paulo 05089-030, São Paulo, Brazil. araujojred@terra.com.br

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yun-Xiaojian Wu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
January 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 January 28; 13(1): 1-18

DOI: 10.4329/wjr.v13.i1.1

ISSN 1949-8470 (online)

SYSTEMATIC REVIEW

Exploration of sex-specific and age-dependent COVID-19 fatality rate in Bangladesh population

Md Abdul Alim Al-Bari, Showna Hossain, Md Kudrat-E Zahan

ORCID number: Md Abdul Alim Al-Bari 0000-0002-1777-3662; Showna Hossain 0000-0002-0568-4363; Md Kudrat-E Zahan 0000-0001-8159-5293.

Author contributions: Al-Bari MAA wrote, critically revised the manuscript and proofread; Hossain S analysed the data; Zahan MKE designed the study; this manuscript is not under review elsewhere, and all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors clearly declare that there are no competing and commercial interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Showna Hossain, Department of Pharmacy, University of Rajshahi, Rajshahi 6205, Bangladesh

Md Kudrat-E Zahan, Department of Chemistry, University of Rajshahi, Rajshahi 6205, Bangladesh

Corresponding author: Md Abdul Alim Al-Bari, PhD, Professor, Department of Pharmacy, University of Rajshahi, Dhaka-Rajshahi Highway, Rajshahi 6205, Bangladesh.
alimalbari347@ru.ac.bd

Abstract

Coronavirus disease-2019 (COVID-19), a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global health emergency and a threat the entire world. The COVID-19 shows a wide spectrum of clinical presentations, severity, and fatality rates. Although the fatal outcomes of the COVID-19 pandemic are evident in all age groups, the most devastating impact on the health consequences and death from COVID-19 are associated with older adults, especially older men. COVID-19 pandemic is affecting different countries in the world especially in the 65+ years age male group. In fact, several genes involved into the regulation of the immune system are strategically placed on the X-chromosome and trigger a gendered mediated antiviral fight. The aim of this study is to explore and exploit whether a relationship exists between male sex and COVID-19 mortality and the relationship is age dependent. Herein we discuss the possible role of physiological and immunological sex differences into the higher morbidity and mortality of SARS-CoV-2 between females and males. Deciphering gender differences in COVID-19 offers a window into the principles of immunity against SARS-CoV-2 infection and this information on ageing dependent gender disparity might contribute to our current understanding of COVID-19 infection and disease treatment.

Key Words: COVID-19; Gender; Sex hormones; Angiotensin-converting enzyme 2; TMPRSS2; TLR7

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: (1) Older age, male sex and acute illness severity are associated with

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Bangladesh

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

Received: October 26, 2020
Peer-review started: October 26, 2020
First decision: November 16, 2020
Revised: November 20, 2020
Accepted: December 16, 2020
Article in press: December 16, 2020
Published online: January 28, 2021

P-Reviewer: El-Arabey AA
S-Editor: Huang P
L-Editor: A
P-Editor: Yuan YY

increased mortality risk; (2) Older age, underlying co-morbidities, social deprivation and ethnicity have been associated with worse outcomes from coronavirus disease-2019 (COVID-19); (3) Sex hormones might be implicated in the age-dependent and sex-specific severity of COVID-19; (4) Male sex hormones usually appear as immunosuppressants, whereas female sex hormones enhances the actions of humoral immunity; and (5) Female sex hormones exert a protective effect of COVID-19 severity on females through direct antiviral activity or immune-mediated mechanisms.

Citation: Al-Bari MAA, Hossain S, Zahan MKE. Exploration of sex-specific and age-dependent COVID-19 fatality rate in Bangladesh population. *World J Radiol* 2021; 13(1): 1-18
URL: https://www.wjgnet.com/1949-8470/full/v13/i1/1.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i1.1

INTRODUCTION

The world is facing a major public health crisis due to the epidemic of coronavirus infection named coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO) caused by SARS-CoV-2 (amplified as severe acute respiratory syndrome coronavirus 2)[1,2]. SARS-CoV-2 infection epidemic originated from Wuhan city, Hubei, China, in December late 2019, has sporadically spread throughout the world. The SARS-CoV-2 that causes COVID-19 is a zoonotic pathogen, which can infect both human and animal. As of today, the 1 October 2020, WHO has reported that the epidemic has blown-out to more than 213 nations and areas with more than 33722075 confirmed cases, more than 1009270 confirmed expiries and more than 25492274 total salvages in around the world (https://covid19.who.int). Several millions of lives have been troubled due to compulsory isolations/quarantines. This epidemic has the power to overburden nationwide healthcare delivery systems and have main repercussions on international economy if SARS-CoV-2 proliferation and virulency power is not contained, or current treatments are not established. The infection is currently constituting a serious health, economic, social, and psychological effects on the whole world as the world is under lock down as a measure to curb the spread of the virus[3]. SARS-CoV-2 is primarily transmitted from person to person through respiratory airborne droplets produced when infected persons cough, sneeze, breathe deeply, or talk within a proximity to uninfected persons. With this emerging combat against this life-threatening virus, the WHO has taken several strategies to interrupt human contacts with others, segregate patients at preliminary stages, recognize and decrease spread from the animal source for minimizing the social and economic impact.

Coronaviruses belong to the family of *Coronaviridae*. SARS-CoV-2 is a beta-coronavirus like the two other viruses that have caused fatal infections over the last couple of decades: The SARS-CoV and the MERS-CoV (amplified as Middle East respiratory syndrome coronavirus). The SARS-CoV-2 is a non-segmented, enveloped, single-stranded, positive-sense RNA virus with a nucleocapsid. Analysis of the viral full genome sequencing has shown that the SARS-CoV-2 is phylogenetically close to the causative agent of a viral outbreak in 2002, SARS-CoV, with which it shares about 79% of its genome[1,2]. Since SARS-CoV-2 is hereditarily and anatomically related to SARS-CoV, it is appearing clear that it has its own exceptional properties that shared to the quick outspread around the world. Despite its similarity to SARS-CoV, its transmission efficiency and diagnostic methods are rather different. The coronavirus crown-like ("corona") morphology is created by transmembrane spike glycoproteins (S proteins) which is essential for SARS-CoV-2 attachment and invasion into host cells *via* formation of homotrimers protruding from the viral surface[3]. The distinguishing factor of SARS-CoV-2 is probably the nucleotide changes in the S protein and its receptor-binding domain (RBD)[4]. The S proteins of SARS-CoV and SARS-CoV-2 show organizational homology and preserved ectodomains, so that previous approaches are applied to stop binding of SARS-CoV to its host cell receptor, angiotensin-converting enzyme 2 (ACE2) through a non-pH dependent endocytosis, since SARS-CoV-2 also employs ACE2 for cell entry[5,6]. In molecular modelling analysis, it has shown similarities between the RBDs of SARS-CoV and SARS-CoV-2 (also called S proteins), which are the most immunogenic part of the virus and probably bind the same ACE2

receptors in order to gain cell entry[7,8], thus suggesting that a similar pathogenic mechanism is involved in both viral infections. Interestingly, ACE2 receptors are not only expressed on alveolar epithelial type II cells, which represent 83% of all ACE2-expressing cells, but also on heart, kidney, endothelium, and gut cells[9]. Thus, ACE2 may create a therapeutical target to control the cell entry of SARS-CoV-2. For example, the clinically used antimalarial drugs chloroquine analogues such as hydroxy-chloroquine have been found to prevent terminal phosphorylation of ACE2 and to raise the pH in lysosomes. Moreover, the glycosylated S protein of SARS-CoV-2 is extremely immune-sensitive to the host, and murine polyclonal antibodies against S protein of SARS-Co-V effectively hinder S-mediated cell entry of SARS-CoV-2, suggesting that cross-neutralizing antibodies targeting preserved S epitopes can be provoked upon immunization[10].

Although SARS symptoms appear with MERS, and COVID-19, the assessed fatality rate of COVID-19 (2.3%) is considerably lesser than SARS (11.0%) and MERS (34.0%) [11,12]. In comparison with SARS and MERS, COVID-19 has outspread very quickly, possibly due to expanded globalization and modification of the virus in closely each environment[12,13]. Although SARS-CoV-2 is less lethal than SARS and MERS-CoV insofar as most patients affected with SARS-CoV-2 may progress from the asymptomatic state or to acute respiratory distress syndrome (ARDS) and septic shock in severe form of the disease. In major cases, coronavirus infected patients show a mild flu-like symptoms, in which the utmost general signs are fever and cough. However, a major portion of the patients (15.7%) who develop severe disease have increased difficulty in breathing because of pneumonia. However, COVID-19 may rapidly develop into SARS characterized by interstitial pneumonia and the rapid development of ARDS or septic shock in older people (> 60 year, up to 10%-20%), especially in those with underlying medical comorbidities, such as hypertension, diabetes, and pulmonary diseases[1,14]. It more interesting that female adults are excluded in the danger group, as small number cases of serious COVID-19 in female have been testified. This takes up questions concerning the molecular mechanisms of gender disparity linked to the COVID-19 sternness.

In some patients the SARS-CoV-2 may associated with terrible symptoms when it infects the lungs initiating a strong inflammatory response, a cytokine storm with extreme levels of acute-phase reactants[15,16]. This hyperinflammatory situation is categorized by increased levels of cytokines, including interleukin-6 (IL-6), monocyte chemoattractant protein 1 and granulocyte-colony stimulating factor as well as appeared with the macrophage activation syndrome like hyperferritinaemia. Here, we report the current understanding of SARS-CoV-2 such as its sociodemographic characteristics included age, sex, smoking, race/ethnicity and level of education as well as its clinical features, imparting the critical information for regulating our responses against the SARS-CoV-2 contagion. We also recapitulate the state-of-the-art inventions on targeting SARS-CoV-2 through a cellular point of interpretation. Understanding and elucidating of cellular and molecular mechanisms of gender disparity associated with the severity of COVID-19 may significantly advance our knowledge of the disease pathogenity, and thus provide to the health professionals as to how to well treat the ageing patients.

MATERIALS AND METHODS

Objectives: The recent COVID-19 pandemic has appeared as a threat to global health. Though current evidence on the epidemiology of the disease is emerging, very little is known about the predictors of recovery. The current objective of the report is to describe the epidemiology of confirmed COVID-19 patients in the United States and Bangladesh and identify predictors of recovery. Data source: We have collected these data by using publicly available data for confirmed cases in the Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) from the Centers for Disease Control and Prevention (CDC), United States from March 07, 2020, to September 19, 2020 (https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html), and (https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html) as well as press release under Ministry of Health and Family Welfare (MOH&FW), Bangladesh (https://corona.gov.bd/press-release). Variables: We have undertaken descriptive analyses of cases stratified by sex, age group, demographic information (*e.g.*, race, ethnicity) and clinical (medical) history (underlying health conditions). Statistical methods: Correlation analysis is performed among all predictors (sex, age group, race and ethnicity) with student's *t*-test, statistical analysis accordingly.

RESULTS

As shown in Figure 1A, the first case of COVID-19 in United States is confirmed on March 7, 2020. There are a small number cases of new infections for about a month. After two months, the figure abruptly has risen at May 30, 2020 (cumulative rate 5.9, 3, 51.6, 136.5 and 266.6 per 100000 population as 0 to 4 year, 5 to 17 year, 18 to 49 year, 50 to 64 year and 65+ year respectively), to reach the peak around end of June and early July (9.1, 4.3, 66.3, 162.0 and 306.9 per 100000 population as 0 to 4 year, 5 to 17 year, 18 to 49 year, 50 to 64 year and 65+ year respectively). It reached continually its peak on the 5 September with 16.8, 9.7, 113.8, 249.8 and 451.2 per 100000 population as 0 to 4 year, 5 to 17 year, 18 to 49 year, 50 to 64 year and 65+ year respectively confirmed cases. Similar case is found in Bangladesh that the rate of death per total infected cases (50.2%) is found in over 60-year-old patients (Figure 2A). The United States' data indicate that mortality rate among younger age group patients with mildly disease is less prominent. This result is consistent with other report that younger patients less than 17 years have slighter COVID-19 severity, with practically no hospitalizations or expiries stated[17]. However, the mortality is higher among elderly patients particularly 65+ years old that is required for intensive care unit admission in hospital. These results are similar to the other reports that the elderly people (aged over 60) were at a high risk of developing into death based on a worldwide data (www.who.int)[17-19].

As in Figure 1B shows on United States data that on May 30, 2020 the curve shows that cumulative rate 94.8 and 83.3 per 100000 population as male and female respectively (adjusted ratio 1.134:1) and gradually reach the peak around end of June and early July (112.4 and 101 per 100000 population as male and female respectively (adjusted ratio 1.11:1). It reached continually its peak on the 5 September with 171.8 and 161.1 per 100000 population as male and female respectively confirmed cases (1.065:1). Interestingly, the prominent data is found in Bangladesh that the rate of death per total infected cases (77.9%) is found in male patients over female patients (22.1%) (Figure 2B). As shown in Figure 1B both adult males and females had similar recovery rates, and their difference is not statistically significant. However, in case of Bangladesh the rate of death in male patients is strongly statistically significant (*P* value < 0.0001). Regarding the sex proportion, there is an apparently indisputable outline that COVID-19 killed more males than females (Box 1). Unlike the fewer statement in the research from the Asian subcontinental areas such as China, South Korea, the data from the United States reflect the male sex is in danger for disease severity[20-22]. To assess the over-all situation about the world, the country-wise data[23], have found that the case-mortality rate among men is about 35% more inflated than women. The sex-disparity is consistent across age groups and regions.

Findings from multiple reports also show that patients who are more than 65 years of age particularly male sex having a higher BMI value (> 35 kg/m^2), co-morbidities such as hypertension, cardiovascular disease (CVD), chronic lung disease, metabolic disease, neurological disease, obesity, renal disease, diabetes, coronary disease, obstructive pulmonary disease, nicotine dependence, and heart failure have vital risk factors for developing COVID-19 complications[24,25] and a high mortality rate[26,27]. Among them, obesity is a critical risk factor which aggravates the COVID-19[28]. In consistent with these views, Figure 3 shows that adult patients are susceptible for COVID-19 having the following serious complications such as CVD (32.6%), chronic lung disease (18.2%), hypertension (56.5%), metabolic disease (41.5%), neurological disease (24.2%), obesity (47.5%) and renal disease (15.2%). In the paediatric cases, the percentages of the infection cases are quite less than the adults. However, in major cases paediatrics are infected with COVID-19 in unknown conditions (49.7%). Delayed hospitalization and microbial infections are also proposed greater danger factors for disease development[27]. Smoking history is also a probable danger issue for emerging severe complications[5].

Baseline patient characteristics are also provided in Figure 4. Black patients are generally more susceptible than white patients with the age group (65+ years old. On May 30, 2020, the cumulative rates are 49.5, 158.5 and 196 per 100000 population as white, black and American Indian/Alaska Native respectively, to reach the peak around end of June and early July (57, 186.2 and 238.8 per 100000 population as white, black and American Indian/Alaska Native respectively). It reached continually its peak on the 5 September with 84.7, 290.6 and 302.4 per 100000 population as white, black and American Indian/Alaska Native respectively confirmed cases. In another report, black patients have a relative risk for hospitalization[29]. After correcting for gender, stage group, and comorbidities, black people have a 1.42 times higher danger of hospitalization for COVID-19 severity in comparison with white patients. The relative danger of death from COVID-19 infection is increased for males than for

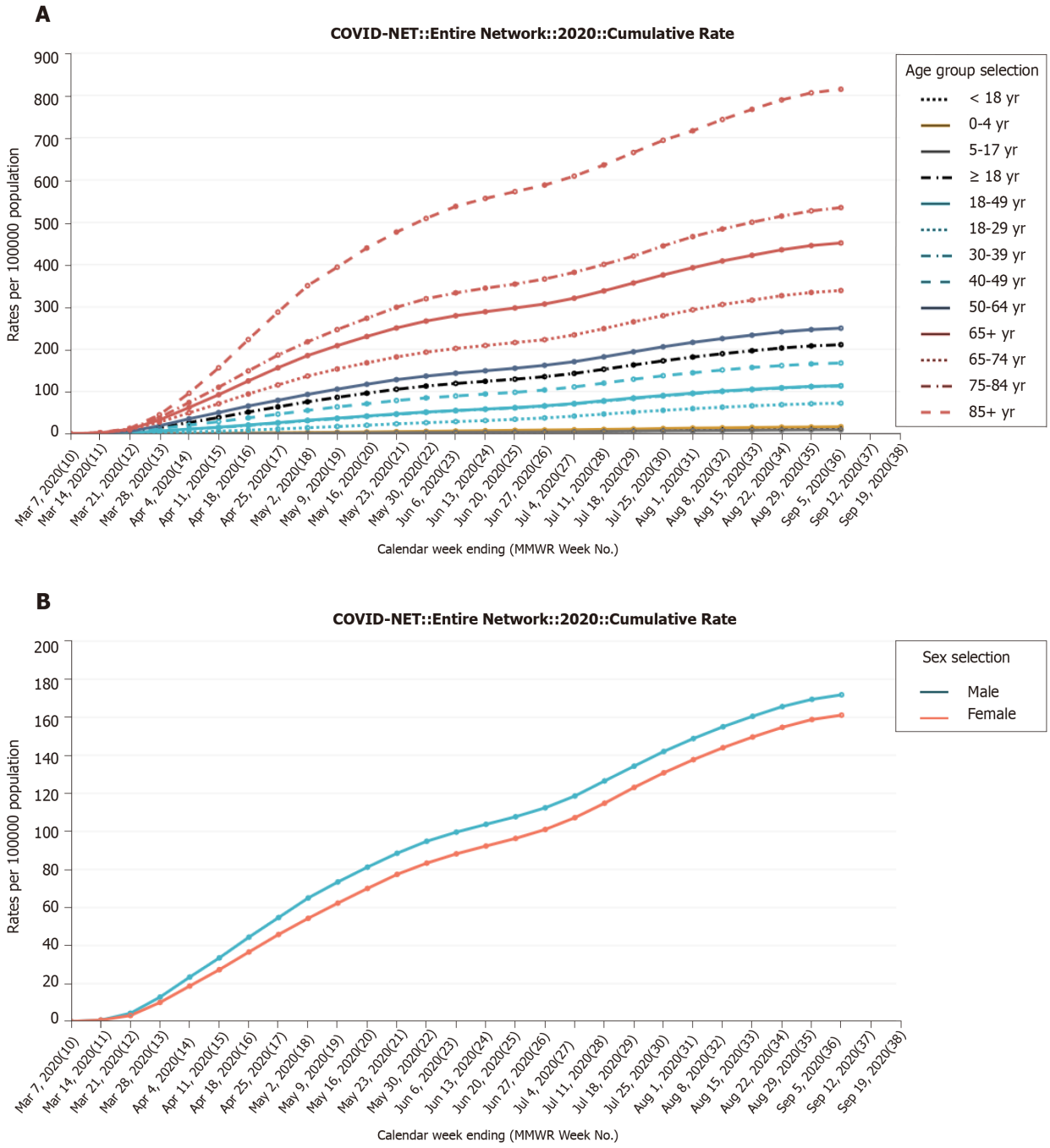


Figure 1 Cumulative rate of infection per 100000 population. A: In different age groups under the Coronavirus Disease-2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html); B: In gender-based fatality rate under the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html).

females in almost all age groups in all nations.

DISCUSSION

The COVID-19 pandemic is causing millions of deaths worldwide and it has become as an emerging threat to the public health globally. Although existing evidence on the epidemiology of the COVID-19 is emergent, a slight is identified about the predictors of salvage. Many countries throughout the world have experienced an unprecedented healthcare crisis caused by the SARS-CoV-2 infection[30,31]. Many parameters likely

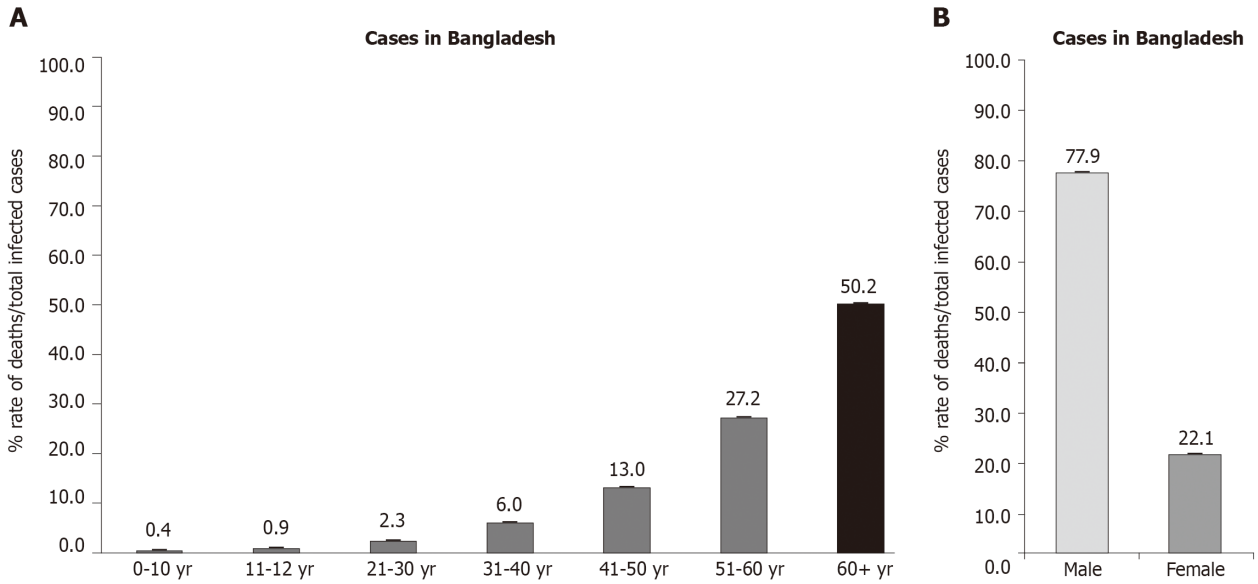


Figure 2 Percentage of rate of death per total infected cases. A: In different age groups in Bangladesh; B: In gender-based disparity in Bangladesh.

contribute to the etiology of the COVID-19 disease. The viral population and way of infection can elucidate why healthcare workforces are at a greater danger; diversities in the genome sequences of the viruses or the genome of the host-cells (*i.e.*, patient's genetic makeup) may consider for the variables detected among different countries and people. At the person level, personal immunity is also a vital forecaster of the disease prognosis, which can be reshuffled by age levels, gender, race, ethnicity as well as the presence of co-morbidities. Gender- and sex-determinants are also important for advising the endemic in interstellar and over time. To exemplify the status of this opinion, data on gender of the COVID-19 deaths in the United States and Bangladesh, recorded until 5th September 2020 were used to evaluate age- and sex-standardized figures in the United States and Bangladesh.

In comparison with disease occurrence, approximately similar distribution is detected among males and females at different age groups according to the WHO case-based surveillance system as of April 18, 2020[32]. However, from data on today in COVID-19, not only the progression of disease severity, but also mortality and fatality rates necessity to be clarified by age and, in addition by sex[33]. Preliminary data suggest that selective persons such as the elderly, males and people with comorbidities, including hypertension, diabetes and obesity, have slight COVID-19 consequences[34,35]. As the pandemic outspread over the United States during the last 4 mo, patterns of high-danger properties explained to emerge and data of poor consequences (specifically high case fatality) among racial and ethnic minorities[34].

A gendered approach to the COVID-19

Evidences suggest that male gender and aged persons are key factors connected to higher danger of severe events and death from COVID-19[36,37]. The enhancing mortality rate from COVID-19 for males (2.4 times) than for females is overall comparable to that originated in other coronaviruses during the past two years, including the SARS-CoV and the MERS-CoV[37-39]. The explanations for the sex differences in COVID-19 are perhaps multifaceted including variations in immune response, higher incidence of pre-existing disease, biological differences between the sexes such as high levels of androgens in men, differences in lifestyle such as smoking habits as well as differences in underlying comorbidities[40-42]. Male are commonly reported to have higher serious pathological conditions, such as CVDs, whereas females tend to have higher non-serious long-lasting disorders, such as skeletal and autoimmune hypersensitive diseases[43]. Thus, the risk of male death from COVID-19 may explain the comparatively more occurrence of causal comorbidities such as CVD, diabetes and chronic lung disease[44].

Mechanistically the age and gender differences in COVID-19 can be explained by the variable expression of an extracellular anchor represented by a cell-surface zinc peptidase, ACE2 which mediates SARS-CoV-2 binding and entry into cells[45,46]. Here

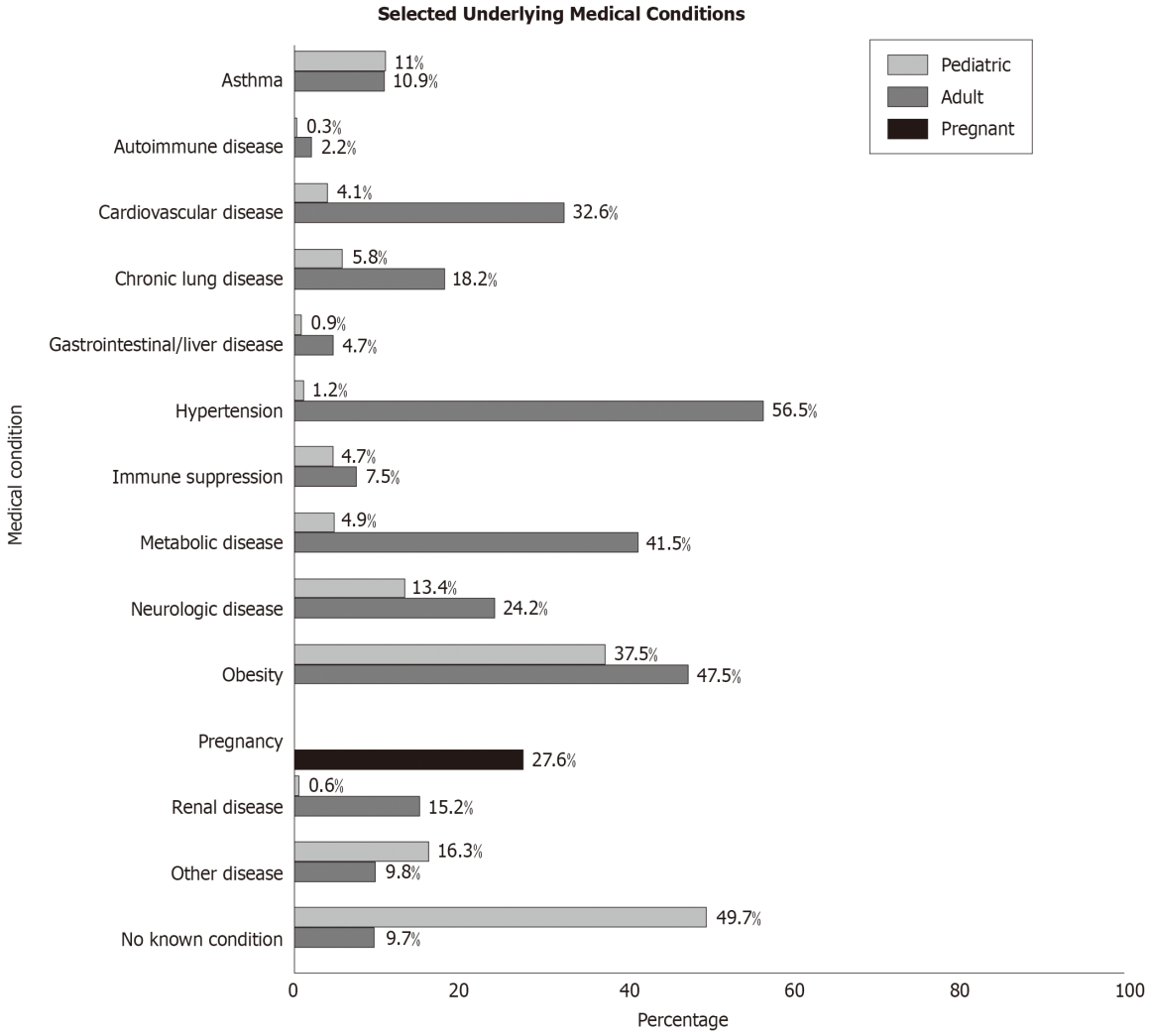


Figure 3 Percentage of selected underlying medical conditions under the coronavirus disease-2019-associated hospitalization surveillance network hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html).

the viral spike (S) protein is indeed a key determinant for transmissibility. Although ACE2 is pivotal for the entry point of the SARS-CoV-2, CD26 receptor also interacts with the S1 domain of the viral S protein and affects its virulence[47-49]. Since ACE2 receptor is abundantly expressed by pneumocytes in the lungs[48], SARS-CoV-2 infection and down-regulated ACE2 lead to higher the expression of angiotensin II (Ang II) that directly causes unregulated inflammatory lung damage[47-49]. Interestingly, ACE2 expression does not denote a completely capable of cell entry receptor as confirmed for SARS-CoV-2, until the cleavage at the S1/S2 and the S2′ site of the S protein operated by TMPRSS2 a 70 kDa membrane-anchored enzyme (type 2 transmembrane serine protease) in order to allow viral-cellular membrane fusion[50]. ACE2 is commonly accountable for altering Ang II into vasodilatory and low immune enhancing variants of angiotensin. Ang II specifically interacts with its type 1 receptors called angiotensin receptors (AT1Rs) in the lung to stimulate inflammation and vasoconstriction *via* induction of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, which enhances cytokine synthesis[6,51]. Low expression of ACE-2 levels and high Ang II expressions turn to enhance the permeability of pulmonary vessels which then consequences in inflammatory damage to the pulmonary tissues[52,53]. The primary culprit of severe COVID-19 is the cytokine storm resulting from an unchecked inflammatory response that damages the lung tissue and causing death in a substantial percentage of cases[54]. In the lungs, ACE2 down-regulation associates with the human ARDS *via* enhanced vascular permeability, increased lung oedema, neutrophil accumulation and worsened lung function[51,55,56]. Moreover, if SARS-CoV-2 causes sepsis, then ARDS occurrence exaggerates the edema, swelling and can cause of death[57]. Additionally, when COVID-19 infection occurs, the

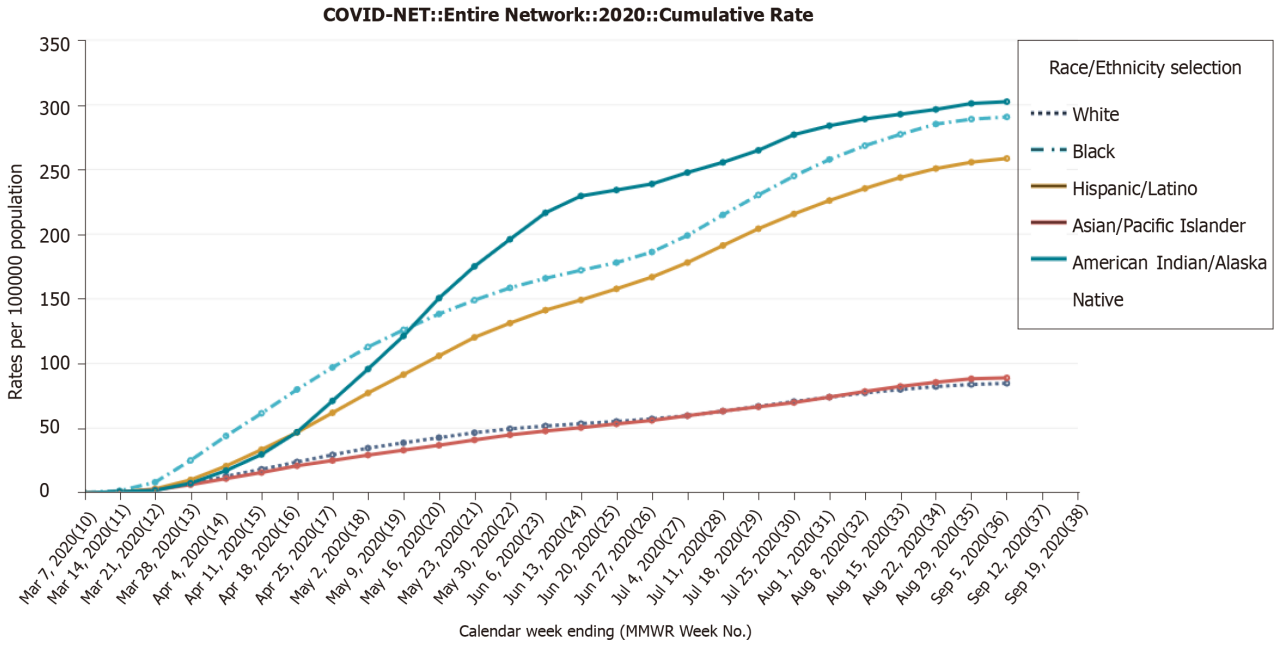


Figure 4 Cumulative rate of infection per 100000 population in baseline characteristics under the coronavirus disease-2019-associated hospitalization surveillance network hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html).

virus SARS-CoV-2 is internalized and stimulates TNF-α converting enzyme, ADAM17 (ADAM metallopeptidase domain 17)[58]. ADAM17 slashes the ACE2 receptors resulting them insensitive to the stimulation of renin–angiotensin–aldosterone system. This is eventually accountable for additional making of cytokines, which worsen the inflammation[59]. In the existence of pre-existing CVD, the cytokine storm can intensify underscoring diseases by infuriating pre-existing heart failure, causing suppression of myocardial activity, enhancing the oxygen demand/supply ratio and endothelial disfunction[59,60]. In this setting, ACE2 could denote the first variable to validate different effects of the infection between sexes.

ACE2 gene is located on the X chromosome (Xp22.2), in the Barr zone. The X chromosome in females (XX genotype) bring twofold as many X-linked genes (> 1000 genes) related to males (XY genotype). The X-linked gene expressions are equivalent between two sexes *via* X chromosome inactivation (XCI) process which transcriptionally deactivates one copy of the X chromosome. XCI is recognized during embryonic development and regularly preserved throughout the life[61,62]. However, a part of X-codified genes (almost 15%-23%) can discharge, fully or partly, from XCI and this privilege is suitable for those genes located in the pseudoautosomal regions (PAR) 1 and 2[32,63]. The *ACE2* gene is located within PAR1 and the influence may not inevitably be an increased expression of ACE2 in women. Male susceptibility to COVID-19 infection may be additional boosted by X-linked inheritance of genetic pleomorphisms as loci of both androgen receptors (ARs) and *ACE2* genes are positioned on the X chromosome[32]. Since ACE2 expression is originated in the testes (specially in Leydig cells)[5,64] serum luteinizing hormone (LH) level is significantly increased. As a result, the proportions of testosterone to LH and follicle stimulating hormone (FSH) to LH are pointedly diminished in males with COVID-19[5]. Thus, it is inevitability to evaluate gonadal role among patients who have improved from the SARS-CoV-2 infection, particularly in reproductive-aged men.

Another exciting finding related to coronaviruses resides on the co-expression of TMPRSS2 together with ACE2. TMPRSS2 is a critical factor in enabling cellular infection by SARS-CoV-2 for priming the viral S protein S1 domain and employing the S2 domain for viral infectivity[50,65,66]. Several speculations may strengthen the role of sex into the expression of TMPRSS2. TMPRSS2 is located on chromosome 21q22.3 and several AR elements are positioned upstream of the transcriptional promoter region[67,68]. Notably, AR activity seems to be required for the transcription of the TMPRSS2[5,69]. It is hypothesized that genetic variation of AR is associated with prostate cancer and androgenetic alopecia is also related to ethnic disparities in COVID-19 death[70]. Androgens powerfully upregulate the TMPRSS2 expression in prostate cancer cells[31,71] and they can also regulate the oncogenic ERG transcription factor (or, more

rarely, other members of the ETS family) when the *TMPRSS2:ERG* fusion gene is formed due to somatic gene reshuffles in prostate cancers[32].

Sex hormones and hormone therapy during COVID-19 pandemic

Sex hormones might be implicated in the age-dependent and sex-specific severity of COVID-19. Sex hormones, *e.g.*, testosterone and oestrogen significantly affect immune responses in both sexes[36,72,73], a part of which are in straight connections between sex hormones and immune cells. Increasing evidence proposes that both sex hormones and hormone therapy could be beneficial in COVID-19 treatment through direct modulation of antiviral activity or immune regulation[32]. Several studies suggest that both high and low testosterone levels can favour severe COVID-19[32,74]. For example, high testosterone levels upregulate TMPRSS2, facilitating the entry of SARS-CoV-2 into host cells *via* ACE2 (Figure 5). A recent analysis supports the hypothesis that androgen-deprivation therapy (ADT) might protect men from SARS-CoV-2 infection[32,75]. An epidemiological data also provision that ADT provide a defensive role in COVID-19 patients with prostate cancer. A mode of clarification for this concept is connected to the viral entry facilitated by TMPRSS2[32,75]. Furthermore, upregulated testosterone expressions can also impart to the progress of microthrombi and venous thromboembolism, which are signs of severe COVID-19 patients[76]. In addition, the 5α-reductase (a well-known converting enzyme to testosterone) inhibitors (dutasteride) can be applicable in COVID-19, by suppressing the ACE2 expressions and the internalization of the spike receptor[32]. Contrarywise, other studies propose that the immune modifying properties of androgens can defend from the non-satisfactory cytokine storm of COVID-19. Preclinical data also recommend that camostat mesylate, which hinders the protease action of TMPRSS2, is able to hinder the entry of SARS-CoV-2 in lung epithelial cells[50]. Preclinical data showed that inhibitors of TMPRSS2 (such as camostat, nafamostat and bromhexine) and of 5α-reductase might be active against SARS-CoV-2[32,50]. Although the androgen-driven concept is fascinating, it remains obscure why younger males with COVID-19, who have greater testosterone levels in comparison to adult males, display diminished sternness and fatality rates[77]. Likewise, it would be unpredicted that aged males who have lesser testosterone levels display amplified sternness and fatality rates to COVID-19. Obesity is a well-known risk factor for CVDs and testosterone levels of obese males are reported to be distinctly lesser than in the non-obese people. Remarkably, the amount of dropping testosterone levels is interrelated to blood glucose levels and lipid profiles[78]. By inclining to obesity, lowered levels of male sex hormones, specifically testosterone, can possibly be involved in the advance of CVDs and COVID-19. Additional experimental and clinical studies are vital to categorize the underlying associations among testosterone levels, obesity and CVDs, and the basic mechanisms. Thus, it is vital to evaluate why-among males with COVID-19-younger age is powerfully defensive against adverse consequences. It is probable that testosterone has a defensive anti-inflammatory action in younger males.

Testosterone is reported to have anti-inflammatory functions *via* suppression of both the cellular and humoral immune systems[52,79]. Testosterone is reported to decrease IL-6 and tumor necrosis factor α (TNF-α) levels *via* suppression of the NF-κB pathway. Down-regulated testosterone expression, as can happen in aging males, has also been correlated with upregulated inflammatory cytokines including IL-6 and may trigger to high risk of pulmonary injury after pneumonia[52]. Androgens usually inhibit the inflammatory signals by reducing the action of the peripheral blood mononuclear cells, and the secretion of inflammatory factors and cytokines, such as IL-1β, IL-2, TNF-α[32,41]. Androgens may also endorse the release of inflammatory cytokines such as IL-10 and TGFβ (transforming growth factor-β) *via* AR signaling pathway[32]. These immune- oppressive actions of androgens could induce COVID-19 infection, but might also suppress the cytokine storm that exemplifies with the most COVID-19 severity.

For the most severe infections, females have been constantly found to stand a greater immune reply than do males. Generally, the women show more immune responses effectively to microorganisms by making greater quantities of interferons (IFN) and antibodies; though this defensive action mediated mainly by estrogen, is reduced in postmenopausal females[52]. In cases of coronaviruses, females have verified a steady survival benefit over males[52]. A large amount of authentication suggests that female sex hormones, particularly estrogens and progesterone might apply a protecting role on women *via* direct antiviral action or immune-protective effects, thus elucidating the greater COVID-19 sternness in post-menopausal females. For instance, expressions of estrogen receptors (abbreviated as ERα and ERβ) occur in a wide variety of immune cells (T, B, NK cells, DCs, macrophages, neutrophils). Additionally, sex hormones are proposed to provide dose-dependent action on immune cells[41,80].

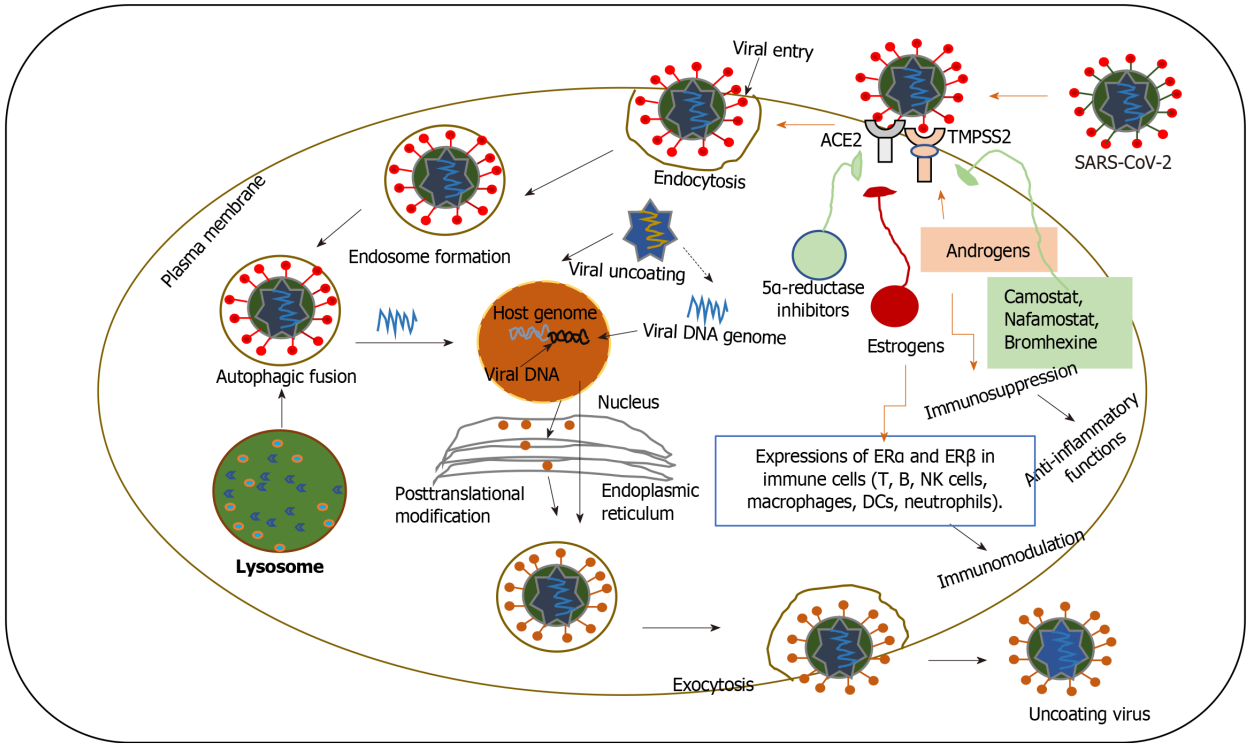


Figure 5 The role of sex hormones and hormone therapies in modulating severe acute respiratory syndrome coronavirus 2 entry in host cells and immune response. The replication cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) begins when the virion binds to the host cell receptor, angiotensin-converting enzyme 2 (ACE2) *via* its spike protein S1 subunit. After receptor binding, the virus gains access to the cytosol by acid-dependent proteolytic cleavage of the S protein into S1 and S2 subunits by a furin, cathepsin, transmembrane serine protease 2 (TMPRSS2), or another protease, followed by S2-assisted fusion of the viral and cellular membranes. In this proposed model, androgens can upregulate the activity of TMPRSS2 which is necessary for the SARS-CoV-2 spike protein priming. Female sex hormones, estrogens might downregulate the ACE2 expression, which is used by SARS-CoV-2 for host cell entry. Androgens suppress the inflammatory responses by decreasing the activity of the peripheral blood mononuclear cells, as well as the release of inflammatory factors and cytokines, such as IL-1β, IL-2, TNF-α. Female sex hormones, estrogens and progesterone exert a protective effect on females, through direct antiviral activity or immune-mediated mechanisms. Estrogen receptors (ERα and ERβ) are expressed in a diverse array of immune cells (T, B, natural killer cells, macrophages, DCs, neutrophils) and modulates immune responses. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; ERs: Estrogen receptors.

Hereafter, age-related changes or menstrual-cycle dependent variations in the female sex hormone levels can affect the collaboration between sex hormones and immune cells. Unexpectedly, it is found that immune responses between both sexes deviate as age upsurges, although the hormonal levels lower with ages[80]. Estrogens can downregulate the expression of ACE2 mRNA in bronchial epithelial cells *in vitro*[81]. Beyond this mechanism, estrogens have also a potential favorable role related to their immune-modulating properties. Notably, testosterone can be transformed to estrogen in peripheral tissues *via* aromatase enzyme, which may provide an anti-inflammatory action. This observation suggests that estrogens can protect females from severe COVID-19 compared to men and that post-menopausal women[81]. Although estrogen has a multifaceted role in modifying the immune system, it is stated to have an anti-inflammatory action at regular biological levels in premenopausal females[82]. In general, inflammatory cytokines, such as IL-6, IL-8 and TNF-α are suppressed by periovulatory doses of estrogen, although minimal estradiol levels can enhance inflammatory factors, which can clarify the proinflammatory states suffered by postmenopausal women. Although postmenopausal women are described to have greater expressions of proinflammatory cytokines including IL-6; these cytokine expressions are suppressed by the application of hormone replacement therapy (HRT)[83]. Therefore, the NF-κB pathway activated by Ang II enhances cytokine production after SARS infection while the NF-κB pathway can be shut down by estrogen and this strategy might be relevant for COVID-19 treatment in female patients.

Progesterone and 17β-estradiol (E2) have distinct roles in modulating innate and adaptive immunity[72] based on concentration[81]. Low concentrations of E2 promote pro-inflammatory cytokine production and stimulate TH1 (T helper type 1) cells,

whereas highly concentrated E2 suppresses cytokine secretion and enhances TH2-cell mediated humoral immunity (Figure 5). In general, progesterone stimulates anti-inflammatory effects and can indulge the $CD4^+$ T skewness from TH1-cells to TH2-cell actions[84]. It has been suggested that a triggered TH2-cell mediated immune response to such as in patients with asthma, might protect against severe COVID-19[85]. Finally, current data propose that progesterone provides a straight antiviral action on SARS-CoV-2 *via* the modification of the Sigma receptors[86]. Moreover, MERS-CoV and SARS-CoV *in vivo* data also support that SERMs (selective estrogen receptor modulators) such tamoxifen and toremifene, may be applicable against COVID-19[87], although emphasizing the necessity of more investigations in patient treatment.

The complex variability of immune responses based on age and sex may also elucidate the age-dependent and sex-selective sternness of COVID-19[54,88]. Our immune system is composed of two distinct arms with different functions: Adaptive and innate immunity. The first line of defence, innate immunity acts against dangerous invaders like SARS-CoV-2 *via* capturing and deactivating pathogenic organisms and initiating inflammation. Classically, acute inflammatory responses lead to a quick accumulation of immune cells and macromolecules at the injurious sites for eliminating the aggressor. However, chronic inflammatory responses can lengthen to affect abundant cellular machineries. Aging phenomena have been correlated with such chronic stimulation of inborn immunity, linked to systemic strengthen in inflammation (called as "inflamm-aging") that might be harmful for the body[89]. The cellular senescence modulates the pathogen clearance during infections, and this mode of action might impart to clarify the age-dependent COVID-19 severity[72]. Additionally, discrete immune responses are confirmed between the sexes, and can consequence in disparity occurrence and vulnerability of males and females to autoimmune diseases, tumours and infections[72]. Acquired immune cells are militarized when the inborn immunity is inadequate to defeat a hazard. Cell mediated immunity specifically B and T cells can eradicate a danger precisely by selectively binding with a certain threat (for example, a small fragment of protein or a part of antigen to SARS-CoV-2). In addition to chronic activation of innate immunity, adaptive immune functions decline with age[90].

Sex differences in immune responses underlying COVID-19 disease

The X chromosome of *Drosophila melanogaster* docks many genes encoding for innate signalling proteins. This can provide a probable clarification for the sex-specific differences into immunity against viral infections. However, Y chromosome encoded *Sry* expression decrease the immune response. It is supported that X chromosome is partly accountable for the over-active respondents of the female immunity. Hence the high incidences of auto-immune diseases may occur in women by contributing to the collapse of self-tolerance[91]. Moreover, the giant X chromosome comprises the greatest number of immune-correlated genes in the full genome[92], including genes that are involved in innate [*e.g.*, *PRRs* (pattern recognition receptors), *TLR7* and *TLR8* and acquired immune responses (*e.g.*, chemokine receptor *CXCR3*). Although inactivation of X chromosome has may preserve correspondent gene expression into the two sexes, a lower number of genes located in the intron regions can escape this mode. Therefore, the products of these genes are exposed in females and the *PRRs*, *TLR7* and *TLR8* are escaped from XCI region[73]. Upon ligand interaction, *TLR7* dimerizes and activates *MyD88* (myeloid differentiation primary response gene 88), MAPK (mitogen-activated protein kinase) cascades, NF-κB pathway as well as IRF (IFN regulatory factor) -7 and IRF-5 activation[93]. In humans, mRNA levels for IRF-5 associate with oestrogen receptor 1 (ER1) levels proposing a possible IRF-5 regulation by transcriptional ER1 level[94]. Besides, IL-6 has been claimed to be critically involved into the down-regulated host immune response of COVID-19 patients[95]. Finally, TLR7 may stimulate B cells to enhanced antibody production.

A current study supports that females with severe COVID-19 cases have a greater amount of serum SARS-CoV-2 IgG in comparison with males, and the production of IgG in the initial phases of contagion looks like to be vigorous in women than in men[96]. It is also discovered distinct sex variances in how the B cell change with age[80]. B cells (numbers and percentages) are lower in older men (> 65+ years)[97] supporting that some of these sex-variances are preserved transversely people. Reduction number of B cells in aged men might consequence in reduction of antibody supply that might weaken the ability of an individual to fight against infectious pathogens. A pilot study suggests that injection of plasma therapy from recovered patients that comprises antibodies are capable to counteract SARS-CoV-2 virus pointedly and upgraded the critically ill COVID-19 patients[98]. But, a biosafety issue is a spectacle called antibody-dependent enhancement (ADE), when non-counteracting antiviral antibodies initiate

the entry into host cells thereby cumulative the SARS-CoV-2 infectivity[98].

It is also found accelerated age-related T cell function declines in men compared to women[80]. For example, incidences of naive T cells reduced with age, principally in $CD8^+$ T cells in both sexes, although females had greater naive T cells in comparison with men in both young and aged persons[99]. Females have been observed to have higher thymic action in comparison with males in all ages[100], which may likely clarify sex-variances in naive T cells. Lymphocytopenia has been reported in severe cases of COVID-19[101] including severe decays in $CD4^+$ and $CD8^+$ T cells. Collected these data support that SARS-CoV-2 may weaken antiviral immunity pointedly and this weakening may have drastic outcomes for aged persons.

Association of frailty with mortality in COVID-19

Irreparable process, human aging causes decrease in cognitive ability with the increase in age. There are many factors accelerating a person's biological age such as diet, exercise, lifestyle and co-morbidities (hypertension, diabetes, obesity). With aging, changes in hematopoietic stem cell (HSC) pool contribute to the functional decline in both innate and adaptive immune systems. Somatic mutations in HSCs is more commonly found in aged persons, where consequence of a mutated HSC and its immune cell offspring is denoted as "clonal hematopoiesis"[102] and associated with COVID-19 morbidity. Mounting evidence support that cardiac comorbidities are common in COVID-19 patients and such patients are in greater risk of mortality. The danger of CVD is two times greater in persons with clonal hematopoiesis[102]. Abnormal clonal hematopoiesis can provoke pro-inflammatory cytokines such as IL-6, IL-1β and IL-8, and inflammatory signals in macrophages and mast cells[102]. Higher levels of cytokines cause a sustained confluency of innate immune cells and a decrease production of acquired immune cells, so that the outcome of clonal hematopoiesis may participate to deprived COVID-19 consequences in aged persons. It is also found that SARS-CoV-2 directly activates mast cells with the subsequent release of proinflammatory cytokines such as IL-1.

The association COVID-19 with age is long-established with aged patients being additional susceptible to die. Principally ACE2 receptors and CD26 are responsible for the increased age-related susceptibility of COVID-19 and both the receptors are highly expressed in senescent cells. Coronaviruses target both ACE2 receptors and CD26 and the overexpression of these receptors in older patients cause augmented fatality rate in COVID-19 patients[29,103]. Ageing, a progressive decline in tissue homeostasis is correlated with chronic inflammatory symptoms. Several factors such as abnormal immune function, cytokines production by senescent cells, NF-κB signaling pathway activation or a defective autophagy response may enhance the activation of inflammatory pathways (*i.e.*, the NOD-like receptor 3 inflammasome). Mounting reports support that cytokines storm is aroused in patients with COVID-19 which is chiefly revealed by enhancing IL-2, IL-7, G-CSF (granulocyte colony stimulating factor), and TNF-α. Of all the cytokines, IL-6 has been observed to be interlinked to extremely severe SARS-CoV-2 infection owing due to amplified viral replication[104]. It is observed that the $CD8^+$ counts in frail COVID-19 patients are dramatically decrease than that in normal patients. $CD4^+$ and $CD8^+$ T cells are also necessary for clearance of viruses during principal infection in the mucosa[105]. Cytotoxic $CD8^+$ T cells can destroy virus mediated infected cells. Thus, frailty-associated decay in immune action may clarify the interlinked between ageing and higher adverse consequences.

CONCLUSION

The emerging COVID-19 pandemic as a global threat and public health challenges throughout the world. This report highlights the importance of multiple risk factors of disease severity and mortality such as old age, male sex, smoking, and comorbidities for the pathobiology and clinical landscape of COVID-19. Mounting evidence suggests that COVID-19 is a sex specific and aged influenced disease and it affects by a wide variety of variables fluctuating from genetic to socioeconomic factors. Therefore, in our considerations, we covered the emerging COVID-19 pandemic infection in the comprehensive and many-sided context of connections. Although it is endeavored to draw hypotheses about gender and ageing specific disparities of SARS-CoV-2 infection, gender equality and frailty should be given the first priority for further investigation to treat COVID-19 infection.

ACKNOWLEDGEMENTS

All of the authors are grateful to the Centers for Disease Control and Prevention (CDC), United States and Ministry of Health and Family Welfare (MOH&FW), Bangladesh for making this data publicly available.

REFERENCES

1 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

2 **Wu F**, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. *Nature* 2020; **579**: 265-269 [PMID: 32015508 DOI: 10.1038/s41586-020-2008-3]

3 **Vellingiri B**, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, Ganesan S, Venugopal A, Venkatesan D, Ganesan H, Rajagopalan K, Rahman PKSM, Cho SG, Kumar NS, Subramaniam MD. COVID-19: A promising cure for the global panic. *Sci Total Environ* 2020; **725**: 138277 [PMID: 32278175 DOI: 10.1016/j.scitotenv.2020.138277]

4 **Kannan S**, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019) - recent trends. *Eur Rev Med Pharmacol Sci* 2020; **24**: 2006-2011 [PMID: 32141569 DOI: 10.26355/eurrev_202002_20378]

5 **Białas AJ**, Kumor-Kisielewska A, Górski P. Ageing, sex, obesity, smoking and COVID-19 - truths, myths and speculations. *Adv Respir Med* 2020; **88**: 335-342 [PMID: 32869267 DOI: 10.5603/ARM.2020.0133]

6 **Groß S**, Jahn C, Cushman S, Bär C, Thum T. SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: From basic science to clinical implications. *J Mol Cell Cardiol* 2020; **144**: 47-53 [PMID: 32360703 DOI: 10.1016/j.yjmcc.2020.04.031]

7 **Yang J**, Petitjean SJL, Koehler M, Zhang Q, Dumitru AC, Chen W, Derclaye S, Vincent SP, Soumillion P, Alsteens D. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun* 2020; **11**: 4541 [PMID: 32917884 DOI: 10.1038/s41467-020-18319-6]

8 **Edwards MJ**, Becker KA, Gripp B, Hoffmann M, Keitsch S, Wilker B, Soddemann M, Gulbins A, Carpinteiro E, Patel SH, Wilson GC, Pöhlmann S, Walter S, Fassbender K, Ahmad SA, Carpinteiro A, Gulbins E. Sphingosine prevents binding of SARS-CoV-2 spike to its cellular receptor ACE2. *J Biol Chem* 2020; **295**: 15174-15182 [PMID: 32917722 DOI: 10.1074/jbc.RA120.015249]

9 **Kuba K**, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; **11**: 875-879 [PMID: 16007097 DOI: 10.1038/nm1267]

10 **Walls AC**, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**: 281-292. e6 [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058]

11 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

12 **Peeri NC**, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, Baghbanzadeh M, Aghamohammadi N, Zhang W, Haque U. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol* 2020; **49**: 717-726 [PMID: 32086938 DOI: 10.1093/ije/dyaa033]

13 **Nieman DC**. Coronavirus disease-2019: A tocsin to our aging, unfit, corpulent, and immunodeficient society. *J Sport Health Sci* 2020; **9**: 293-301 [PMID: 32389882 DOI: 10.1016/j.jshs.2020.05.001]

14 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, 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]

15 **Fung SY**, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. *Emerg Microbes Infect* 2020; **9**: 558-570 [PMID: 32172672 DOI: 10.1080/22221751.2020.1736644]

16 **Ruscitti P**, Berardicurti O, Barile A, Cipriani P, Shoenfeld Y, Iagnocco A, Giacomelli R. Severe COVID-19 and related hyperferritinaemia: more than an innocent bystander? *Ann Rheum Dis* 2020;

79: 1515-1516 [PMID: 32434816 DOI: 10.1136/annrheumdis-2020-217618]
17 **CDC COVID-19 Response Team**. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 343-346 [PMID: 32214079 DOI: 10.15585/mmwr.mm6912e2]
18 **COVID-19 National Emergency Response Center**, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention. Coronavirus Disease-19: The First 7,755 Cases in the Republic of Korea. *Osong Public Health Res Perspect* 2020; **11**: 85-90 [PMID: 32257774 DOI: 10.24171/j.phrp.2020.11.2.05]
19 **COVID-19 Surveillance Group**. Characteristics of COVID-19 patients dying in Italy: Report based on available data on March 26th, 2020 [cited 25 May 2020]. Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_26_marzo_eng.pdf
20 **Xie Y**, Wang Z, Liao H, Marley G, Wu D, Tang W. Epidemiologic, clinical, and laboratory findings of the COVID-19 in the current pandemic: systematic review and meta-analysis. *BMC Infect Dis* 2020; **20**: 640 [PMID: 32867706 DOI: 10.1186/s12879-020-05371-2]
21 **Das AK**, Gopalan SS. Epidemiology of COVID-19 and Predictors of Recovery in the Republic of Korea. *Pulm Med* 2020; 2020: 7291698 [PMID: 32774918 DOI: 10.1155/2020/7291698]
22 **Zheng H**, Tan J, Zhang X, Luo A, Wang L, Zhu W, Hébert HL, Meng W, Smith BH, Colvin LA, Hu J. Impact of sex and age on respiratory support and length of hospital stay among 1792 patients with COVID-19 in Wuhan, China. *Br J Anaesth* 2020; **125**: e378-e380 [PMID: 32773217 DOI: 10.1016/j.bja.2020.07.001]
23 **Pareek M**, Bangash MN, Pareek N, Pan D, Sze S, Minhas JS, Hanif W, Khunti K. Ethnicity and COVID-19: an urgent public health research priority. *Lancet* 2020; **395**: 1421-1422 [PMID: 32330427 DOI: 10.1016/S0140-6736(20)30922-3]
24 **Petrilli CM**, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; **369**: m1966 [PMID: 32444366 DOI: 10.1136/bmj.m1966]
25 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
26 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]
27 **Li X**, Wang L, Yan S, Yang F, Xiang L, Zhu J, Shen B, Gong Z. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. *Int J Infect Dis* 2020; **94**: 128-132 [PMID: 32251805 DOI: 10.1016/j.ijid.2020.03.053]
28 **El-Arabey AA**, Abdalla M. Metformin and COVID-19: A novel deal of an old drug. *J Med Virol* 2020; **92**: 2293-2294 [PMID: 32347974 DOI: 10.1002/jmv.25958]
29 **Vahidy FS**, Nicolas JC, Meeks JR, Khan O, Pan A, Jones SL, Masud F, Sostman HD, Phillips R, Andrieni JD, Kash BA, Nasir K. Racial and ethnic disparities in SARS-CoV-2 pandemic: analysis of a COVID-19 observational registry for a diverse US metropolitan population. *BMJ Open* 2020; **10**: e039849 [PMID: 32784264 DOI: 10.1136/bmjopen-2020-039849]
30 **Carter P**, Anderson M, Mossialos E. Health system, public health, and economic implications of managing COVID-19 from a cardiovascular perspective. *Eur Heart J* 2020; **41**: 2516-2518 [PMID: 32320040 DOI: 10.1093/eurheartj/ehaa342]
31 **Moula AI**, Micali LR, Matteucci F, Lucà F, Rao CM, Parise O, Parise G, Gulizia MM, Gelsomino S. Quantification of Death Risk in Relation to Sex, Pre-Existing Cardiovascular Diseases and Risk Factors in COVID-19 Patients: Let's Take Stock and See Where We Are. *J Clin Med* 2020; **9**: 2685 [PMID: 32825068 DOI: 10.3390/jcm9092685]
32 **Salvati L**, Biagioni B, Vivarelli E, Parronchi P. A gendered magnifying glass on COVID-19. *Clin Mol Allergy* 2020; **18**: 14 [PMID: 32774170 DOI: 10.1186/s12948-020-00129-2]
33 **Bhopal R**. Covid-19 worldwide: we need precise data by age group and sex urgently. *BMJ* 2020; **369**: m1366 [PMID: 32245830 DOI: 10.1136/bmj.m1366]
34 **Goyal MK**, Simpson JN, Boyle MD, Badolato GM, Delaney M, McCarter R, Cora-Bramble D. Racial and/or Ethnic and Socioeconomic Disparities of SARS-CoV-2 Infection Among Children. *Pediatrics* 2020; **146**: e2020009951 [PMID: 32759379 DOI: 10.1542/peds.2020-009951]
35 **Grasselli G**, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574-1581 [PMID: 32250385 DOI: 10.1001/jama.2020.5394]
36 **Cattrini C**, Bersanelli M, Latocca MM, Conte B, Vallome G, Boccardo F. Sex Hormones and Hormone Therapy during COVID-19 Pandemic: Implications for Patients with Cancer. *Cancers (Basel)* 2020; **12**: 2325 [PMID: 32824674 DOI: 10.3390/cancers12082325]
37 **Karlberg J**, Chong DS, Lai WY. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *Am J Epidemiol* 2004; **159**: 229-231 [PMID: 14742282 DOI:

10.1093/aje/kwh056]
38 **Matsuyama R**, Nishiura H, Kutsuna S, Hayakawa K, Ohmagari N. Clinical determinants of the severity of Middle East respiratory syndrome (MERS): a systematic review and meta-analysis. *BMC Public Health* 2016; **16**: 1203 [PMID: 27899100 DOI: 10.1186/s12889-016-3881-4]
39 **Leong HN**, Earnest A, Lim HH, Chin CF, Tan C, Puhaindran ME, Tan A, Chen MI, Leo YS. SARS in Singapore--predictors of disease severity. *Ann Acad Med Singap* 2006; **35**: 326-331 [PMID: 16829999]
40 **Bartz D**, Chitnis T, Kaiser UB, Rich-Edwards JW, Rexrode KM, Pennell PB, Goldstein JM, O'Neal MA, LeBoff M, Behn M, Seely EW, Joffe H, Manson JE. Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All: A Review. *JAMA Intern Med* 2020; **180**: 574-583 [PMID: 32040165 DOI: 10.1001/jamainternmed.2019.7194]
41 **Klein SL**, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016; **16**: 626-638 [PMID: 27546235 DOI: 10.1038/nri.2016.90]
42 **Jin JM**, Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health* 2020; **8**: 152 [PMID: 32411652 DOI: 10.3389/fpubh.2020.00152]
43 **Scheel-Hincke LL**, Möller S, Lindahl-Jacobsen R, Jeune B, Ahrenfeldt LJ. Cross-national comparison of sex differences in ADL and IADL in Europe: findings from SHARE. *Eur J Ageing* 2020; **17**: 69-79 [PMID: 32158373 DOI: 10.1007/s10433-019-00524-y]
44 **Global Health 50/50**. Sex, gender and COVID-19: overview and resources 2020 [cited 27 June, 2020]. Available from: https://globalhealth5050.org/covid19
45 **Oudit GY**, Pfeffer MA. Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-19. *Eur Heart J* 2020; **41**: 1818-1820 [PMID: 32388547 DOI: 10.1093/eurheartj/ehaa414]
46 **Bunyavanich S**, Do A, Vicencio A. Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults. *JAMA* 2020; **323**: 2427-2429 [PMID: 32432657 DOI: 10.1001/jama.2020.8707]
47 **Wu C**, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, Zheng M, Chen L, Li H. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B* 2020; **10**: 766-788 [PMID: 32292689 DOI: 10.1016/j.apsb.2020.02.008]
48 **Gheblawi M**, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res* 2020; **126**: 1456-1474 [PMID: 32264791 DOI: 10.1161/CIRCRESAHA.120.317015]
49 **Vankadari N**, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. *Emerg Microbes Infect* 2020; **9**: 601-604 [PMID: 32178593 DOI: 10.1080/22221751.2020.1739565]
50 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280. e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]
51 **Jia H**. Pulmonary Angiotensin-Converting Enzyme 2 (ACE2) and Inflammatory Lung Disease. *Shock* 2016; **46**: 239-248 [PMID: 27082314 DOI: 10.1097/SHK.0000000000000633]
52 **Al-Lami RA**, Urban RJ, Volpi E, Algburi AMA, Baillargeon J. Sex Hormones and Novel Corona Virus Infectious Disease (COVID-19). *Mayo Clin Proc* 2020; **95**: 1710-1714 [PMID: 32753145 DOI: 10.1016/j.mayocp.2020.05.013]
53 **Gurwitz D**. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020; **81**: 537-540 [PMID: 32129518 DOI: 10.1002/ddr.21656]
54 **Shi Y**, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020; **27**: 1451-1454 [PMID: 32205856 DOI: 10.1038/s41418-020-0530-3]
55 **Khan A**, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Crit Care* 2017; **21**: 234 [PMID: 28877748 DOI: 10.1186/s13054-017-1823-x]
56 **Nicholls J**, Peiris M. Good ACE, bad ACE do battle in lung injury, SARS. *Nat Med* 2005; **11**: 821-822 [PMID: 16079870 DOI: 10.1038/nm0805-821]
57 **Park TK**, Yang JH, Jeon K, Choi SH, Choi JH, Gwon HC, Chung CR, Park CM, Cho YH, Sung K, Suh GY. Extracorporeal membrane oxygenation for refractory septic shock in adults. *Eur J Cardiothorac Surg* 2015; **47**: e68-e74 [PMID: 25425551 DOI: 10.1093/ejcts/ezu462]
58 **Santos RAS**, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. *Am J Physiol Heart Circ Physiol* 2019; **316**: H958-H970 [PMID: 30707614 DOI: 10.1152/ajpheart.00723.2018]
59 **Wang K**, Gheblawi M, Oudit GY. Angiotensin Converting Enzyme 2: A Double-Edged Sword. *Circulation* 2020; **142**: 426-428 [PMID: 32213097 DOI: 10.1161/CIRCULATIONAHA.120.047049]
60 **Sun H**, Ning R, Tao Y, Yu C, Deng X, Zhao C, Meng S, Tang F, Xu D. Risk Factors for Mortality

in 244 Older Adults With COVID-19 in Wuhan, China: A Retrospective Study. *J Am Geriatr Soc* 2020; **68**: E19-E23 [PMID: 32383809 DOI: 10.1111/jgs.16533]

61 **Schurz H**, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. *Hum Genomics* 2019; **13**: 2 [PMID: 30621780 DOI: 10.1186/s40246-018-0185-z]

62 **Márquez EJ**, Trowbridge J, Kuchel GA, Banchereau J, Ucar D. The lethal sex gap: COVID-19. *Immun Ageing* 2020; **17**: 13 [PMID: 32457811 DOI: 10.1186/s12979-020-00183-z]

63 **Helena Mangs A**, Morris BJ. The Human Pseudoautosomal Region (PAR): Origin, Function and Future. *Curr Genomics* 2007; **8**: 129-136 [PMID: 18660847 DOI: 10.2174/138920207780368141]

64 **Wang Z**, Xu X. scRNA-seq Profiling of Human Testes Reveals the Presence of the ACE2 Receptor, A Target for SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells. *Cells* 2020; **9**: 920 [PMID: 32283711 DOI: 10.3390/cells9040920]

65 **Liu PP**, Blet A, Smyth D, Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. *Circulation* 2020; **142**: 68-78 [PMID: 32293910 DOI: 10.1161/CIRCULATIONAHA.120.047549]

66 **Alexander SPH**, Armstrong JF, Davenport AP, Davies JA, Faccenda E, Harding SD, Levi-Schaffer F, Maguire JJ, Pawson AJ, Southan C, Spedding M. A rational roadmap for SARS-CoV-2/COVID-19 pharmacotherapeutic research and development: IUPHAR Review 29. *Br J Pharmacol* 2020; **177**: 4942-4966 [PMID: 32358833 DOI: 10.1111/bph.15094]

67 **Stopsack KH**, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. *TMPRSS2* and COVID-19: Serendipity or Opportunity for Intervention? *Cancer Discov* 2020; **10**: 779-782 [PMID: 32276929 DOI: 10.1158/2159-8290.CD-20-0451]

68 **Robinson EL**, Alkass K, Bergmann O, Maguire JJ, Roderick HL, Davenport AP. Genes encoding ACE2, TMPRSS2 and related proteins mediating SARS-CoV-2 viral entry are upregulated with age in human cardiomyocytes. *J Mol Cell Cardiol* 2020; **147**: 88-91 [PMID: 32818486 DOI: 10.1016/j.yjmcc.2020.08.009]

69 **Wambier CG**, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *J Am Acad Dermatol* 2020; **83**: 308-309 [PMID: 32283245 DOI: 10.1016/j.jaad.2020.04.032]

70 **McCoy J**, Wambier CG, Vano-Galvan S, Shapiro J, Sinclair R, Ramos PM, Washenik K, Andrade M, Herrera S, Goren A. Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia. Are anti-androgens a potential treatment for COVID-19? *J Cosmet Dermatol* 2020; **19**: 1542-1543 [PMID: 32333494 DOI: 10.1111/jocd.13455]

71 **Gebhard C**, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* 2020; **11**: 29 [PMID: 32450906 DOI: 10.1186/s13293-020-00304-9]

72 **Klein SL**, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. *Trans R Soc Trop Med Hyg* 2015; **109**: 9-15 [PMID: 25573105 DOI: 10.1093/trstmh/tru167]

73 **Ghosh S**, Klein RS. Sex Drives Dimorphic Immune Responses to Viral Infections. *J Immunol* 2017; **198**: 1782-1790 [PMID: 28223406 DOI: 10.4049/jimmunol.1601166]

74 **Pozzilli P**, Lenzi A. Commentary: Testosterone, a key hormone in the context of COVID-19 pandemic. *Metabolism* 2020; **108**: 154252 [PMID: 32353355 DOI: 10.1016/j.metabol.2020.154252]

75 **Montopoli M**, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, Carbone GM, Cavalli A, Pagano F, Ragazzi E, Prayer-Galetti T, Alimonti A. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol* 2020; **31**: 1040-1045 [PMID: 32387456 DOI: 10.1016/j.annonc.2020.04.479]

76 **Walker RF**, Zakai NA, MacLehose RF, Cowan LT, Adam TJ, Alonso A, Lutsey PL. Association of Testosterone Therapy With Risk of Venous Thromboembolism Among Men With and Without Hypogonadism. *JAMA Intern Med* 2020; **180**: 190-197 [PMID: 31710339 DOI: 10.1001/jamainternmed.2019.5135]

77 **Golan R**, Scovell JM, Ramasamy R. Age-related testosterone decline is due to waning of both testicular and hypothalamic-pituitary function. *Aging Male* 2015; **18**: 201-204 [PMID: 26075536 DOI: 10.3109/13685538.2015.1052392]

78 **Cao J**, Chen TM, Hao WJ, Li J, Liu L, Zhu BP, Li XY. Correlation between sex hormone levels and obesity in the elderly male. *Aging Male* 2012; **15**: 85-89 [PMID: 22452321 DOI: 10.3109/13685538.2012.666585]

79 **Traish A**, Bolanos J, Nair S, Saad F, Morgentaler A. Do Androgens Modulate the Pathophysiological Pathways of Inflammation? *J Clin Med* 2018; **7**: 549 [PMID: 30558178 DOI: 10.3390/jcm7120549]

80 **Márquez EJ**, Chung CH, Marches R, Rossi RJ, Nehar-Belaid D, Eroglu A, Mellert DJ, Kuchel GA, Banchereau J, Ucar D. Sexual-dimorphism in human immune system aging. *Nat Commun* 2020; **11**: 751 [PMID: 32029736 DOI: 10.1038/s41467-020-14396-9]

81 **Villa A**, Rizzi N, Vegeto E, Ciana P, Maggi A. Estrogen accelerates the resolution of inflammation in macrophagic cells. *Sci Rep* 2015; **5**: 15224 [PMID: 26477569 DOI: 10.1038/srep15224]

82 **Gaskins AJ**, Wilchesky M, Mumford SL, Whitcomb BW, Browne RW, Wactawski-Wende J, Perkins NJ, Schisterman EF. Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. *Am J Epidemiol* 2012; **175**: 423-431 [PMID: 22306563 DOI:

10.1093/aje/kwr343]

83 **Giefing-Kröll C**, Berger P, Lepperdinger G, Grubeck-Loebenstein B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging Cell* 2015; **14**: 309-321 [PMID: 25720438 DOI: 10.1111/acel.12326]

84 **Piccinni MP**, Giudizi MG, Biagiotti R, Beloni L, Giannarini L, Sampognaro S, Parronchi P, Manetti R, Annunziato F, Livi C. Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *J Immunol* 1995; **155**: 128-133 [PMID: 7541410]

85 **Liu S**, Zhi Y, Ying S. COVID-19 and Asthma: Reflection During the Pandemic. *Clin Rev Allergy Immunol* 2020; **59**: 78-88 [PMID: 32468411 DOI: 10.1007/s12016-020-08797-3]

86 **Gordon DE**, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, Eckhardt M, Soucheray M, Bennett MJ, Cakir M, McGregor MJ, Li Q, Meyer B, Roesch F, Vallet T, Mac Kain A, Miorin L, Moreno E, Naing ZZC, Zhou Y, Peng S, Shi Y, Zhang Z, Shen W, Kirby IT, Melnyk JE, Chorba JS, Lou K, Dai SA, Barrio-Hernandez I, Memon D, Hernandez-Armenta C, Lyu J, Mathy CJP, Perica T, Pilla KB, Ganesan SJ, Saltzberg DJ, Rakesh R, Liu X, Rosenthal SB, Calviello L, Venkataramanan S, Liboy-Lugo J, Lin Y, Huang XP, Liu Y, Wankowicz SA, Bohn M, Safari M, Ugur FS, Koh C, Savar NS, Tran QD, Shengjuler D, Fletcher SJ, O'Neal MC, Cai Y, Chang JCJ, Broadhurst DJ, Klippsten S, Sharp PP, Wenzell NA, Kuzuoglu-Ozturk D, Wang HY, Trenker R, Young JM, Cavero DA, Hiatt J, Roth TL, Rathore U, Subramanian A, Noack J, Hubert M, Stroud RM, Frankel AD, Rosenberg OS, Verba KA, Agard DA, Ott M, Emerman M, Jura N, von Zastrow M, Verdin E, Ashworth A, Schwartz O, d'Enfert C, Mukherjee S, Jacobson M, Malik HS, Fujimori DG, Ideker T, Craik CS, Floor SN, Fraser JS, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**: 459-468 [PMID: 32353859 DOI: 10.1038/s41586-020-2286-9]

87 **Zhou Y**, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov* 2020; **6**: 14 [PMID: 32194980 DOI: 10.1038/s41421-020-0153-3]

88 **Scully EP**, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* 2020; **20**: 442-447 [PMID: 32528136 DOI: 10.1038/s41577-020-0348-8]

89 **Furman D**, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, Slavich GM. Chronic inflammation in the etiology of disease across the life span. *Nat Med* 2019; **25**: 1822-1832 [PMID: 31806905 DOI: 10.1038/s41591-019-0675-0]

90 **Goronzy JJ**, Weyand CM. Successful and Maladaptive T Cell Aging. *Immunity* 2017; **46**: 364-378 [PMID: 28329703 DOI: 10.1016/j.immuni.2017.03.010]

91 **Libert C**, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. *Nat Rev Immunol* 2010; **10**: 594-604 [PMID: 20651746 DOI: 10.1038/nri2815]

92 **Bianchi I**, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. *J Autoimmun* 2012; **38**: J187-J192 [PMID: 22178198 DOI: 10.1016/j.jaut.2011.11.012]

93 **Petes C**, Odoardi N, Gee K. The Toll for Trafficking: Toll-Like Receptor 7 Delivery to the Endosome. *Front Immunol* 2017; **8**: 1075 [PMID: 28928743 DOI: 10.3389/fimmu.2017.01075]

94 **Griesbeck M**, Ziegler S, Laffont S, Smith N, Chauveau L, Tomezsko P, Sharei A, Kourjian G, Porichis F, Hart M, Palmer CD, Sirignano M, Beisel C, Hildebrandt H, Cénac C, Villani AC, Diefenbach TJ, Le Gall S, Schwartz O, Herbeuval JP, Autran B, Guéry JC, Chang JJ, Altfeld M. Sex Differences in Plasmacytoid Dendritic Cell Levels of IRF5 Drive Higher IFN-α Production in Women. *J Immunol* 2015; **195**: 5327-5336 [PMID: 26519527 DOI: 10.4049/jimmunol.1501684]

95 **Coomes EA**, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis. *Rev Med Virol* 2020; **30**: 1-9 [PMID: 32845568 DOI: 10.1002/rmv.2141]

96 **Zeng F**, Dai C, Cai P, Wang J, Xu L, Li J, Hu G, Wang Z, Zheng F, Wang L. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: A possible reason underlying different outcome between sex. *J Med Virol* 2020; **92**: 2050-2054 [PMID: 32383183 DOI: 10.1002/jmv.25989]

97 **Piasecka B**, Duffy D, Urrutia A, Quach H, Patin E, Posseme C, Bergstedt J, Charbit B, Rouilly V, MacPherson CR, Hasan M, Albaud B, Gentien D, Fellay J, Albert ML, Quintana-Murci L; Milieu Intérieur Consortium. Distinctive roles of age, sex, and genetics in shaping transcriptional variation of human immune responses to microbial challenges. *Proc Natl Acad Sci USA* 2018; **115**: E488-E497 [PMID: 29282317 DOI: 10.1073/pnas.1714765115]

98 **Shen C**, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; **323**: 1582-1589 [PMID: 32219428 DOI: 10.1001/jama.2020.4783]

99 **Olson NC**, Doyle MF, Jenny NS, Huber SA, Psaty BM, Kronmal RA, Tracy RP. Decreased naive and increased memory CD4(+) T cells are associated with subclinical atherosclerosis: the multi-

ethnic study of atherosclerosis. *PLoS One* 2013; **8**: e71498 [PMID: 24009662 DOI: 10.1371/journal.pone.0071498]

100 **Clave E**, Araujo IL, Alanio C, Patin E, Bergstedt J, Urrutia A, Lopez-Lastra S, Li Y, Charbit B, MacPherson CR, Hasan M, Melo-Lima BL, Douay C, Saut N, Germain M, Trégouët DA, Morange PE, Fontes M, Duffy D, Di Santo JP, Quintana-Murci L, Albert ML, Toubert A; Milieu Intérieur Consortium. Human thymopoiesis is influenced by a common genetic variant within the TCRA-TCRD locus. *Sci Transl Med* 2018; **10**: eaao2966 [PMID: 30185651 DOI: 10.1126/scitranslmed.aao2966]

101 **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]

102 **Jaiswal S**, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, McConkey M, Gupta N, Gabriel S, Ardissino D, Baber U, Mehran R, Fuster V, Danesh J, Frossard P, Saleheen D, Melander O, Sukhova GK, Neuberg D, Libby P, Kathiresan S, Ebert BL. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *N Engl J Med* 2017; **377**: 111-121 [PMID: 28636844 DOI: 10.1056/NEJMoa1701719]

103 **Sargiacomo C**, Sotgia F, Lisanti MP. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? *Aging (Albany NY)* 2020; **12**: 6511-6517 [PMID: 32229706 DOI: 10.18632/aging.103001]

104 **Franceschi C**, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* 2018; **14**: 576-590 [PMID: 30046148 DOI: 10.1038/s41574-018-0059-4]

105 **Ma Y**, Hou L, Yang X, Huang Z, Yang X, Zhao N, He M, Shi Y, Kang Y, Yue J, Wu C. The association between frailty and severe disease among COVID-19 patients aged over 60 years in China: a prospective cohort study. *BMC Med* 2020; **18**: 274 [PMID: 32892742 DOI: 10.1186/s12916-020-01761-0]

World Journal of Radiology

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

World J Radiol 2021 January 28; 13(1): 19-28

DOI: 10.4329/wjr.v13.i1.19

ISSN 1949-8470 (online)

MINIREVIEWS

Systemic arterio-venous thrombosis in COVID-19: A pictorial review

Abhinaya Shankar, Baskaran Varadan, Dillibabu Ethiraj, Hemanth Sudarsanam, Abdul Rahman Hakeem, Srinivasan Kalyanasundaram

ORCID number: Abhinaya Shankar 0000-0002-3300-6359; Baskaran Varadan 0000-0001-9760-5281; Dillibabu Ethiraj 0000-0002-4892-1939; Hemanth Sudarsanam 0000-0001-8514-9477; Abdul Rahman Hakeem 0000-0001-7266-3848; Srinivasan Kalyanasundaram 0000-0002-1253-6430.

Author contributions: Shankar A, Varadan B, Ethiraj D and Sudarsanam H contributed in writing the article and generating figures; Hakeem AR and Kalyanasundaram S critically revised the article; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Abhinaya Shankar, Baskaran Varadan, Dillibabu Ethiraj, Hemanth Sudarsanam, Srinivasan Kalyanasundaram, Department of Radiology, Dr. Rela Institute and Medical Centre, Chennai 600044, India

Abdul Rahman Hakeem, HPB Surgery and Liver Transplantation, The Leeds Teaching Hospitals NHS Trust, Leeds LS97TF, West Yorkshire, United Kingdom

Corresponding author: Srinivasan Kalyanasundaram, MD, Chief Doctor, Department of Radiology, Dr. Rela Institute and Medical Centre, 7, CLC Works Road, Chromepet, Chennai 600044, India. srinivasan.k@relainstitute.com

Abstract

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Systemic complications include cardiovascular, neurological, hepatic, renal and altered coagulation. Derangements in haemostasis with SARS-CoV-2 infection have been termed COVID-19 associated coagulopathy (CAC). CAC is postulated to be one of the significant causes for sudden deaths in this pandemic, with infection of endothelial cells and subsequent endotheliitis through angiotensin-converting enzyme-2 receptors playing a key role in the pathogenesis. In this pictorial review, we describe the imaging findings in a multitude of extrapulmonary arterial (aorta, cerebral, mesenteric, renal and peripheral arterial system) and venous thrombotic phenomena detected on contrast-enhanced computed tomography and magnetic resonance imaging of COVID-19 patients which could not be attributed to any other causes. Knowledge of incidence of these complications, lowering the threshold for diagnostic imaging in symptomatic patients and timely radiological detection can play a vital role in subsequent management of these critically ill patients.

Key Words: COVID-19; Coronavirus; Thrombus; Arterial; Aorta; Tomography

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Coronavirus disease 2019 (COVID-19) disease is a systemic illness with multi-organ system manifestations. Coagulopathy in the setting of COVID-19 has a unique pathophysiology with a propensity for both arterial and venous thrombosis.

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: India

Peer-review report's scientific quality classification

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

Received: November 23, 2020
Peer-review started: November 23, 2020
First decision: December 7, 2020
Revised: December 13, 2020
Accepted: December 22, 2020
Article in press: December 22, 2020
Published online: January 28, 2021

P-Reviewer: Deng B
S-Editor: Gao CC
L-Editor: A
P-Editor: Wang LYT

These phenomena may be clinically occult with imaging playing a vital role in detection and management. A high degree of clinical suspicion with a low threshold for cross sectional imaging can positively alter outcomes during this ongoing pandemic.

Citation: Shankar A, Varadan B, Ethiraj D, Sudarsanam H, Hakeem AR, Kalyanasundaram S. Systemic arterio-venous thrombosis in COVID-19: A pictorial review. *World J Radiol* 2021; 13(1): 19-28
URL: https://www.wjgnet.com/1949-8470/full/v13/i1/19.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i1.19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) began as no more than a cluster of pneumonia cases first reported in the Hubei province of China in December 2019. From its origin till date however, it has swept across the globe; emerging as one of the most far-reaching pandemics in human history. The most common presentation of COVID-19 is related to infection of the respiratory epithelial cells by the virus and ranges from mild upper or lower respiratory tract symptoms to hypoxic respiratory failure requiring oxygen therapy and in some instances, mechanical ventilation. Systemic complications include cardiovascular, neurological, hepatic and renal dysfunction, as well as altered coagulation[1]. Derangements in haemostasis occurring in patients with SARS-CoV-2 infection have been termed COVID-19 associated coagulopathy (CAC). CAC is postulated to be one of the significant causes for sudden deaths in this pandemic especially those occurring out of hospitals[2]. Literature is still emerging regarding the epidemiology and pathophysiology behind CAC with reported incidence of venous and arterial thromboembolism between 10%-25% among the COVID-19 admitted patients, with increase in incidence up to 31%-59% amongst those in intensive care[3-5]. The pro-coagulant state has been attributed to macrophage and endothelial cell mediated processes culminating in the acceleration of fibrin synthesis and suppression of its degradation[2]. Infection of endothelial cells through angiotensin-converting enzyme-2 (ACE-2) receptors is believed to be a characteristic unique to corona viruses and this plays a key role in pathogenesis[2,6]. Although CAC shares some common underlying mechanisms causing widespread micro/macro thrombi with conditions like sepsis induced coagulopathy, disseminated intravascular coagulation, hemophagocytic and hemolytic uremic syndromes; it has a few distinctive features not previously described in these conditions; and has emerged as a new category of coagulopathy[2]. The most common alterations in coagulation parameters in CAC include markedly elevated D-dimer levels; mild to moderate thrombocytopenia and prolonged prothrombin time[2,7].

Initially, a possible association between SARS-CoV-2 viral infection and pulmonary vascular thromboembolism was proposed in multiple case reports emerging from global hotspots when patients who developed sudden onset cardiac or respiratory deterioration or both at any time during the course of the disease, also had elevated D-dimer levels and a positive pulmonary angiography[8-12]. Subsequently, in a research article by Kaminetzky *et al*[13], a higher incidence of pulmonary embolism was recorded amongst the COVID-19 positive cohort. The study concluded that pulmonary embolism could indeed be a cause for acute deterioration in these patients. In addition, it suggested that D-dimer levels could be used for risk categorization.

In this pictorial review, we describe the imaging findings in a multitude of extrapulmonary arterial and venous thrombotic phenomena detected in cross sectional imaging (computed tomography/magnetic resonance imaging, CT/MRI) of COVID-19 patients which could not be attributed to other causes. Knowledge of incidence of these complications and early radiological detection can play a key role in subsequent management of these critically ill patients, often determining the outcomes.

CEREBRAL VASCULATURE

Arterial system

Stroke is characterised by neuronal injury with a manifest clinical deficit secondary to a vascular cause. It encompasses parenchymal infarction, intracerebral and subarachnoid haemorrhage[14]. Stroke is an important cause of morbidity and mortality world over. The causal relationship between infections and stroke has been researched in the past and has been deemed probable. Bacteria, viruses, fungi and a few parasites have been recognised as primary etiological or contributory factors of stroke[15]. The most important mechanism of stroke in infections is the stimulation of a systemic inflammatory response and consequent generalised procoagulant state or a localised effect on atherosclerotic plaques making them prone to rupture[16]. Other means of pathogenesis include effects on vasculature — vessel wall inflammation (*e.g.*, Varicella- Zoster, Epstein-Barr, Cytomegalovirus) and/or vessel wall remodelling (*e.g.*, human immunodeficiency virus), emboli from cardiac causes including valves (*e.g.*, infectious endocarditis due to staphylococcus, streptococcus, HACEK group of bacteria) and from dilated chambers (dilated cardiomyopathy in Chagas disease)[15].

Stroke is one of the neurological complications associated with SARS-CoV-2 attributed to CAC (Figure 1A-D). One of the interesting mechanisms includes binding with and depletion of ACE-2 receptors reducing its vasodilatory and anti-inflammatory effects[17]. Literature regarding epidemiology of stroke in COVID-19 is still emerging and the exact incidence is yet to be established. Some interesting imaging observations include large vessel involvement in a relatively younger population even in the absence of established risk factors, concordant multiple vessel (both cerebral and systemic) thrombosis, unusual sites of thrombi, greater thrombus load and poorer functional outcomes due to contributory effects of hypoxia from lung and myocardial involvement[18].

Venous system

Cerebral venous thrombosis (CVT) is less common when compared to other types of stroke and affects a different patient demographic, those of a comparatively younger age group with a notable female preponderance. The most important risk factors for CVT are genetic and acquired causes of thrombophilia including pregnancy, puerperium, intake of contraceptive pills, infections and neoplasms (CNS, systemic). Most common infections associated with CVT include oto-mastoiditis, sinusitis and facial infections with an overall declining trend in the modern antibiotic era[19]. CVT seldom presents with focal neurological deficit like typical stroke. The symptoms vary depending on the site of thrombosis, chronicity and patient age. Headache is the most common initial and in many instances, the only presenting symptom[20]. MRI with venography is the investigation of choice to confirm the diagnosis (Figure 2A-D).

Cases of CVT are being increasingly reported during this pandemic, CAC most likely being the underlying mechanism. Clinicians need to maintain a high index of suspicion while treating COVID-19 patients with persistent headache irrespective of presence of other neurological symptoms[21]. A low threshold for ordering radiological investigations in these patients can potentially alter therapeutic decision making. Imaging in CVT includes demonstration of the thrombus as a loss of flow void in baseline images and absence of flow related signal in venography[19]. Associated complications including venous infarcts, intra and extra-axial haemorrhages.

THORACIC AORTA

Aortic mural thrombus (AMT) is a rare entity defined by an intraluminal filling defect with an attachment to the intima. Two types have been described namely sessile and pedunculated with the latter having a higher incidence of peripheral embolization and related complications. AMT is usually associated with regional vessel wall abnormalities like atherosclerosis, aneurysm, vasculitis and dissection. Primary AMT without underlying wall pathology is extremely rare and one multicentre study including more than 10000 autopsies reported its incidence at approxiately 0.45% and that of major vessel occlusion contributive to mortality up to 6%[22]. CAC is one cause of such aortic thrombosis likely due to endothelial inflammation[2]. It is usually the radiologist who first comes across this finding and alerts the clinicians, aiding in subsequent management depending on the site, size of thrombus and patients' hemodynamic and respiratory status (Figure 3A and B).

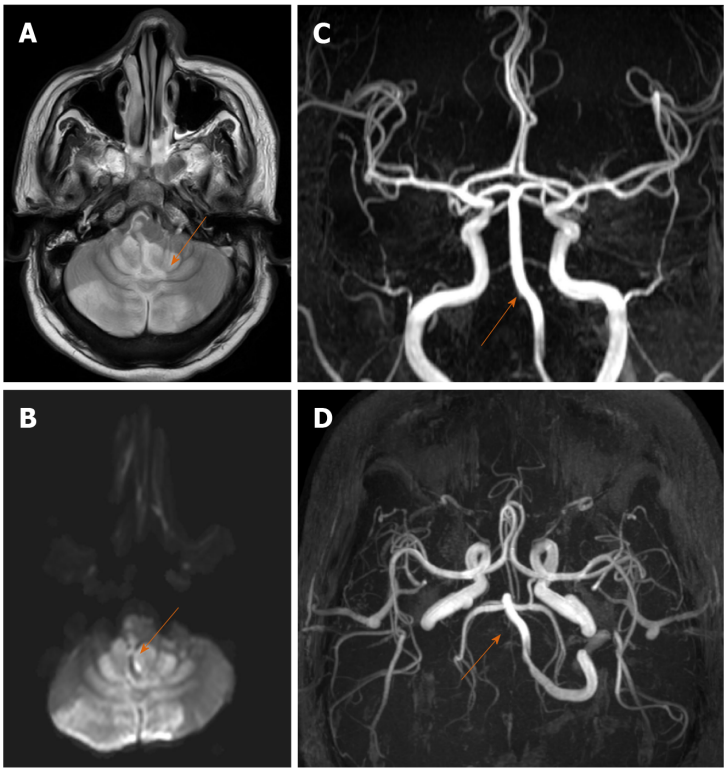


Figure 1 A 35-year-old male with posterior circulation stroke. A and B: Axial sections of magnetic resonance imaging brain (T2W, diffusion sequences) show areas of high signal in both cerebellar hemispheres, vermis and brainstem suggestive of acute infarcts; C and D: Magnetic resonance artery coronal and axial sections show complete non visualization of right vertebral artery (arrow) suggestive of thrombosis.

ABDOMINAL VASCULATURE

Mesenteric vessels

Mesenteric ischemia is an uncommon, potentially fatal abdominal emergency. It is characterised by interrupted blood supply to the gastrointestinal tract with resulting mural ischemia progressing from a reversible mucosal stage to irreversible transmural necrosis and subsequently more adverse outcomes. Hence, a very important prognostic factor is the temporal relation between symptom onset and initiation of revascularization with mortality rate increasing from 12% in the initial 12 h to nearly a 100% when there is a delay of more than 48 h[23]. Contrast-enhanced CT (CECT) is the investigation of choice for diagnosis and exclusion of other causes of acute abdomen. The presentation can be nonspecific with abdominal pain being the most frequent and consistent symptom[24].

Causes of ischemia are most commonly arterial, either embolic (approxiately 40%-50% cases) or in situ thrombosis of a vessel with pre-existing luminal narrowing (approxiately 25%-30%), the latter being more common in the elderly (> 70 years). Mesenteric venous occlusion as a cause of ischemia is less common (approxiately 5%-10%), and usually occurs in a much younger population with hypercoagulable states. Non-occlusive mesenteric ischemia is a condition with diffuse small and large bowel involvement without identifiable focal stenotic or occlusive vascular pathology usually occurring in generalised low flow states like cardiogenic or hypovolemic shock[23,25].

The role of imaging in mesenteric ischemia is two-fold and includes diagnosis and prognostication. A systematic approach should be followed including evaluation of vasculature (assessment of presence and extent of occlusive/partial filling defects, mural atherosclerotic changes), bowel (for presence of dilation, mural enhancement, thickening/thinning, pneumatosis), mesentery and additionally signs of perforation (wall discontinuity, pneumoperitoneum)[23,25].

Mesenteric ischemia has been reported in patients with severe COVID-19 disease with underlying causative mechanisms including CAC, direct enterocyte infection, microvascular thrombosis in the gut wall and non-occlusive ischemia[26]. Concomitant arterial and venous mesenteric thrombosis has been reported with COVID-19 disease[27] (Figure 4A-D). Knowledge of this complication and timely investigation followed by intervention can help reduce associated mortality from this condition.

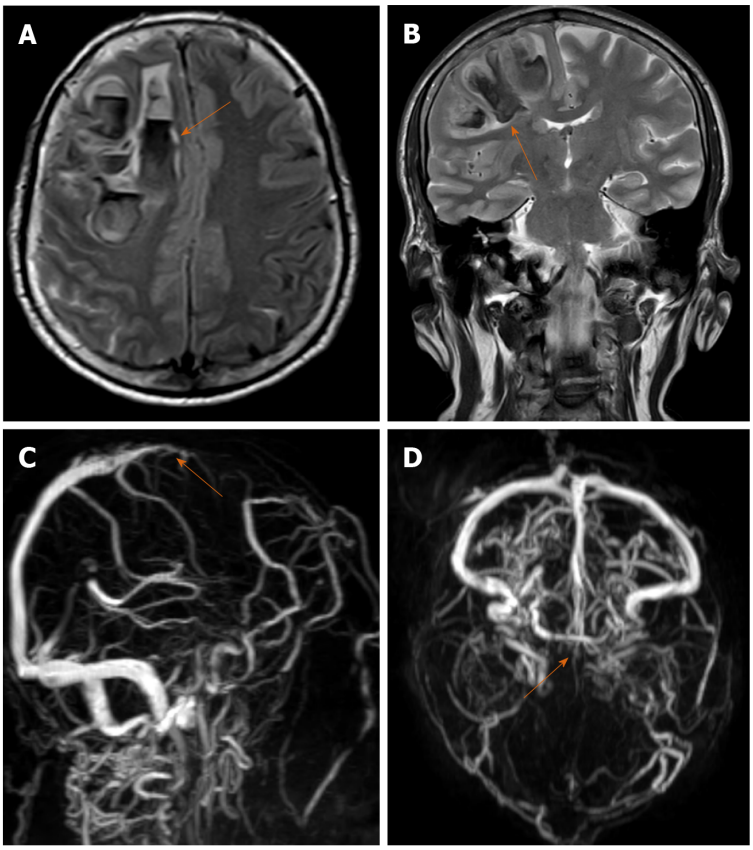


Figure 2 A 61-year-old male with Dural venous thrombosis. A and B: Axial and coronal sections of magnetic resonance imaging brain (T2WI sequence) show acute hemorrhage (arrow) in right frontal lobe with left sided midline shift; C and D: Magnetic resonance venography sagittal oblique and axial sections show absent flow related signal in anterior third of superior sagittal sinus suggestive of thrombosis.

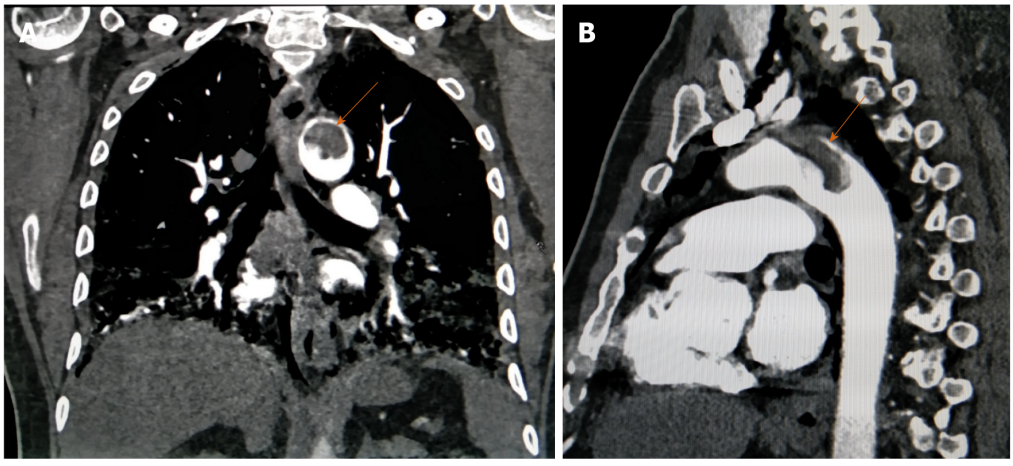


Figure 3 A 64-year-old male with aortic mural thrombosis. A and B: Coronal and sagittal sections of arterial phase of contrast-enhanced computed tomography thorax show pedunculated thrombus in aortic arch suggestive of aortic mural thrombus.

Renal artery

Renal artery thrombosis may be secondary to embolic phenomena or in situ thrombosis. The most common source of emboli are cardiac, usually secondary to either structural (valvular abnormalities, cardiomyopathy) or functional abnormalities (arrhythmias, myocardial infarction) or from the aorta (aneurysms, atherosclerosis). In situ thrombosis could be secondary to vasculitis, trauma or dissection[28]. Absence of these predisposing factors raises the possibility of de-novo thrombosis secondary to

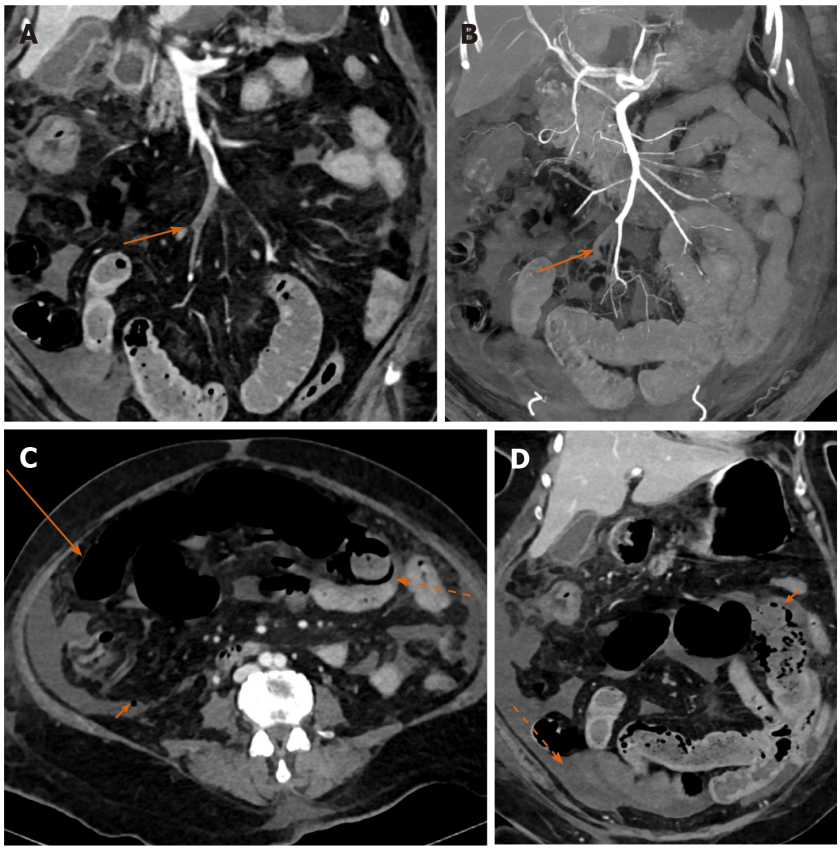


Figure 4 A 65-year-old female with acute mesenteric ischemia. A: Coronal reformatted image of contrast-enhanced computed tomography (CECT) abdomen shows filling defects (orange arrow) in ileal branches of superior mesenteric artery suggestive of thrombosis; B: Coronal reformatted image of CECT abdomen shows occlusion of accompanying tributaries of superior mesenteric vein (SMV) with superior extension of thrombus into the main stem of SMV; C: Axial CECT image showing dilated small bowel with paper thin wall (long orange arrow), circumferential pneumatosis (dotted orange arrow) and foci of free extraluminal air (small orange arrow) indicating transmural bowel necrosis with perforation; D: Coronal CECT image showing a bowel segment with absent mural enhancement (solid orange arrow), and ascites (dotted arrow).

CAC (Figure 5A and B). The importance of identification of renal artery thrombosis lies in the fact that it is a treatable cause of renal dysfunction. Indeed because of its non-specific clinical presentation (most commonly unilateral flank pain) radiologists play a key role in detection and management which entails anticoagulation measures and endovascular intervention as indicated.

PERIPHERAL VASCULATURE

Arteries

Peripheral arterial disease (PAD) is characterised by reduced or absent forward flow in major systemic vessels excluding the cerebrovascular and coronary circulations. It affects the lower limb arteries more frequently with the most common cause being atherosclerosis. Other less common causes include thromboembolism, vasculitis, degenerative and dysplastic conditions of vessel wall. Risk factors for PAD include diabetes, obesity, hypertension, hyperlipidemia, smoking (strongest association) and a positive family history. Clinically PAD is classified based on patient presentation into four categories: Asymptomatic, intermittent claudication, acute and chronic limb ischemia on the basis of American Heart Association/American College of Cardiology guidelines[29]. Amongst this acute limb ischemia due to any cause is an emergency since the rapidity of developing occlusion precludes collateral pathway formation, thereby threatening limb viability. The most common mechanism of acute limb ischemia is rupture of pre-existing atheromatous plaque with thrombus formation and vessel occlusion.

CT angiography plays an important role in management by classification of PAD based on location, lesion length [short (< 5 cm) *vs* long], degree of luminal narrowing

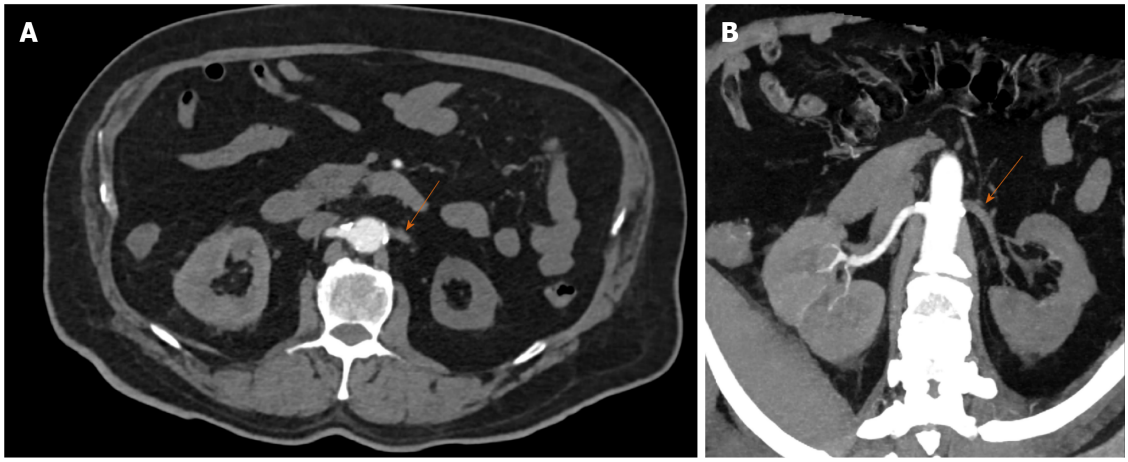


Figure 5 A 74-year-old male with renal artery thrombosis. A and B: Axial baseline and oblique coronal reformatted maximum intensity projection images of arterial phase contrast-enhanced computed tomography images showing hypodense filling defect involving left renal artery from ostium to hilum and its segmental branches with non-enhancement of left kidney suggestive of left renal artery thrombosis with infarct.

and status of distal vessels (most important consideration in revascularisation procedures)[30] (Figure 6A-C). Functional classification (Fontaine/Rutherford) along with radiological investigations help guide the course of treatment planning between conservative, endovascular and surgical[31]. A retrospective study by Goldman *et al*[32]. during the pandemic situation (January to April 2020) witnessed an elevated positivity rate amongst CT angiographic studies performed for claudication symptoms in COVID-19 patients with a higher clot burden and worse prognosis (higher incidence of amputation and/or death) in test population when compared with control group.

Deep venous system

A recently published meta-analysis of literature with reference to the prevalence of deep vein thrombosis and venous thromboembolism in COVID-19 patients estimated these at approxiately 20% and 30% respectively[33]. Prevalence was higher amongst patients with a higher BMI, those belonging to an older age group and with a more severe illness. The prothrombotic state induced by SARS-CoV-2 has led to the question of whether pulmonary thrombi in this disease originate from peripheral veins or develop in situ, the significance being the difference in composition and subsequently choice of anticoagulation. This article brings attention to the requirement of appropriate screening protocols in all COVID-19 patients. Therapeutic strategies including choice of anticoagulant, dosage and duration are beyond the scope of this review.

CONCLUSION

Although SARS-CoV-2 is primarily a respiratory virus, COVID-19 is more of a systemic illness with multiorgan involvement. Coagulopathy associated with this condition can affect both arterial and venous systems with catastrophic effects depending on the site and severity of thrombosis. Many of these phenomena can be clinically silent or obscure in presentation. Imaging therefore remains the cornerstone in arriving at the appropriate diagnosis with a potential to alter the course of disease progression by advocating timely management.

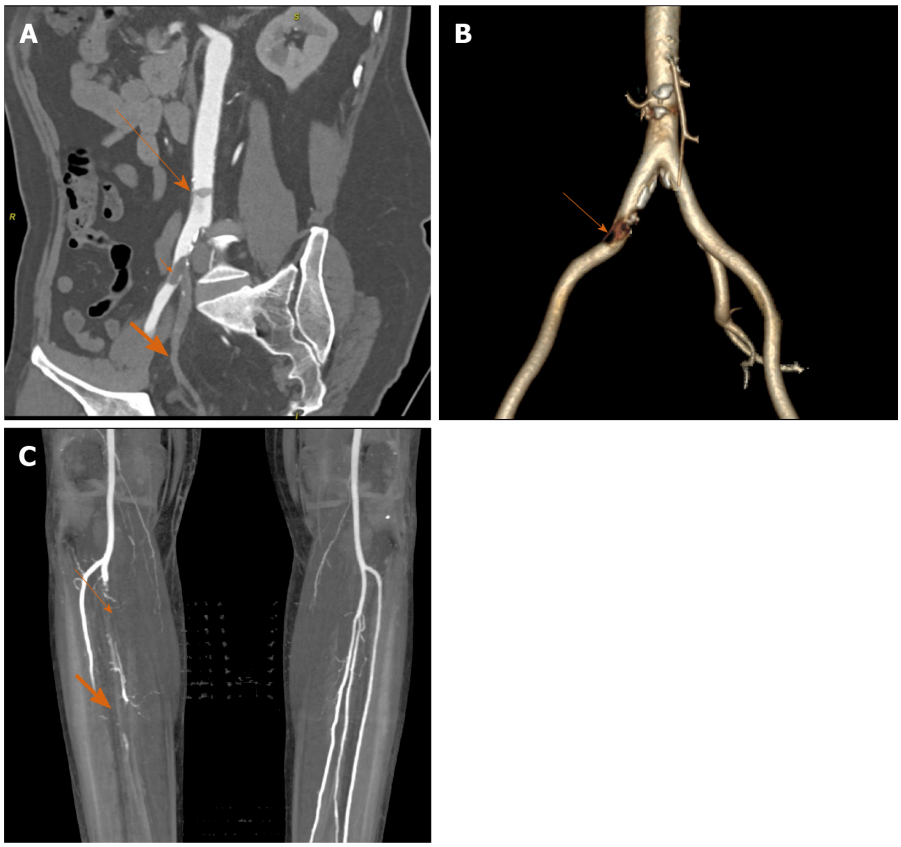


Figure 6 A 51-year-old male with peripheral arterial disease. A: Coronal oblique reformatted image of contrast-enhanced computed tomography abdomen shows mall mural thrombus in abdominal aorta (long arrow); and another partially occluding thrombus at right common iliac artery (short arrow) bifurcation extending into external iliac branch and synchronous complete thrombosis of right internal iliac artery (broad orange arrow); B: Three-dimensional reconstructed image shows defect in right common iliac artery and complete non visualization of right internal iliac artery; C: Coronal maximum intensity projection image of computed tomography angiography of bilateral lower limbs shows filling defect in right tibio-peroneal trunk just beyond origin with poor distal reformation (thin arrow), and non-opacification of mid and distal third of right anterior tibial artery (broad orange arrow).

REFERENCES

1 **Wiersinga WJ**, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; **324**: 782-793 [PMID: 32648899 DOI: 10.1001/jama.2020.12839]

2 **Iba T**, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. *Crit Care* 2020; **24**: 360 [PMID: 32552865 DOI: 10.1186/s13054-020-03077-0]

3 **Mezalek ZT**, Khibri H, Ammouri W, Bouaouad M, Haidour S, Harmouche H, Maamar M, Adnaoui M. COVID-19 Associated Coagulopathy and Thrombotic Complications. *Clin Appl Thromb Hemost* 2020; **26**: 1076029620948137 [PMID: 32795186 DOI: 10.1177/1076029620948137]

4 **Middeldorp S**, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020; **18**: 1995-2002 [PMID: 32369666 DOI: 10.1111/jth.14888]

5 **Klok FA**, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; **191**: 145-147 [PMID: 32291094 DOI: 10.1016/j.thromres.2020.04.013]

6 **Woehl B**, Lawson B, Jambert L, Tousch J, Ghassani A, Hamade A. 4 Cases of Aortic Thrombosis in Patients With COVID-19. *JACC Case Rep* 2020; **2**: 1397-1401 [PMID: 32835285 DOI: 10.1016/j.jaccas.2020.06.003]

7 **Levi M**, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020; **7**: e438-e440 [PMID: 32407672 DOI: 10.1016/S2352-3026(20)30145-9]

8 **Danzi GB**, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J* 2020; **41**: 1858 [PMID: 32227120 DOI: 10.1093/eurheartj/ehaa254]

9 **Xie Y**, Wang X, Yang P, Zhang S. COVID-19 complicated by acute pulmonary embolism. *RSNA*

2020; **2**: e200067 [DOI: 10.1148/ryct.2020200067]
10 **Ullah W**, Saeed R, Sarwar U, Patel R, Fischman DL. COVID-19 Complicated by Acute Pulmonary Embolism and Right-Sided Heart Failure. *JACC Case Rep* 2020; **2**: 1379-1382 [PMID: 32313884 DOI: 10.1016/j.jaccas.2020.04.008]
11 **Rotzinger DC**, Beigelman-Aubry C, von Garnier C, Qanadli SD. Pulmonary embolism in patients with COVID-19: Time to change the paradigm of computed tomography. *Thromb Res* 2020; **190**: 58-59 [PMID: 32302782 DOI: 10.1016/j.thromres.2020.04.011]
12 **Hékimian G**, Lebreton G, Bréchot N, Luyt CE, Schmidt M, Combes A. Severe pulmonary embolism in COVID-19 patients: a call for increased awareness. *Crit Care* 2020; **24**: 274 [PMID: 32487231 DOI: 10.1186/s13054-020-02931-5]
13 **Kaminetzky M**, Moore W, Fansiwala K, Babb JS, Kaminetzky D, Horwitz LI, McGuinness G, Knoll A, Ko JP. Pulmonary Embolism on CTPA in COVID-19 Patients. *RSNA* 2020; **2**: e200308 [DOI: 10.1148/ryct.2020200308]
14 **Sacco RL**, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition; Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 2064-2089 [PMID: 23652265 DOI: 10.1161/STR.0b013e318296aeca]
15 **Fugate JE**, Lyons JL, Thakur KT, Smith BR, Hedley-Whyte ET, Mateen FJ. Infectious causes of stroke. *Lancet Infect Dis* 2014; **14**: 869-880 [PMID: 24881525 DOI: 10.1016/S1473-3099(14)70755-8]
16 **Epstein SE**, Zhou YF, Zhu J. Infection and atherosclerosis: emerging mechanistic paradigms. *Circulation* 1999; **100**: e20-e28 [PMID: 10421626 DOI: 10.1161/01.cir.100.4.e20]
17 **Hess DC**, Eldahshan W, Rutkowski E. COVID-19-Related Stroke. *Transl Stroke Res* 2020; **11**: 322-325 [PMID: 32378030 DOI: 10.1007/s12975-020-00818-9]
18 **John S**, Kesav P, Mifsud VA, Piechowski-Jozwiak B, Dibu J, Bayrlee A, Elkambergy H, Roser F, Elhammady MS, Zahra K, Hussain SI. Characteristics of Large-Vessel Occlusion Associated with COVID-19 and Ischemic Stroke. *AJNR Am J Neuroradiol* 2020; **41**: 2263-2268 [PMID: 32855182 DOI: 10.3174/ajnr.A6799]
19 **Ferro JM**, Canhão P. Cerebral venous sinus thrombosis: update on diagnosis and management. *Curr Cardiol Rep* 2014; **16**: 523 [PMID: 25073867 DOI: 10.1007/s11886-014-0523-2]
20 **Cumurciuc R**, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1084-1087 [PMID: 16024884 DOI: 10.1136/jnnp.2004.056275]
21 **Poillon G**, Obadia M, Perrin M, Savatovsky J, Lecler A. Cerebral venous thrombosis associated with COVID-19 infection: Causality or coincidence? *J Neuroradiol* 2020 [PMID: 32437707 DOI: 10.1016/j.neurad.2020.05.003]
22 **Yang S**, Yu J, Zeng W, Yang L, Teng L, Cui Y, Shi H. Aortic floating thrombus detected by computed tomography angiography incidentally: five cases and a literature review. *J Thorac Cardiovasc Surg* 2017; **153**: 791-803 [DOI: 10.1016/j.jtcvs.2016.12.015]
23 **Garzelli L**, Nuzzo A, Copin P, Calame P, Corcos O, Vilgrain V, Ronot M. Contrast-Enhanced CT for the Diagnosis of Acute Mesenteric Ischemia. *AJR Am J Roentgenol* 2020; **215**: 29-38 [PMID: 32374661 DOI: 10.2214/AJR.19.22625]
24 **Nuzzo A**, Corcos O. [Management of mesenteric ischemia in the era of intestinal stroke centers: The gut and lifesaving strategy]. *Rev Med Interne* 2017; **38**: 592-602 [PMID: 28259479 DOI: 10.1016/j.revmed.2017.01.018]
25 **Navas-Campo R**, Moreno-Caballero L, Ezponda Casajús A, Muñoz DI. Acute mesenteric ischemia: a review of the main imaging techniques and signs. *Radiologia* 2020; **62**: 336-348 [PMID: 32386783 DOI: 10.1016/j.rx.2020.02.001]
26 **Parry AH**, Wani AH, Yaseen M. Acute Mesenteric Ischemia in Severe Coronavirus-19 (COVID-19): Possible Mechanisms and Diagnostic Pathway. *Acad Radiol* 2020; **27**: 1190 [PMID: 32475635 DOI: 10.1016/j.acra.2020.05.016]
27 **de Barry O**, Mekki A, Diffre C, Seror M, El Hajjam M, Carlier RY. Arterial and venous abdominal thrombosis in a 79-year-old woman with COVID-19 pneumonia. *Radiol Case Rep* 2020; **15**: 1054-1057 [PMID: 32351657 DOI: 10.1016/j.radcr.2020.04.055]
28 **Kawashima A**, Sandler CM, Ernst RD, Tamm EP, Goldman SM, Fishman EK. CT evaluation of renovascular disease. *Radiographics* 2000; **20**: 1321-1340 [PMID: 10992021 DOI: 10.1148/radiographics.20.5.g00se141321]
29 **Conte SM**, Vale PR. Peripheral Arterial Disease. *Heart Lung Circ* 2018; **27**: 427-432 [PMID: 29150158 DOI: 10.1016/j.hlc.2017.10.014]
30 **Fleischmann D**, Hallett RL, Rubin GD. CT angiography of peripheral arterial disease. *J Vasc Interv Radiol* 2006; **17**: 3-26 [PMID: 16415129 DOI: 10.1097/01.rvi.0000191361.02857.de]
31 **Sena G**, Gallelli G. An increased severity of peripheral arterial disease in the COVID-19 era. *J Vasc Surg* 2020; **72**: 758 [PMID: 32360372 DOI: 10.1016/j.jvs.2020.04.489]
32 **Goldman IA**, Ye K, Scheinfeld MH. Lower-extremity Arterial Thrombosis Associated with COVID-

19 Is Characterized by Greater Thrombus Burden and Increased Rate of Amputation and Death. *Radiology* 2020; **297**: E263-E269 [PMID: 32673190 DOI: 10.1148/radiol.2020202348]

33 **Di Minno A**, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. *Semin Thromb Hemost* 2020; **46**: 763-771 [PMID: 32882719 DOI: 10.1055/s-0040-1715456]

World Journal of Radiology

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

World J Radiol 2021 January 28; 13(1): 29-39

DOI: 10.4329/wjr.v13.i1.29

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Retrospective Study

Magnetic resonance imaging findings of redundant nerve roots of the cauda equina

Erkan Gökçe, Murat Beyhan

ORCID number: Erkan Gökçe 0000-0003-3947-2972; Murat Beyhan 0000-0002-8630-4632.

Author contributions: Gökçe E designed and supervised the study; Beyhan M collected the data; Gökçe E and Beyhan M participated in literature research and manuscript preparation, and read and approved the final version.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Tokat Gaziosmanpasa University Faculty of Medicine (No. 19- KAEK-099).

Informed consent statement: Patients were not required to give informed consent for the study as the figures from the picture archiving and communication system were studied retrospectively.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

Erkan Gökçe, Murat Beyhan, Department of Radiology, Tokat Gaziosmanpasa University, Faculty of Medicine, Tokat 60100, Turkey

Corresponding author: Erkan Gökçe, MD, Chief Doctor, Department of Radiology, Tokat Gaziosmanpasa University, Faculty of Medicine, Kaleardı Mah., Muhittin Fisunoglu Cad., Tokat 60100, Turkey. drerkangokce@gmail.com

Abstract

BACKGROUND

Redundant nerve roots (RNRs) of the cauda equina are often a natural evolutionary part of lumbar spinal canal stenosis secondary to degenerative processes characterized by elongated, enlarged, and tortuous nerve roots in the superior and/or inferior of the stenotic segment. Although magnetic resonance imaging (MRI) findings have been defined more frequently in recent years, this condition has been relatively under-recognized in radiological practice. In this study, lumbar MRI findings of RNRs of the cauda equina were evaluated in spinal stenosis patients.

AIM

To evaluate RNRs of the cauda equina in spinal stenosis patients.

METHODS

One-hundred and thirty-one patients who underwent lumbar MRI and were found to have spinal stenosis between March 2010 and February 2019 were included in the study. On axial T2-weighted images (T2WI), the cross-sectional area (CSA) of the dural sac was measured at L2-3, L3-4, L4-5, and L5-S1 levels in the axial plane. CSA levels below 100 mm^2 were considered stenosis. Elongation, expansion, and tortuosity in cauda equina fibers in the superior and/or inferior of the stenotic segment were evaluated as RNRs. The patients were divided into two groups: Those with RNRs and those without RNRs. The CSA cut-off value resulting in RNRs of cauda equina was calculated. Relative length (RL) of RNRs was calculated by dividing the length of RNRs at mid-sagittal T2WI by the height of the vertebral body superior to the stenosis level. The associations of CSA leading to RNRs with RL, disc herniation type, and spondylolisthesis were evaluated.

RESULTS

Fifty-five patients (42%) with spinal stenosis had RNRs of the cauda equina. The

reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Turkey

Peer-review report's scientific quality classification

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

Received: July 24, 2020
Peer-review started: July 24, 2020
First decision: November 14, 2020
Revised: November 26, 2020
Accepted: December 4, 2020
Article in press: December 4, 2020
Published online: January 28, 2021

P-Reviewer: Peng BG, Xie Q
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Wang LYT

average CSA was 40.99 ± 12.76 mm² in patients with RNRs of the cauda equina and 66.83 ± 19.32 mm² in patients without RNRs. A significant difference was found between the two groups for CSA values ($P < 0.001$). Using a cut-off value of 55.22 mm² for RNRs of the cauda equina, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) values of 96.4%, 96.1%, 89.4%, and 98.7% were obtained, respectively. RL was 3.39 ± 1.31 (range: 0.93-6.01). When the extension of RNRs into the superior and/or inferior of the spinal canal stenosis level was evaluated, it was superior in 54.5%, both superior and inferior in 32.8%, and inferior in 12.7%. At stenosis levels leading to RNRs of the cauda equina, 29 disc herniations with soft margins and 26 with sharp margins were detected. Disc herniation type and spondylolisthesis had no significant relationship with RL or CSA of the dural sac with stenotic levels ($P > 0.05$). As the CSA of the dural sac decreased, the incidence of RNRs observed at the superior of the stenosis level increased ($P < 0.001$).

CONCLUSION

RNRs of the cauda equina are frequently observed in patients with spinal stenosis. When the CSA of the dural sac is < 55 mm², lumbar MRIs should be carefully examined for this condition.

Key Words: Cauda equina; Dural sac; Lumbar spine; Magnetic resonance imaging; Redundant nerve roots; Spinal stenosis

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In this study, magnetic resonance imaging findings of redundant nerve roots (RNRs) of the cauda equina were evaluated in patients with lumbar stenosis. The stenotic segment cross-sectional area (CSA) cut-off value that could lead to RNRs of the cauda equina was detected as 55.22 mm². In patients with RNRs of the cauda equina, the average CSA was significantly lower than in patients who did not have RNRs. Disc herniation type and spondylolisthesis were not significantly associated with the relative length or CSA of the dural sac. It was found that the incidence of RNRs observed at the superior of the stenosis level increased as the CSA decreased.

Citation: Gökçe E, Beyhan M. Magnetic resonance imaging findings of redundant nerve roots of the cauda equina. *World J Radiol* 2021; 13(1): 29-39
URL: https://www.wjgnet.com/1949-8470/full/v13/i1/29.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i1.29

INTRODUCTION

The term redundant nerve roots (RNRs) of the cauda equina was first used by Cresmann and Pawl[1-3]. It is a condition in which nerve roots of the cauda equina have accompanying tortuosity and elongation and it develops secondary to spinal stenosis. It is not a new or separate disease but often a natural evolutionary part of lumbar spinal canal stenosis secondary to degenerative processes[4]. The developmental mechanism of this non-congenital elongated nerve root is probably the trapping of the nerve root at the level of stenosis. The most common symptoms in RNRs of the cauda equina are pain in the lower back and leg[3]. It has been reported that in patients with RNRs of the cauda equina, leg pain, paresthesia, and difficulty in walking are more pronounced than in patients with lumbar stenosis without RNRs and that they derive limited benefit from decompression surgery[4-6]. Radiologically, RNRs of the cauda equina were initially defined as serpiginous filling defects due to partial or total stenosis that prevents the passage of contrast material on myelography. Along with the increasing use of magnetic resonance imaging (MRI) for imaging the spinal canal, it is now predominantly considered as an MRI finding[2,4,7-14]. However, this condition has been relatively underrecognized in radiological practice[2,4]. The aim of the present study was to evaluate the imaging findings of RNRs of the cauda equina detected on the lumbar MRI of spinal stenosis patients.

MATERIALS AND METHODS

The reports of 7424 patients in the picture archive and communication system (PACS) (SECTRA IDS7 PACS, Sweden) who underwent lumbar MRI in our hospital for various reasons between March 2010 and February 2019 were retrospectively examined for the expression "spinal stenosis". One hundred and sixty-seven patients who were found to have the term "spinal stenosis" in lumbar MRI reports in PACS were examined for the presence of RNRs. One hundred and thirteen (67.7%) of these patients were female and 54 (32.3%) were male. The mean age was 60.7 ± 11.3 years (range 28-90). Sixty (35.9%) patients had low back pain, 54 (32.3%) had back and leg pain, 21 (12.6%) had leg pain, 13 (7.8%) had both low back and leg pain and claudication, nine (5.4%) had low back pain and claudication, eight (4.8%) had claudication and two (1.2%) had leg pain and claudication. Until 2017, MRI examinations were carried out using an 8-channel 1.5 T MRI machine (GE Signa Excite HD; GE Healthcare, Milwaukee, United States). A 16-channel 1.5 T MRI machine (GE Signa Explorer SV 25; GE Healthcare, Milwaukee, United States,) was used after 2017. A phased array spine coil was used on the lumbar MRI. Sequences and parameters obtained on lumbar MRI examinations were, respectively: sagittal plane T2-weighted (T2W) fast spin echo (FSE) sequences (TR: 3008 ms, TE: 91.9 ms, NEX: 2, slice thickness: 4 mm, gap distance: 1 mm, FOV: 29 cm, matrix: 320 x 224); sagittal plane T1W FSE sequences (TR: 602 ms, TE: 8.7 ms, NEX: 1.5, slice thickness: 4 mm, gap distance: 1 mm, FOV: 29 cm, matrix: 320 × 224); axial plane T2W (TR: 4647 ms, TE: 91.8 ms, NEX: 2, slice thickness: 4 mm, gap distance: 1 mm, FOV: 18 cm, matrix: 320 × 192). In those patients with spinal stenosis on lumbar MRI, the presence of RNRs was evaluated with consensus by two radiologists with 14 (E.G.) and eight (M.B.) years of work experience. Thirty-six patients with a history of craniospinal operations or spondylodiscitis and whose lumbar MRI examination was not of optimal image quality were excluded from the study. The number of patients not included in this study and the reasons for exclusion are shown in Table 1.

Radiological evaluation

Elongation, expansion, and tortuosity in the stenotic segment superior and/or inferior of the cauda equina fibers on lumbar MRI were evaluated as RNRs of the cauda equina (Figure 1A). On T2W axial images in the PACS system, cross-sectional area (CSA) of the dural sac was manually drawn and measured at the narrowest section at L2-3, L3-4, L4-5, and L5-S1 intervertebral disc space levels in each patient (Figure 1B). Patients with CSAs under 100 mm^2 at any of these spinal levels were considered to have spinal stenosis. Patients were divided into two groups: Those with stenosis and RNRs of the cauda equina and those with stenosis but without RNRs. In patients with spinal stenosis and RNRs at multiple levels, the narrowest CSA of the dural sac level was considered to be the level leading to RNRs of the cauda equina. Stenosis levels resulting in RNRs of the cauda equina and whether the RNRs were inferior or superior to the stenosis level were evaluated (Figures 1-3). On the T2W mid-sagittal MR image, relative length (RL) of RNRs was calculated by dividing the distance from the maximum stenosis level to the farthest level where redundant roots could be observed by the height of the vertebrae body superior to the stenosis level (Figure 3B). The association between the localization of RL and RNRs according to the stenotic segment and CSA of the dural sac was examined. On sagittal plane MR images of the patients with RNRs of the cauda equina, the disc herniation type was classified based on Poureisa *et al*[11] study's as soft margin when the disc causing stenosis in the intervertebral disc space on the midsagittal image was indented into the dural sac with a wide angle, while it was classified as sharp margin when it was indented with an acute angle (Figure 4). In patients with RNRs of the cauda equina, the presence of spondylolisthesis and its association with the CSA of the dural sac were investigated.

Ethical considerations

The study was approved by the Ethics Committee of the Tokat Gaziosmanpasa University Medical School (No: 19-KAEK-099).

Statistical analyses

Data for continuous variables are shown as mean and standard deviation, whereas data for categorical variables are expressed as frequency and percentage. Independent samples *t*-test or one-way ANOVA test were used to compare the variable means between/among the groups. Receiver operating characteristic (ROC) analysis was employed to determine the power of CSA of the dural sac of stenotic segments in

Table 1 Number of patients and reasons for their exclusion from the study

The reason for exclusion	*n*
Spinal or cranial surgery history	29
Poor image quality	3
Spondylodiscitis	2
Spinal metastasis	1
Stenosis due to synovial cyst	1
Total	36

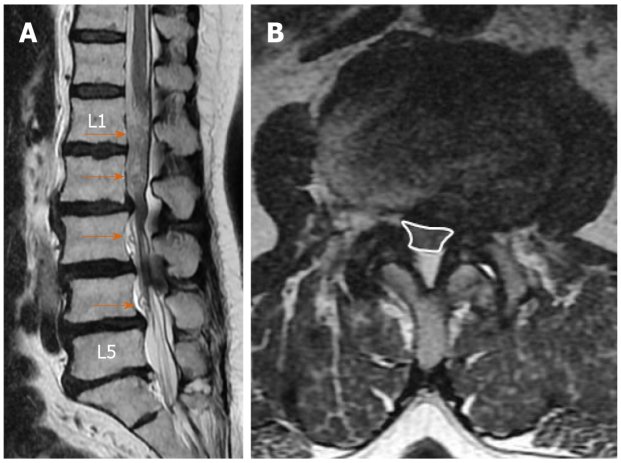


Figure 1 Seventy-one-year-old female patient with lumbar spondylosis. A: Redundant nerve roots (arrows) secondary to the stenosis at both the superior and inferior of the stenosis at the L2-L3 level, which are more prominent at the superior, are shown; B: On the axial T2-weighted image, the cross-sectional area of the dural sac was 41.60 mm^2 at the stenosis level (L2-L3).

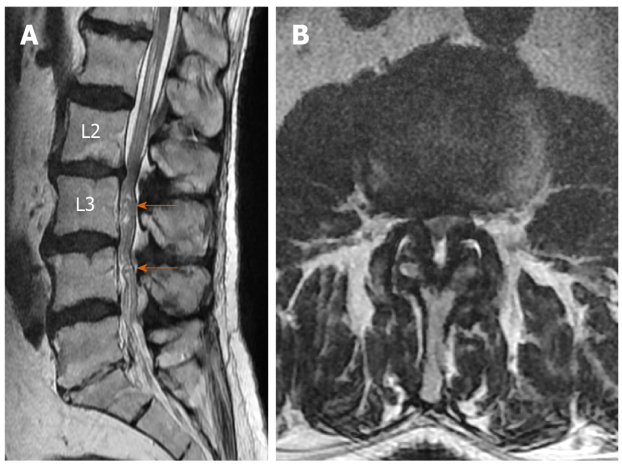


Figure 2 Seventy-one-year-old male patient with lumbar spondylosis. A: On the sagittal T2-weighted image, redundant nerve roots (arrows) secondary to the stenosis at L2-L3 level are shown at the inferior of stenosis level; B: On the axial T2-weighted image passing through L2-L3 intervertebral disc space level, marked stenosis due to ligamentum flavum and facet joint hypertrophy and disc herniation (cross-sectional area was 41.33 mm^2) are shown.

predicting RNRs of the cauda equina. *P* values < 0.05 were considered significant. Analyses were performed using SPSS 22.0 (Chicago, IL, United States).

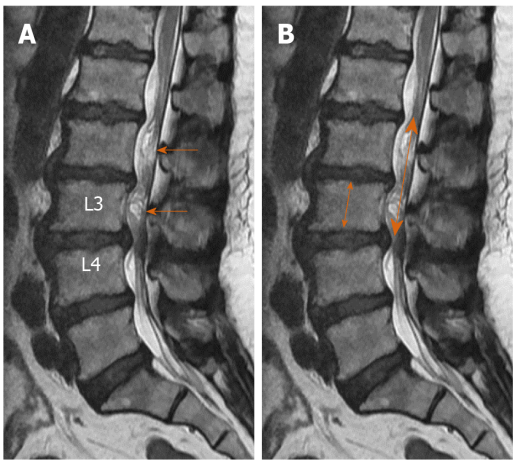


Figure 3 Forty-seven-year-old female patient with lumbar spondylosis. A: On the sagittal T2-weighted image, redundant nerve roots at the superior of the stenosis level secondary to the stenosis at the L3-L4 intervertebral disc space (arrows) are shown; B: Relative length was calculated by dividing the length of redundant nerve roots (thick arrow) by the vertebra height at the superior of stenosis level (thin arrow).

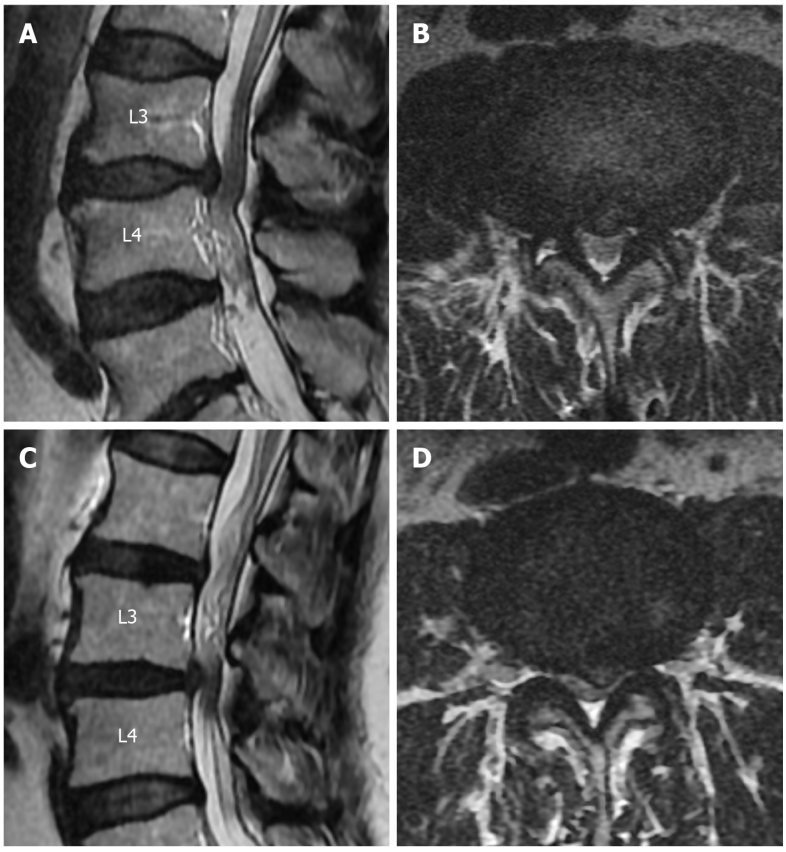


Figure 4 Soft and sharp margin types of disc herniation into the dural sac. A: On the sagittal T2-weighted image, soft margin disc herniation at the level of L3-L4 intervertebral disc space and redundant nerve roots at the inferior of the stenosis are shown; B: The axial T2-weighted images of soft margin disc herniation are shown; C: On the sagittal T2-weighted image, sharp margin disc herniation at the L3-L4 intervertebral disc space and redundant nerve roots at its superior are shown; D: Axial T2-weighted image of sharp disc herniation is shown.

RESULTS

On lumbar MRI examination of the 131 patients (90 females and 41 males) included in the study, central spinal canal stenosis was detected at one or more levels. In 76 of these patients (58.0%), cauda equina fibers were found with normal appearance, while 55 (42.0%) were found to have RNRs of the cauda equina. The mean age of patients

with RNRs of the cauda equina was 62.38 ± 10.37 years (range: 37-80), while patients without RNRs had an average age of 59.26 ± 10.97 years (range: 40-90). There was no significant difference in average age between the patients with RNRs of the cauda equina and the spinal stenosis patients without RNRs (P = 0.103). CSA ranged from 14.94 to 77.83 mm^2 (mean 40.99 ± 12.76) in patients with RNRs of the cauda equina and from 17.57 to 99.22 mm^2 (mean 66.83 ± 19.32) in the stenosis group without RNRs. The difference in CSA values between the two groups was significant (P < 0.001). CSAs of dural sacs according to disc space levels in the stenotic patients without RNRs and stenotic patients with RNRs of the cauda equina are shown in Table 2. Using a cut-off value of ≤ 55.22 mm^2 based on ROC analysis for CSA of the dural sac that could lead to RNRs of the cauda equina in stenotic segments, the area under the curve (AUC) was 0.96, sensitivity was 0.92, and specificity was 0.91, while the positive predictive value was 0.88 and the negative predictive value was 0.94 (P < 0.001) (Figure 5).

RL of RNRs varied from 0.93 to 6.01 (mean: 3.39 ± 1.31). In terms of the extension of RNRs to superior and/or inferior spinal canal stenosis levels, 30 patients (54.5%) had superior, 18 patients (32.8%) had both superior and inferior, and seven patients (12.7%) had inferior extension only. As CSA decreased at the level of stenosis in the spinal canal (*i.e.*, as stenosis became apparent), the RNRs were more prevalently observed at the superior of the stenosis level (P < 0.001). RL of RNRs increased significantly in redundant roots extending to both superior and inferior compared to those extending only to superior or inferior (P < 0.001). However, there was no significant relationship between CSA values and RL that led to the cauda equina (P = 0.305). Table 3 shows the statistical relationship of the localization level (superior, inferior, and both superior and inferior) of RNRs with RL and CSA measurements of the dural sac at extension levels of RNRs.

There were 29 disc herniations of soft margins and 26 disc herniations of sharp margins to the dural sac at the RNRs of the cauda equina levels. Disc herniation types were not significantly associated with CSAs or RL of RNRs of the cauda equina. The relationships of the disc herniation type at the stenosis levels causing RNRs with the CSAs and RL of the RNRs of the cauda equina are shown in Table 4. Spondylolisthesis was detected in 12 patients with RNRs of the cauda equina. However, these spondylolistheses were not significantly associated with CSA of the dural sac in patients with RNRs of the cauda equina (P = 0.280).

DISCUSSION

RNRs of the cauda equina are characterized by the presence of enlarged, elongated, and tortuous nerve roots at the subarachnoid distance adjacent to the stenosis area of the spinal canal[1-14]. Redundancy of nerve roots is probably a pathological consequence of chronic pressure force at the spinal canal stenosis zone level[2,9]. Basic pathological findings in patients with RNRs of the cauda equina are demyelination, damage to and reduction in the number of nerve fibers, and the proliferation of Schwann cells and endoneural fibrosis[2,9,10]. In the study by Savarese *et al*[4], the CSA cut-off value that led to RNRs of the cauda equina was found to be 55 mm^2. In our study, the cut-off value for the CSA of the dural sac leading to RNRs of the cauda equina (55.22 mm^2) was very close to the reported value in that study. RNRs could also be observed as inferior or superior to the stenosis level but were usually superior to the spinal canal stenosis level. Kawasaki *et al*[12] found that RNRs were superior to the stenosis level in all cases. Poureisa *et al*[11], on the other hand, reported that in 84% of cases RNRs were superior to the stenosis level, while in 16% they were inferior to the stenosis. In the present study, 54.5% of RNRs were superior to the stenosis level, while in 12.7% of cases RNRs were inferior to the stenosis level and 32.8% of the cases had both configurations. The different results in previous studies in terms of the localizations of the RNRs could be due to the differences in study populations. Similar to the study by Poureisa *et al*[11], we observed a significant relationship between the stenosis level in the spinal canal and the frequency of RNRs superior to the level of stenosis. In addition, similar to Poureisa *et al*[11], the degree of stenosis in the spinal canal was not associated with the RL of RNRs. The data in the literature and the findings of our study indicate that the frequency of RNRs superior to the stenosis was associated with the degree of stenosis. This suggested that RNRs develop more easily with the fixation of nerve roots between the narrow segment and conus medullaris due to limitation of the nerve roots by conus medullaris in the superior direction.

Poureisa *et al*[11] investigated the relationship between the RNRs of the cauda equina and the disc herniation with soft or sharp configuration into the dural sac and found

Table 2 Cross-sectional areas of the dural sac at lumbar intervertebral disc levels in patients with spinal stenosis without redundant nerve roots and with redundant nerve roots of the cauda equina on lumbar magnetic resonance imaging

Intervertebral discal space levels	Cross-sectional area without redundant nerve roots of the cauda equina, mean ± SD dev (range) mm^2	Cross-sectional area with redundant nerve roots of the cauda equina, mean ± SD dev (range) mm^2
L2-L3	130.85 ± 38.56 (48.68-240.56)	93.84 ± 34.63 (39.40-194.50)
L3-L4	100.90 ± 31.50 (38.86-176.00)	68.87 ± 31.23 (25.42-164.59)
L4-L5	78.92 ± 22.69 (21.03-126.02)	61.05 ± 35.76 (14.94-163.92)
L5-S1	102.56 ± 43.27 (17.57-251.53)	97.11 ± 41.90 (15.05-211.13)

SD: Standard deviation.

Table 3 Association of localization level of redundant nerve roots with relative length of redundant nerve roots and cross-sectional area

	Localization level of redundant nerve roots			*P* value
	Inferior (*n* = 7), mean ± SD	Superior (*n* = 30), mean ± SD	Inferior + Superior (*n* = 18), mean ± SD	
Relative length of redundant nerve roots	2.07 ± 0.67 (a)[1]	2.95 ± 1.09 (a)	4.66 ± 0.73 (b)	< 0.001
Cross sectional area (mm^2)	49.27 ± 8.06 (a)	35.61 ± 9.78 (b)	46.77 ± 14.73 (a)	0.001

[1]One-way ANOVA test was used for statistical comparisons. The means with the same letters (a or b) in the same line are not significantly different. SD: Standard deviation.

Table 4 The relationships between the disc herniation type at the stenosis levels causing redundant nerve roots, the relative length of redundant nerve roots, and the cross-sectional area of the dural sac of redundant nerve roots of the cauda equina

	Type of disc herniation		*P* value
	Soft margin (*n* = 29), mean ± SD	Sharp margin (*n* = 26), mean ± SD	
Relative length of RNRs	3.3 ± 1.42	3.5 ± 1.2	0.562
CSA of RNRs of the cauda equina (mm^2)	39.62 ± 12.02	42.54 ± 13.62	0.401

RNRs: Redundant nerve roots; CSA: Cross-sectional area of dural sac; SD: Standard deviation.

that 85.3% of the cases with RNRs of the cauda equina had sharp margin type disc herniation, and this association was significant. However, only 47.3% of patients with RNRs of the cauda equina in the present study had sharp margin type herniation and the type of disc herniation was not significantly associated with CSAs and RL of RNRs of the cauda equina. Due to these contradictory results, it would be beneficial to carry out further studies with broader series.

In recent years, MRI findings of RNRs of the cauda equina have been identified and the frequency of RNRs of the cauda equina in patients with lumbar canal stenosis was reported to be in the range of 33.8%-69.3%, while a frequency of 8.2% was reported in elderly Japanese cadavers[2,4,5,10,11,13]. In our study, the frequency of RNRs of the cauda equina was 42.0% in 131 patients with lumbar spinal stenosis, and this rate was within the limits specified in the literature.

In an anatomical study carried out by Suzuki *et al*[10], RNRs were observed in fibers passing through the spinal canal stenosis area but no redundancy was found in roots not passing through that area. Demyelination and axonal loss are thought to be the results of constant mechanical compression of nerve roots trapped in the spinal stenosis area[10]. Suzuki *et al*[10] examined the topographic distribution of levels where RNRs of the cauda equina were observed and found that 33.3% were at S1 level, 33.3% at S2 level, 16% at L5, and 17.3% were inferior to S2 roots. Min *et al*[6], on the other hand, reported that RNRs of the cauda equina were most commonly observed at L4-L5 (78.2%) followed by L3-L4 levels (17.4%). In contrast, Poureisa *et al*[11] reported L3-L4

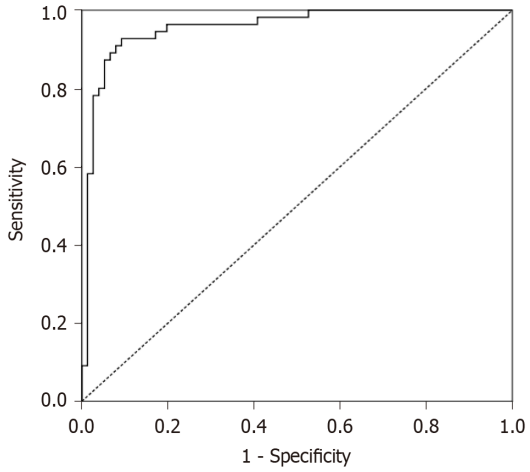


Figure 5 Receiver operating characteristic curve with a cut-off value of 55.22 mm² or less for the cross-sectional area of the dural sac.

level as the most common localization for RNRs of the cauda equina (38.7%) followed by L2-L3 level (30.7%). Similar to Min *et al*[6], RNRs of the cauda equina were most common at the L4-L5 level with 45.4% and at the L3-L4 level with 32.7% in the present study. Different frequencies of RNRs of the cauda equina at different levels of intervertebral disc spaces in the literature could reflect the ethnic structural differences in the study populations.

In a study based on the RL of RNRs measurements on the midsagittal image on sagittal lumbar MR images, a statistically significant relationship was reported between the length of the affected nerve roots and clinical findings[6]. RL of RNRs was also calculated in the present study, but its relationship with clinical findings could not be evaluated as our study was based solely on radiological findings.

There is also a study in the literature that assessed the relationship between spondylolisthesis and RNRs of the cauda equina[4]. In that study, Savarese *et al*[4] found that spondylolisthesis increases the risk of cauda equina and is an independent risk factor for RNRs of the cauda equina. Nevertheless, no significant relationship was determined between spondylolisthesis and RNRs of the cauda equina in the present study. Therefore, it might be useful to perform large series studies that explore the relationship between spondylolisthesis and RNRs.

Suzuki *et al*[10] found that patients with RNRs of the cauda equina are more likely to be older, have longer symptom duration, and have more intense neurological findings and symptoms compared to patients with spinal canal stenosis without RNRs. Similarly, Min *et al*[6] and Poureisa *et al*[11] reported that patients with RNRs of the cauda equina were significantly older. Min *et al*[6] found no difference between the patients with and without RNRs of the cauda equina in terms of the duration of symptoms. However, they noted that better postoperative results were achieved in the patient group without RNRs[6]. Similarly, the average age of patients with RNRs of the cauda equina was higher than the patients without RNRs, but the difference was not significant.

In patients with RNRs of the cauda equina, serpentine-shaped lesions and/or loop-shaped lesions that cause filling defects are observed on conventional myelography. In their studies, Ono *et al*[5] found that in 97.6% of loop-shaped lesions detected on conventional myelography, positive findings were found on MRI examination, while only 23.5% of the serpentine-shaped lesions turned out to have positive findings on MRI. Serpiginous filling defects on myelography have been defined in dural or intradural arteriovenous malformations (AVM), and they constitute one of the important differential diagnoses[2,14]. Although less frequently, plexiform neurofibroma or neurinoma can also lead to thickening and redundancy in nerve roots. Diseases such as arachnoiditis, chronic inflammatory demyelinating polyneuropathy, and some hereditary neuropathies can lead to hypertrophic neuropathy, but no relationship was reported between such entities and the serpiginous nerve roots of the cauda equina[2].

RNRs of the cauda equina should be considered first in the presence of enlarged, elongated, and tortuous or serpiginous nerve roots, which do not contain prominent pathological signals on MRI in the area adjacent to lumbar spinal canal stenosis in patients with spondyloarthrosis[2-6]. However, it is essential to distinguish between AVM and arteriovenous fistula (AVF) on MRI. In AVM or AVF, intradural serpiginous

veins and coronal venous plexus ectasia are generally observed on MRI. AVMs may appear with signs of subarachnoid hemorrhage or medullary ischemia on imaging[2,8,14]. On MRI of dural AVFs, abnormal signals are usually observed in the spinal cord on the T2W series. Another important MRI finding in most patients with AVF is excessive contrast-enhancement of coronal venous plexus on contrast-enhanced series[2,14].

RNRs of the cauda equina are typically associated with spinal canal stenosis, and clinically neurological claudication is observed in the patient[2]. However, the literature has controversial findings on the association of RNRs of the cauda equina with the clinic and its treatment[5,9,10,12]. Some authors noted that since the damage to affected nerve roots is irreversible, neurological healing cannot be achieved and decompressive surgery will not contribute to recovery[2,9,10]. It was reported that the decline of stenosis symptoms after surgical decompression was rare in patients with typical RNRs of the cauda equina and that complaints of dysesthesia and paresthesia often persisted[2,13]. However, a recent study reported that intermittent claudication disappeared in all patients after decompression surgery[12]. Ono *et al*[5] mentioned that the severity of the disease was greater in patients for whom RNRs of the cauda equine were diagnosed with MRI compared to those for whom the diagnosis was made clinically only and that this difference negatively affected surgical outcomes. Kawasaki *et al*[12], on the other hand, reported that in 84% of patients undergoing surgical decompression, MRI findings of RNRs of the cauda equina disappeared two weeks later.

The present study has some limitations. The first is that the radiological and clinical findings of the patients cannot be correlated due to the retrospective and radiological basis of the study. As the examination of the patient during MRI is performed in a neutral position, it was reported that spinal stenosis patients could get over the disease in cases of mild intensity[2,5]. The second limitation was that lumbar MRI examinations performed in the supine (neutral) position rather than standing or axial loading might have led to lower stenosis measurements than the actual degree of stenosis. A third limitation was that since the narrowest level of CSA of the dural sac level was considered the level that caused RNRs of the cauda equina in patients with multiple levels of spinal stenosis, the effects of the narrow segments at other levels had to be ignored.

CONCLUSION

In conclusion, the present study showed that RNRs of the cauda equina are not uncommon in patients with lumbar spinal canal stenosis. RNRs of the cauda equina are frequently observed in the superior of the stenosis level but can also be observed in both inferior and superior, and less frequently in inferior localizations only. Patients who undergo lumbar MRI and are found to have dural sac CSA of 55 mm^2 or lower should be carefully evaluated for RNRs of the cauda equina, and when present, the findings of the RNRs of the cauda equina should definitely be reported.

ARTICLE HIGHLIGHTS

Research background

Redundant nerve roots (RNRs) of the cauda equina are often defined as the development of elongated, enlarged, and tortuous nerve roots at the superior and/or inferior of the lumbar canal stenosis and as secondary to it due to degenerative processes. Clinically, they can lead to lower back and leg pain, paresthesia, and neurogenic claudication in patients.

Research motivation

The radiological diagnosis of RNRs of the cauda equina was previously made with conventional myelography, while magnetic resonance imaging (MRI) findings have been more commonly defined in recent years. Nevertheless, this condition has been relatively under-recognized in radiological practice. Therefore, there is a need to keep this issue on the agenda by discussing it in light of the literature.

Research objectives

In this study, lumbar MRI findings of RNRs of the cauda equina were evaluated in spinal stenosis patients. Cross-sectional area (CSA) of the dural sac at the stenosis level

that could lead to RNRs of the cauda equina and how the cauda equina nerve roots are affected by this stenosis (redundant segment length and extensions, *etc.*) were investigated.

Research methods

On lumbar MRI of patients with stenosis, dural sac CSA levels of less than 100 mm^2 at the intervertebral disc space were considered stenosis, and levels leading to lumbar stenosis were determined. Statistical differences between the CSA levels that led to RNRs of the cauda equina and those that did not lead to RNRs were investigated. Relative length (RL) was calculated by dividing the length of RNRs on sagittal T2-weighted images by the vertebrae corpus height adjacent to the stenotic segment superior. The relationships of herniation type into the dural sac (soft or sharp margins) and spondylolisthesis with CSA and RL were investigated.

Research results

RNRs of the cauda equina were observed in 42% of patients with spinal stenosis. Mean CSA was 40.99 ± 12.76 mm^2 in patients with RNRs of the cauda equina and 66.83 ± 19.32 mm^2 in patients without RNRs ($P < 0.001$). Using a cut-off value of 55.22 mm^2 for CSA leading to RNRs of the cauda equina, the sensitivity was 96.4%, specificity 96.1%, positive predictive value (PPV) 89.4%, and negative predictive value (NPV) 98.7%. RL varied from 0.93 to 6.01 (mean: 3.39 ± 1.31). Of all RNRs, 54.5% were at the superior of stenosis level, 32.8% at both superior and inferior of stenosis level, and 7% at inferior of stenosis. Soft margin disc type was observed in 29 and sharp margin type was found in 26 of the disc herniations at the stenosis levels that led to RNRs of the cauda equina. Disc herniation type and spondylolisthesis were not significantly associated with RL or CSA of the dural sac with stenotic levels ($P > 0.05$). As the CSA of the dural sac decreased, the frequency of RNRs at the superior of the stenosis level increased ($P < 0.001$).

Research conclusions

RNRs of the cauda equina are not uncommon in patients with lumbar spinal canal stenosis. Although RNRs of the cauda equina are frequently observed at the superior of stenosis level, a considerable percentage of them can also be found at both superior and inferior, and at a lower rate at the inferior localization. The possibility of RNRs of the cauda equina is high in patients with dural sac CSA of 55 mm^2 or less.

Research perspectives

Although clinical and treatment outcomes are controversial, lumbar stenosis patients with marked reductions in CSA of the dural sac on MRI should be carefully evaluated for RNRs of the cauda equina. In these patients, tortuosity, elongation, and extension findings indicating redundancy in nerve roots should be reported as this could contribute to efficient treatment of the patients.

ACKNOWLEDGEMENTS

We thank Demir O for his help with the statistical analyses.

REFERENCES

1 **Cressman MR**, Pawl RP. Serpentine myelographic defect caused by a redundant nerve root. Case report. *J Neurosurg* 1968; **28**: 391-393 [PMID: 5643934 DOI: 10.3171/jns.1968.28.4.0391]
2 **Nogueira-Barbosa MH**, Savarese LG, Herrero CFPS, Defino HLA. Redundant nerve roots of the cauda equina: review of the literature. *Radiol Bras* 2012; **45**: 155-159 [DOI: 10.1590/S0100-39842012000300007]
3 **Hakan T**, Celikoğlu E, Aydoseli A, Demir K. The redundant nerve root syndrome of the Cauda equina. *Turk Neurosurg* 2008; **18**: 204-206 [PMID: 18597240]
4 **Savarese LG**, Ferreira-Neto GD, Herrero CF, Defino HL, Nogueira-Barbosa MH. Cauda equina redundant nerve roots are associated to the degree of spinal stenosis and to spondylolisthesis. *Arq Neuropsiquiatr* 2014; **72**: 782-787 [PMID: 25337731 DOI: 10.1590/0004-282x20140135]
5 **Ono A**, Suetsuna F, Irie T, Yokoyama T, Numasawa T, Wada K, Toh S. Clinical significance of the redundant nerve roots of the cauda equina documented on magnetic resonance imaging. *J Neurosurg Spine* 2007; **7**: 27-32 [PMID: 17633484 DOI: 10.3171/SPI-07/07/027]
6 **Min JH**, Jang JS, Lee SH. Clinical significance of redundant nerve roots of the cauda equina in

lumbar spinal stenosis. *Clin Neurol Neurosurg* 2008; **110**: 14-18 [PMID: 17881117 DOI: 10.1016/j.clineuro.2007.08.005]

7 **Duncan AW**, Kido DK. Serpentine cauda equina nerve roots. *Radiology* 1981; **139**: 109-111 [PMID: 7208911 DOI: 10.1148/radiology.139.1.7208911]

8 **Hacker DA**, Latchaw RE, Yock DH Jr, Ghosharjura K, Gold LH. Redundant lumbar nerve root syndrome: myelographic features. *Radiology* 1982; **143**: 457-461 [PMID: 6280235 DOI: 10.1148/radiology.143.2.6280235]

9 **Suzuki K**, Takatsu T, Inoue H, Teramoto T, Ishida Y, Ohmori K. Redundant nerve roots of the cauda equina caused by lumbar spinal canal stenosis. *Spine (Phila Pa 1976)* 1992; **17**: 1337-1342 [PMID: 1334281 DOI: 10.1097/00007632-199211000-00013]

10 **Suzuki K**, Ishida Y, Ohmori K, Sakai H, Hashizume Y. Redundant nerve roots of the cauda equina: clinical aspects and consideration of pathogenesis. *Neurosurgery* 1989; **24**: 521-528 [PMID: 2540446 DOI: 10.1227/00006123-198904000-00006]

11 **Poureisa M**, Daghighi MH, Eftekhari P, Bookani KR, Fouladi DF. Redundant nerve roots of the cauda equina in lumbar spinal canal stenosis, an MR study on 500 cases. *Eur Spine J* 2015; **24**: 2315-2320 [PMID: 26071946 DOI: 10.1007/s00586-015-4059-y]

12 **Kawasaki Y**, Seichi A, Zhang L, Tani S, Kimura A. Dynamic Changes of Cauda Equina Motion Before and After Decompressive Laminectomy for Lumbar Spinal Stenosis With Redundant Nerve Roots: Cauda Equina Activation Sign. *Global Spine J* 2019; **9**: 619-623 [PMID: 31448195 DOI: 10.1177/2192568218821344]

13 **Tsuji H**, Tamaki T, Itoh T, Yamada H, Motoe T, Tatezaki S, Noguchi T, Takano H. Redundant nerve roots in patients with degenerative lumbar spinal stenosis. *Spine (Phila Pa 1976)* 1985; **10**: 72-82 [PMID: 3983705 DOI: 10.1097/00007632-198501000-00012]

14 **Gilbertson JR**, Miller GM, Goldman MS, Marsh WR. Spinal dural arteriovenous fistulas: MR and myelographic findings. *AJNR Am J Neuroradiol* 1995; **16**: 2049-2057 [PMID: 8585493]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 February 28; 13(2): 40-52

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 2 February 28, 2021

ORIGINAL ARTICLE

Observational Study

World Journal of Radiology

Monthly Volume 13 Number 2 February 28, 2021

Contents

ABOUT COVER

Miguel A De Gregorio, BM BCh, MD, PhD, Chief Doctor, Professor, Research Scientist, Department of Radiology Medicine Faculty, University of Zaragoza, Zaragoza 50009, Spain. mgregori@unizar.es

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yun-Xiaojian Wu*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
February 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 February 28; 13(2): 40-52

DOI: 10.4329/wjr.v13.i2.40

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Observational Study

Cone beam computed tomographic evaluation of pharyngeal airway in North Indian children with different skeletal patterns

Anuraj Singh Kochhar, Maninder Singh Sidhu, Ritasha Bhasin, Gulsheen Kaur Kochhar, Himanshu Dadlani, Jagpreet Sandhu, Bobby Virk

ORCID number: Anuraj Singh Kochhar 0000-0001-6611-6143; Maninder Singh Sidhu 0000-0002-2481-7109; Ritasha Bhasin 0000-0002-6198-7756; Gulsheen Kaur Kochhar 0000-0001-5881-3512; Himanshu Dadlani 0000-0002-7354-1962; Jagpreet Sandhu 0000-0001-5449-0306; Bobby Virk 0000-0002-4063-7108.

Author contributions: Kochhar AS contributed conceptualization, data curation, and formal analysis; Sidhu MS contributed investigation and methodology; Bhasin R contributed software, supervision, and validation; Kochhar GK contributed visualization, and wrote review and edited; Dadlani H contributed data curation, and wrote original draft preparation; Sandhu J contributed Project administration and resources; Virk B contributed methodology and validation; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved for by our Institutional Review Board (Approval No. SGTDC/PPL/Com./E.C). Dated 14/08/2010.

Informed consent statement: All

Anuraj Singh Kochhar, Former Orthodontist, Max Hospital, Gurgaon 122001, India

Maninder Singh Sidhu, Department of Orthodontics, Faculty of Dental Sciences, SGT University, Gurugram 122001, India

Ritasha Bhasin, Faculty of Dentistry, University of Toronto, Toronto M5G 1G6, Canada

Gulsheen Kaur Kochhar, Department of Pediatric and Preventive Dentistry, National Dental College and Hospital, Derabassi 140507, Punjab, India

Himanshu Dadlani, Department of Periodontology, Kalka Dental College, Uttar Pradesh 210507, India

Himanshu Dadlani, Senior Consultant, Department of Dental Surgery, Max Hospital, Gurgaon 122001, India

Jagpreet Sandhu, Formerly at Department of Orthodontics, Genesis Institute of Dental Sciences, Punjab 152001, India

Bobby Virk, Chief Orthodontist, Smile With Braces, Puyallup, WA 98371, United States

Corresponding author: Himanshu Dadlani, MDS, Professor, Department of Periodontology, Kalka Dental College, Meerut, Uttar Pradesh 210507, India. himdent@hotmail.com

Abstract

BACKGROUND

In growing patients with skeletal discrepancies, early assessment of functional factors can be vital for the restoration of normal craniofacial growth.

AIM

To compare airway volumes in patients with mandibular retrognathism with the normal anteroposterior skeletal relationship, thereby assessing the association between cephalometric variables and airway morphology.

METHODS

Cone-beam computed tomography volume scans, and lateral cephalograms, 3-dimensional airway volume and cross-sectional areas of 120 healthy children (54 boys and 66 girls mean age 15.19 ± 1.28) which were done for orthodontic

assessment were evaluated. The subjects were divided into 2 groups based on the angle formed between point A, Nasion and point B (ANB) values and cephalometric variables (such as anterior and posterior facial height, gonial angle *etc*.) airway volumes, and cross-sectional measurements were compared using independent *t* tests. Pearson's correlation coefficient test was used to detect any relationship of different parts of the airway and between airway volume and 2-dimensional cephalometric variables.

RESULTS

Means and standard deviations for cephalometric, cross-sectional, and volumetric variables were compared. ANB, mandibular body length and facial convexity were statistically highly significant ($P < 0.01$) whereas condylion to point A, nasal airway and total airway volume ($P < 0.05$) were statistically significant. The nasal airway volume and the superior pharyngeal airway volume had a positive correlation ($P < 0.01$), nasal airway was correlated to middle ($P < 0.05$) and total airway superior had a relation with middle ($P < 0.05$), inferior and total airway ($P < 0.05$), middle was related to all other airways; inferior was also related to all the airways except nasal. Lateral cephalometric values were positively correlated with the airway volume with Frankfurt Mandibular Plane Angle and facial convexity showed significant correlations with total airway volume ($P < 0.05$). Additionally, ANB angle was significantly correlated with total airway volume and superior airway ($P < 0.05$).

CONCLUSION

The mean total airway volume in patients with retrognathic mandible was significantly smaller than that of patients with a normal mandible.

Key Words: Pharyngeal airway; Cone beam computed tomography; Skeletal pattern; Malocclusion; Retrognathic; Airway volume

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: With the advent of cone beam computed tomography, analysis of airway has become possible. Patients who present with retrognathic jaw or anterior-posterior skeletal discrepancy have been contemplated to have reduced pharyngeal airway. When comparing the airway volumes of 120 healthy individuals with mandibular retrognathism and normal anteroposterior skeletal relationship, the mean total airway volume of patients with the angle formed between point A, Nasion and point B (ANB) more than 4 was significantly smaller than that of patients with ANB less than 4. The sub-volumes in the pharyngeal airway showed a positive correlation with each other. Frankfurt Mandibular Plane Angle and facial convexity and mandibular body length also had a significant interrelationship with total volume of airway.

Citation: Kochhar AS, Sidhu MS, Bhasin R, Kochhar GK, Dadlani H, Sandhu J, Virk B. Cone beam computed tomographic evaluation of pharyngeal airway in North Indian children with different skeletal patterns. *World J Radiol* 2021; 13(2): 40-52
URL: https://www.wjgnet.com/1949-8470/full/v13/i2/40.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i2.40

INTRODUCTION

Respiratory function plays a substantial role in orthodontic diagnosis and treatment planning. An association between the respiratory mode and facial morphology has been observed in various studies utilizing cephalograms[1]. Furthermore, a link between Class II Division 1 malocclusion and upper pharyngeal airway obstruction as well as mouth breathing, was demonstrated by Angle[2] in 1907. Various authors have presented characteristics related to obstructed breathing[1]. Primary clinical features of respiratory obstruction syndrome have been identified by Ricketts[3] as tonsil and adenoid enlargement, narrow nostrils, open bite, cross bite, and tongue thrusting.

study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: No additional data are available. The original anonymous dataset is available on request from the corresponding author.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: India

Peer-review report's scientific quality classification

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

Received: November 24, 2020
Peer-review started: November 24, 2020
First decision: December 21, 2020
Revised: December 27, 2020
Accepted: January 28, 2021
Article in press: January 28, 2021

Published online: February 28, 2021

P-Reviewer: Mani V, Xie Q
S-Editor: Gao CC
L-Editor: A
P-Editor: Wang LYT

The role of the upper anatomy in the craniofacial complex development is usually considered substantial[4]. Impaired breathing can be a result of narrow pharyngeal airway, which can further lead to diminished levels of growth hormone in growing children or obstructive sleep apnea in mature individuals. Diminished airway associated with obstructive sleep apnea tends to be typical in patients with Angle class II malocclusion, displaying retrognathic mandible and sagittal discrepancy[5,6].

Early diagnosis and evaluation of the functional factors in growing children with skeletal discrepancy and features of adenoid hypertrophy (adenoid faces) might be pivotal to restore proper craniofacial growth and treatment outcome stability. Pharyngeal airway measurements have usually been conducted by landmark identification followed by measurements of different lengths and areas in the pharyngeal region[7-9].

Although there is an avalanche of studies regarding airway morphology and its effects on craniofacial growth, most studies have used 2-dimensional (2D) techniques, frontal or lateral cephalograms, with inadequate assessment of length and areas. A technique for 3-dimensional (3D) visualization, utilized frequently is computed tomography[10]. However, a huge impediment to its use is the large radiation dose[11]. The radiation dose can be minimized to one-fifth, while not compromising on quality, with modern cone beam computed tomography (CBCT), due to which it is becoming increasingly popular[12].

Volumetric measurements of the pharyngeal airway space (PAS) and, narrowing or obstruction can be localized utilizing CBCT[13]. As narrowing or obstruction of the pharyngeal airway can be present in patients with altered maxillo-mandibular relationship and can be associated with sleep, as well as Obstructive Sleep Apnoea Syndrome, this analysis can be beneficial in the orthodontic diagnosis and planning orthognathic surgery[14]. Therefore, the aim of the present study was to compare the pharyngeal airway volumes in children with varying anteroposterior maxillo-mandibular relationships (ANB angles that is the angle formed between point A, Nasion and Point B) and study the possible correlations between different cephalometric variables and the airway morphology in these children.

MATERIALS AND METHODS

Following the ethical clearance from the institutional review board, records of 150 children who visited the outpatient Department of Orthodontics were examined. Of this, CBCT scans of 120 healthy North Indian children (54 boys and 66 girls mean age 15.19 ± 1.28) were selected, after the following exclusion criteria was applied: History of any upper respiratory infection, pharyngeal pathology (like adenoid hypertrophy and tonsillitis) or a history of adenoid or tonsil removal (Table 1).

CBCT volume scans of all subjects were obtained by using the I-Cat CBCT unit (Imaging Sciences Hatfield, PA, United States), and the imaging protocol used a 17 cm × 21 cm field of view to include the entire craniofacial anatomy. The images were standardized with the subject seated in a chair, machine settings of 120 kV-5 mA-0.25 mm voxel, and scan time of 20 s. Patients, following the standard protocol of acquiring the scans in a natural head position, and their jaws in maximum intercuspation with the lips and tongue in resting position were used. For volume evaluation/measurement and cephalometric analysis, the axial images were transferred to InVivo Dental software (Anatomage, San Jose, CA, United States) The 3D images were reoriented using the Frankfort horizontal (FH) plane as the reference plane for uniformity and to reduce errors. A line joining the right and left portions, located in the most latero-superior point of the external auditory meatus, to the right orbitale was constructed as the FH plane (Figure 1).

2D cephalometric images were derived from the CBCT scans by using SUPER CEPH feature of the software In Vivo Dental, and the images were imported into Nemoceph® (Dental Studio NX 2006 version 6.0) (Figure 2). Landmark identifications and physical measurements were performed by the same investigator. Using the software Downs, Steiner, Jarabak, Mc Namara and Tweed Merrifield analysis were done in order to classify patients (Tables 1 and 2).

Cross-sectional views of the pharyngeal airway in the 5 planes: a, represents the length (axial slice) or height (frontal slice) of the airway defined by the greatest distance in the anteroposterior or vertical direction of the airway cross-section; b is the width of the airway defined by the greatest distance in the right and left directions of the airway cross-section and 5 volumes A, right lateral view and B, frontal view of volume rendered images. a, Anterior nasal plane; b, posterior nasal plane; c, upper

Table 1 Sample characteristics

	Group IANB < 4		Group II ANB > 4		Total
	Male	Female	Male	Female	
Subjects (*n*)	26	30	28	36	120
Age (yr)	13-17	13-17	13-17	13-17	15.19 ± 1.28

ANB: The angle formed between point A, Nasion and point B.

Table 2 Two-dimensional cephalometric variables, cross-sectional planes and volumes of the 3-dimensional pharyngeal airway

Two-dimensional cephalometric variables	
(1) Gonial angle: Angle formed between line drawn tangent to the lower border of the mandible and another line tangent to the distal border of the ascending ramus and the condyle on both sides; (2) Anterior facial height (AFH): Distance between the Nasion and Menton (Me); (3) Posterior facial height (PFH): Distance between Sella (S) to Gonion(Go); (4) PFH/AFH: Ratio of AFH and the PFH; (5) FMA: Frankfurt Mandibular Plane Angle formed by the intersection of the Frankfort horizontal plane and the mandibular plane; (6) ANB: The angle formed between point A, Nasion and Point B; (7) Facial convexity: Formed by the intersection of line from Nasion to point A, to point A to pogonion(Po); (8) Condylion to point A (Co-PtA); (9) Condylion to gnathion (Co-Gn); and (10) Mandibular body length (Mand-BL): Distance from gonion to pogonion	
Cross-sectional planes and volumes of the 3D pharyngeal airway	
Anterior nasal plane (Ana plane)	Plane passing through anterior nasal spine (ANS) and perpendicular to FH
Posterior nasal plane (Pna plane)	Plane passing through posterior nasal spine (PNS)and perpendicular to FH
Upper pharyngeal plane (Uph plane)	Plane passing through PNS parallel to FH
Middle pharyngeal plane (Mph plane)	Plane passing through lower margin of the soft palate and parallel to FH
Lower pharyngeal plane (Lph plane)	Plane passing through superior margin of the epiglottis and parallel to FH
Volume	
Nasal airway	Airway formed by the planes between Ana and Pna
Superior pharyngeal airway	Airway formed by the planes between Pna and Uph
Middle pharyngeal airway	Airway formed by the planes between Uph and Mph
Inferior pharyngeal airway	Airway formed by the planes between Mph and Lph planes
Total airway	Airway extending between Ana plane to Lph plane

FH: Frankfurt horizontal; 3D: Three-dimensional.

pharyngeal plane; d, middle pharyngeal plane; and e, lower pharyngeal plane (Table 3 and Figures 3 and 4). Cross-sectional planes of the nasal cavity were perpendicular to the FH plane, whereas the pharyngeal cross-sections are parallel to the FH plane. Although these cross-sections are not directly perpendicular to the long axis of the airway, the FH plane was used as a reference plane to standardize the plane orientation and minimize error in identifying the studied cross-sectional planes. Cross-sectional measurements, that is width and length, were computed in frontal and axial views to provide linear accuracy.

Volumetric renderings of the subjects' CBCT scans were acquired with the In Vivo Dental software, and we proceeded with volumetric analysis of the defined airways. 3D image inversion to convert negative image to a positive value was done, which is required as the airway is a void space. This process removes the hard and soft tissues of the image around the airway and embodies the airway spaces of the craniofacial region including the paranasal sinuses and other empty spaces. Furthermore, to isolate the required airway section and remove structures that were not necessary, sculpting was performed which was an inherent feature of the software. Threshold values were thereafter altered to remove the artifacts and enhance the selected region of airway. Lastly, designated airway volume was computed in cubic millimeters.

Statistical analysis

Descriptive statistics including the mean and standard deviation for each group were calculated by using SPSS for Windows software (version 20). Differences between

Table 3 Correlations of sections of the airway with each other

	Nasal airway	Superior airway	Middle airway	Inferior airway	Totalairway
Nasal airway					
Pearson correlation	1	0.085	0.471[a]	0.386	0.879[b]
Sig.(2-tailed)		0.722	0.036	0.093	0
n	120	120	120	120	120
Superior airway					
Pearson correlation	0.85	1	0.494[a]	0.651[b]	0.4623[a]
Sig.(2-tailed)	0.722	-	0.027	0.002	0.04
n	120	120	120	120	120
Middle airway					
Pearson correlation	0.471[a]	0.494[a]	1	0.763[b]	0.779[b]
Sig.(2-tailed)	0.036	0.027	-	0	0
n	120	120	120	120	120
Inferior airway					
Pearson correlation	0.386	0.651[b]	0.763[b]	1	0.744[b]
Sig.(2-tailed)	0.093	0.002	0	-	0
n	120	120	120	120	120
Totalairway					
Pearson correlation	0.879[b]	0.4623[a]	0.779[b]	0.744[b]	1
Sig.(2-tailed)	0	0.04	0	0	-
n	120	120	120	120	120

[a]Correlation is significant at 0.05 level.
[b]Correlation is significant at 0.01 level.

groups were tested by using independent *t* tests. Pearson's correlation coefficient test was used to detect any relationship of different parts of the airway and between airway volume and 2D cephalometric variables.

RESULTS

Means and standard deviations for cephalometric, cross-sectional, and volumetric variables were compared. Table 4 gives the comparison results of groups I and II. ANB, mandibular body length, facial convexity were statistically highly significant ($P < 0.01$) whereas condylion to point A, nasal airway and total airway volume ($P < 0.05$) were statistically significant. Cross-sectional and volumetric measurements at different levels when compared were statistically insignificant. However, total airway volume was significantly greater in group I ($P < 0.05$).

Table 3 show the correlations among the studied variables. The nasal airway volume and the superior pharyngeal airway volume had a positive correlation ($P < 0.01$), nasal airway was correlated to middle ($P < 0.05$) and total airway superior had a relation with middle ($P < 0.05$), inferior and total airway ($P < 0.05$), middle was related to all other airways, inferior was also related to all the airways except nasal (Table 5). Lateral cephalometric values were positively correlated with the airway volume with Frankfurt Mandibular Plane Angle (FMA) and facial convexity showed significant correlations with total airway volume ($P < 0.05$). Additionally, ANB angle was significantly correlated with total airway volume and superior airway ($P < 0.05$).

Table 4 Descriptive statistics of groups I and II

Group	Group I ANB < 4		Group II ANB > 4		*P* value
	mean	SD	mean	SD	
Ana height	29.63	4.69	30.06	6.73	0.871
Ana width	13.81	1.98	15.24	3.61	0.273
Ana C. area	194.41	13.93	218.14	52.41	0.22
Pna height	29.95	7.85	28.73	8.70	0.744
Pna width	23.88	3.06	24.14	4.84	0.884
Pna C. area	257.85	74.25	284.32	78.01	0.448
Uph length	19.28	6.61	17.54	4.19	0.503
Uph width	26.01	4.81	24.14	7.87	0.522
Uph C. area	293.37	71.56	314.97	99.76	0.58
Mph length	11.67	3.47	11.54	3.60	0.935
Mph width	22.66	5.87	20.16	8.26	0.439
Mph C. area	226.32	85.90	213.25	102.48	0.76
Lph length	14.77	7.93	11.88	3.07	0.286
Lph width	24.44	5.19	28.90	6.76	0.111
Lph C. area	231.31	83.23	199.84	78.36	0.399
Gonial angle	126.37	7.79	125.24	7.55	0.748
AFH	108.38	6.08	112.12	4.86	0.152
PFH	73.06	5.42	71.81	7.58	0.672
PFH/AFH, %	67.47	4.49	64.02	5.83	0.152
FMA	25.06	3.61	27.48	6.02	0.281
ANB	2.85	1.56	6.14	1.02	< 0.001[b]
MAND-BL	66.94	3.74	61.61	4.27	0.008[b]
Facial convexity	5.17	3.57	10.76	4.56	0.007[b]
Co-pt A	82.10	6.09	82.68	3.44	0.802
Co-pt GN	109.83	5.54	103.72	6.42	0.035[a]
Nasal airway	36407.36	2526.59	30446.00	7060.88	0.037[a]
Superior airway	5563.27	1350.80	4559.67	1263.62	0.106
Middle airway	5322.45	2124.81	4213.89	1291.90	0.188
Inferior airway	5487.82	2018.25	5077.67	1521.36	0.621
Total airway	52780.91	6435.84	44297.22	8662.49	0.022[a]

[a]Correlation is significant at 0.05 level.
[b]Correlation is significant at 0.01 level.
ANB: The angle formed between point A, Nasion and point B; Ana: Anterior nasal; Pna: Posterior nasal; Uph: Upper pharyngeal; Mph: Middle pharyngeal; Lph: Lower pharyngeal; AFH: Anterior facial height; PFH: Posterior facial height; FMA: Frankfurt Mandibular Plane Angle; Mand-BL: Mandibular body length; Co-PtA: Condylion to point; GN: Gnathion; SD: Standard deviation.

DISCUSSION

In the last few decades' airway assessment has been done using nasal resistance and airflow tests, nasoendoscopy and lateral cephalograms[15]. In the current study, CBCT produced anatomically precise images, sans magnification or distortion were reconstructed 3 dimensionally to completely understand the pharyngeal airway anatomy of growing children in all dimensions (sagittal, transverse and frontal)[11,14]. Generally, a requisite for 3D imaging such as conventional CT or magnetic resonance

Table 5 Correlations between the 2-dimensional cephalometric variables and the 3-dimensional volumetric measurements of the airway

	Nasal airway	Superior airway	Middle airway	Inferior airway	Total airway
Gonial angle					
Pearson correlation	-0.021	0.135	0.098	-0.019	0.024
Sig.(2-tailed)	0.928	0.571	0.681	0.937	0.918
n	120	120	120	120	120
AFH					
Pearson correlation	0.055	0.201	0.057	0.342	0.154
Sig.(2-tailed)	0.818	0.395	0.811	0.14	0.517
n	120	120	120	120	120
PFH					
Pearson correlation	0.159	0.172	0.124	0.319	0.23
Sig.(2-tailed)	0.503	0.47	0.602	0.171	0.329
n	120	120	120	120	120
PFH/AFH, %					
Pearson correlation	0.133	0.057	0.086	0.113	0.142
Sig.(2-tailed)	0.576	0.813	0.717	0.636	0.55
n	120	120	120	120	120
FMA					
Pearson correlation	-0.372	-0.314	-0.377	-0.411	-0.473[a]
Sig.(2-tailed)	0.106	0.178	0.102	0.072	0.035
n	120	120	120	120	120
ANB					
Pearson correlation	-0.364	-0.408	-0.197	-0.152	-0.389
Sig.(2-tailed)	0.115	0.034[a]	0.405	0.522	0.22[a]
n	120	120	120	120	120
Mand-BL					
Pearson correlation	0.136	0.523[a]	0.038	0.184	0.225
Sig.(2-tailed)	0.567	0.018	0.874	0.436	0.341
n	120	120	120	120	120
Facial convexity					
Pearson correlation	-0.362	-0.306	-0.221	-0.22	-0.391
Sig.(2-tailed)	0.116	0.189	0.349	0.351	0.088
n	120	120	120	120	120
Co-pt A					
Pearson correlation	0.127	0.324	0.289	0.469[a]	0.3
Sig.(2-tailed)	0.594	0.163	0.217	0.037	0.199
n	120	120	120	120	120
Co-pt GN					
Pearson correlation	0.301	0.296	0.012	0.225	0.303
Sig.(2-tailed)	0.197	0.204	0.959	0.34	0.194
n	120	120	120	120	120

[a]Correlation is significant at 0.05 level. AFH: Anterior facial height.
PFH: Posterior facial height; FMA: Frankfurt Mandibular Plane Angle; Co-PtA: Condylion to point; GN: Gnathion; ANB: The angle formed between point A, Nasion and point B; Mand-BL: Mandibular body length.

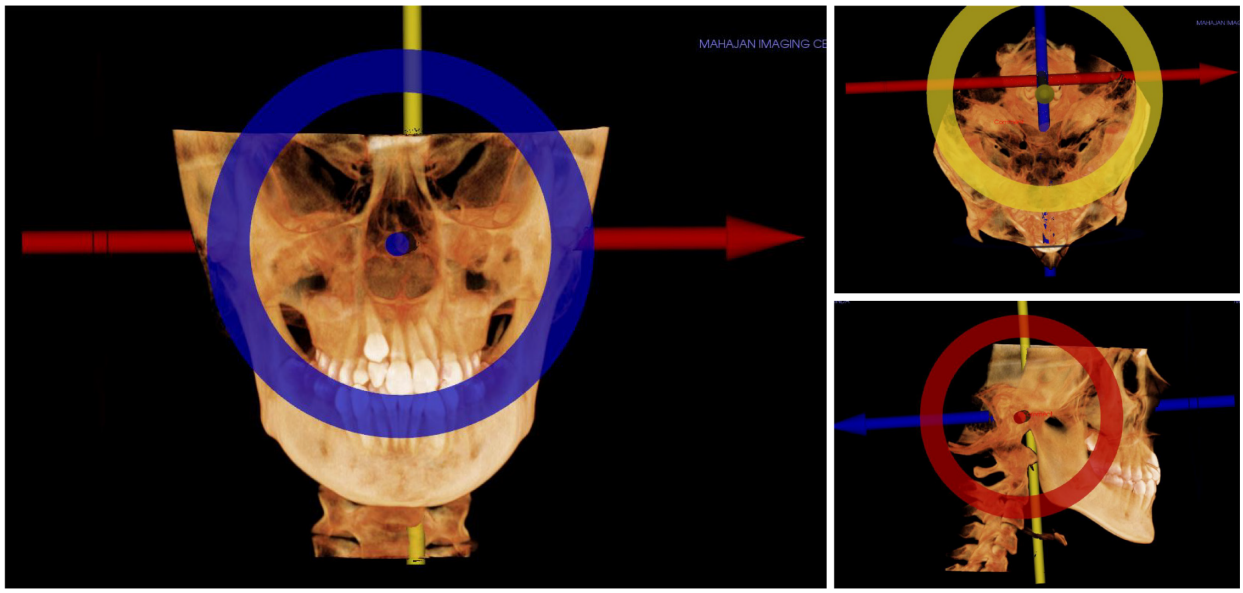


Figure 1 Standardisation of the images.

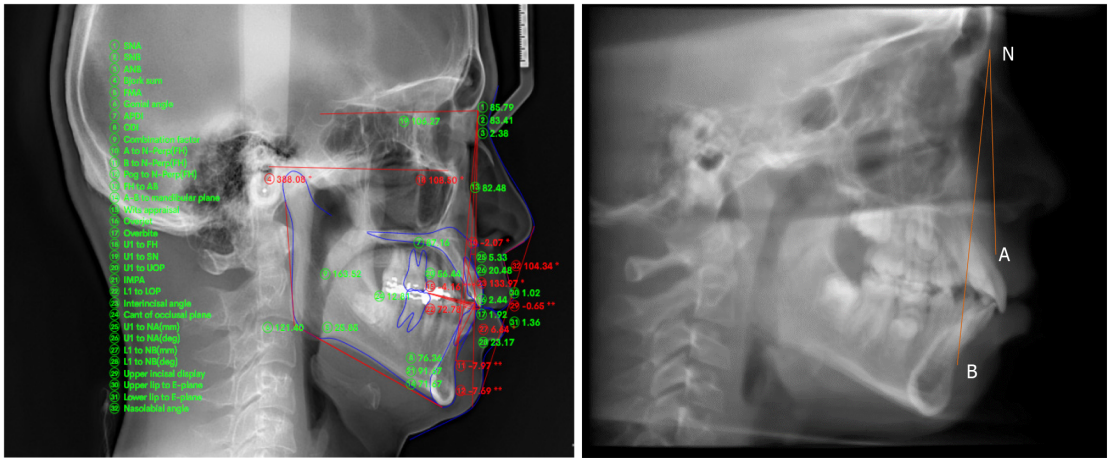


Figure 2 Cone beam computed tomography derived cephalogram and analysis.

imaging is for the patients to be supine. However, due to the effect of gravity on the soft tissues enveloping the oropharyngeal cavity, there are substantial anatomical changes in the airway[16].

Hsu *et al*[17] further found that the minimum of PAS and linear distance along perpendicular changes from the most upper anterior point of the hyoid bone to mandibular plane, as the position of body is changed from upright to supine[17]. Nevertheless, in recent times, advancements in CBCT have permitted axial CT images to be acquired in upright sitting posture, which is more valid for our study.

Owing to this study's retrospective design, direct examination of the nasopharyngeal functions of the patients was not possible and previous clinical charts and diagnoses for orthodontic treatment were used to select subjects. Nonetheless, a study by Laine-Alava *et al*[18] stated that there is no effect of a history or symptoms of upper respiratory disease on variables related to naso-respiratory function when the

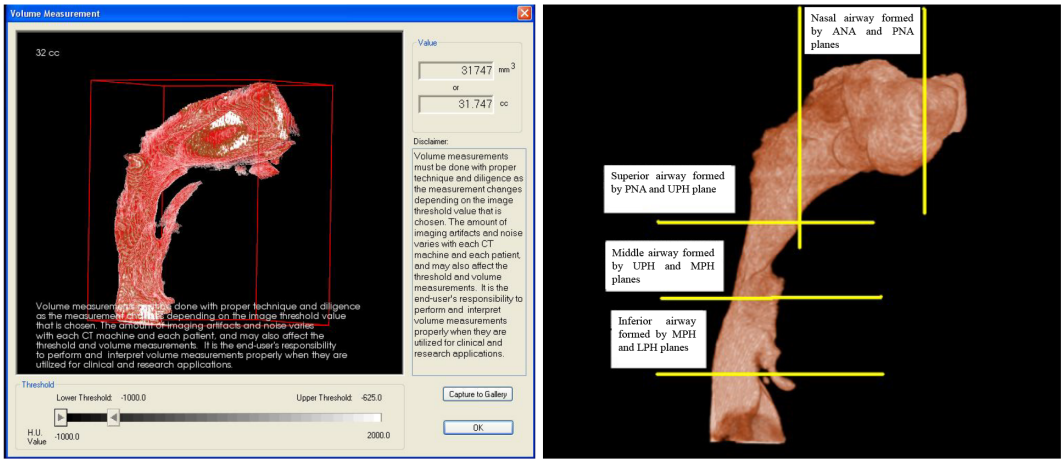


Figure 3 Airway isolated with the software and various referencing plane. ANA: Anterior nasal; PNA: Posterior nasal; UPH: Upper pharyngeal; MPH: Middle pharyngeal; LPH: Lower pharyngeal.

measurements are made during an asymptomatic period, which justifies the retrospective format of our study[18].

2D lateral cephalometric images were created from the CBCT scans to allocate the subjects to the 2 groups, and to assess correlations among the cephalometric parameters and the pharyngeal airway volumes. Linear accuracy of the CBCT-derived lateral cephalometric images has been studied in the past[19,20]. The classification of the subjects based on their anteroposterior skeletal relationships, was done utilizing north Indian standards for the ANB angle[21].Additionally, previously it has been demonstrated that the prepubertal ANB angle and the angle of convexity measured have high prediction accuracy for postpubertal anteroposterior jaw relationships[19,22]. In the current study, the anteroposterior analyses displayed statistically significant differences further confirming that the ANB angle, which was used to classify our subjects, was a reliable parameter[22].

Previous studies have presented excellent intra-rater reliability values of InVivo 5 software, hence in the present study the InVivo 5 software was used to analyse the pharyngeal volume[14,23]. In the current study, no sexual dimorphism in any cross-sectional and volumetric measurements was observed between the two sexes. These findings were in agreement with the study by Ceylan *et al*[24] and de Freitas *et al*[25]. Similarly, in a study by Xu *et al*[26] in 2019, no significant difference was observed in patient sexas well as age.

In groups I and II ANB, mandibular body length and facial convexity were statistically highly significant ($P < 0.01$) whereas condylion to point A, nasal airway and total airway volume ($P < 0.05$) were statistically significant. Although group I demonstrated greater cross-sectional areas and volumetric measurements of the sub-regions of the pharyngeal airway, this was statistically insignificant signifying lack of correlation between segmental airway capacities and mandibular deficiencies. This was in accordance with Di Carlo *et al*[27] who did not find a direct correlation between individual skeletal patterns, and overall upper airway anatomy. Moreover, former 2D studies also asserted a lack of relationship between airway dimensions and malocclusion class[24,25]. Ceylan *et al*[24] stated that despite skeletal anteroposterior relationship changes, the airway dimensions remain constant, owing to postural changes in the pharyngeal structures. However, certain authors emphasized that upper airway dimensions vary according to different skeletal classes, developmental ages, and gender[1].

Nasal airway was positively correlated with middle and total airways. This may be justified by the location of the 2 sections, that are just superior to hard palate and not anatomically adjacent, yet there is direct correlation of their volumetric dimensions. The sections superior airway with middle, inferior and total airway and inferior airway with superior, middle and total airway display significant correlations. According to Ricketts[3] and Dunn *et al*[28], a restricted nasopharyngeal airway width is associated with mouth breathing, because it is readily obstructed by adenoid enlargement. Total airway was positively correlated with all superior, middle and inferior airways in our study.

The negative correlation of the ANB angle and the total airway can be explained by

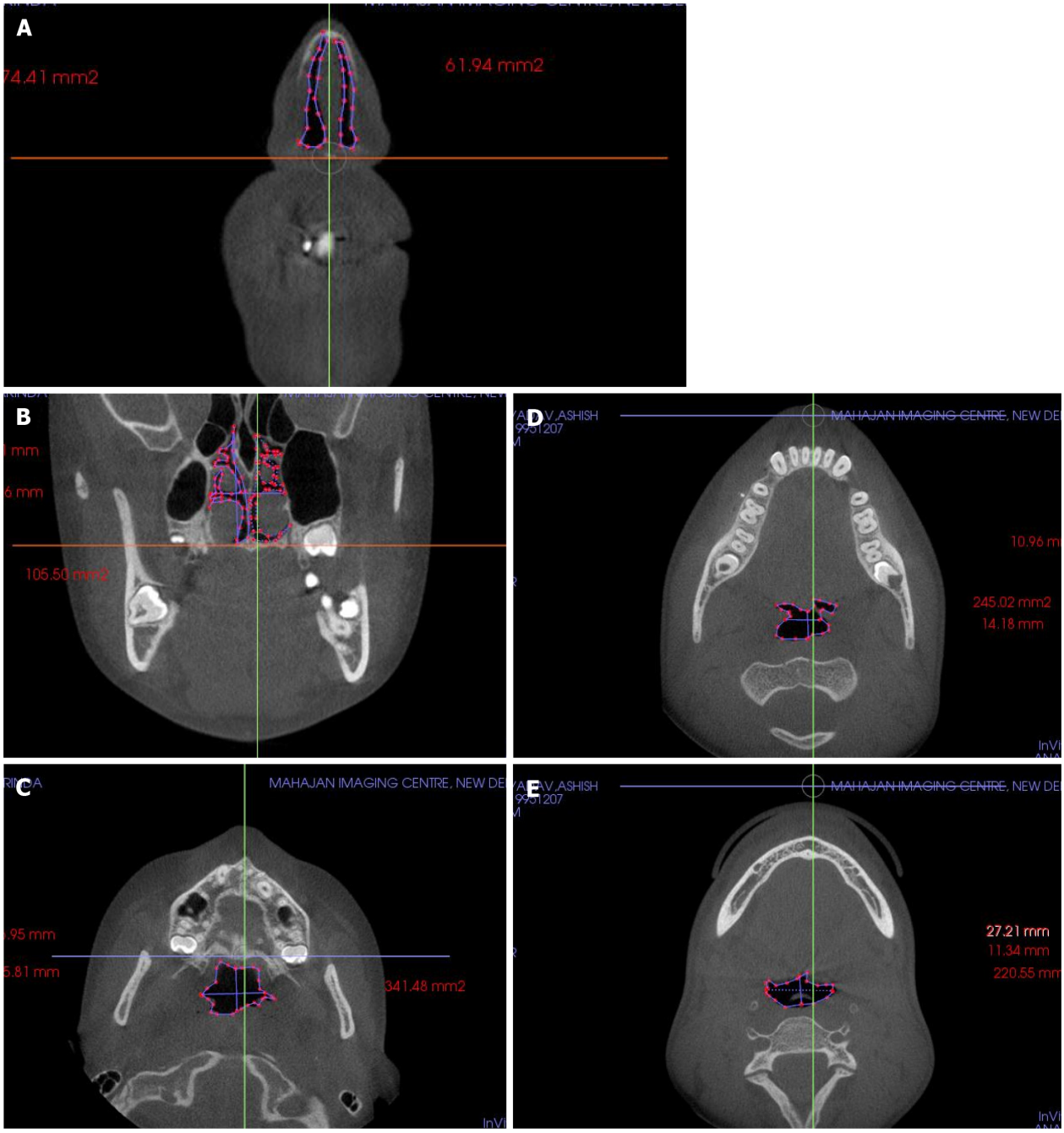


Figure 4 Horizontal section showing airway. A: Nasal; B: Superior; C: Middle; D and E: Inferior airway.

group I (ANB less than 4) having significantly greater airway volume than group II (ANB more than 4). Mandibular body length and total airway volume were both significantly greater in group I, demonstrating a positive correlation. Total airway volume had significant association with ANB angle and mandibular body length (anterior-posterior discriminants) supporting the intergroup comparison of different anterior-posterior skeletal patterns in the study. Similar results were observed by Lopatienė *et al*[29], where statistically significantly narrower airways were found in patients with ANB more than 4.

Alhammadi *et al*[30] and Xu *et al*[26] also concluded that patients with skeletal Class II presented with reduced glossopharyngeal airway volume, larger total minimum constricted area in average faces and more nasal minimum constricted area in long faces. Hwang *et al*[31] reported that a constricted nasopharyngeal airway is associated with retruded mandible and maxilla.

A significant correlation exists between the skeletal facial pattern and upper airway dimensions according to a study done by Shokri *et al*[32], who concluded that the total

airway volume and the mean airway area of class III patients were larger than those in class II patients.

Limitation

In the present study we did not evaluate class III malocclusion patients, also all the patients were scanned in a sitting upright position so conclusion about obstructive sleep apnea cannot be derived. But there is strong evidence from the large sample size that mandible backward position is correlated with reduced airway.

CONCLUSION

The mean total airway volume of patients with ANB more than 4 was significantly smaller than that of patients with ANB less than 4. The sub volumes in the pharyngeal airway showed a positive correlation with each other. FMA and facial convexity and mandibular body length also had a significant interrelationship with total volume of airway.

ARTICLE HIGHLIGHTS

Research background

Diminished airway associated with obstructive sleep apnea tends to be typical in patients with Angle class II malocclusion, displaying retrognathic mandible and sagittal discrepancy. Early diagnosis and evaluation of the functional factors in growing children with skeletal discrepancy and features of adenoid hypertrophy (adenoid faces) might be pivotal to restore proper craniofacial growth and treatment outcome stability.

Research motivation

A lot of data has been published related to the identification of airway in the general population, even comparing different cone beam computed tomography machines for the same. However, there is a paucity of data on tomographic evaluation of airways in different skeletal patterns, which is often challenging due to their morphology and plays a vital role in their treatment planning.

Research objectives

Comparing the airway volumes in patients with mandibular retrognathism and those with the normal anteroposterior skeletal relationship.

Research methods

Cone-beam computed tomography volume scans, and lateral cephalograms, 3-dimensional airway volume and cross-sectional areas of 120 healthy children which were done for orthodontic assessment was evaluated. The subjects were divided into 2 groups based on the angle formed between point A, Nasion and Point B (ANB) values and cephalometric variables (such as anterior and posterior facial height, gonial angle *etc*.) airway volumes, and cross-sectional measurements were compared using independent *t* tests. Pearson's correlation coefficient test was used to detect any relationship of different parts of the airway and between airway volume and 2-dimensional cephalometric variables.

Research results

Means and standard deviations for cephalometric, cross-sectional, and volumetric variables were compared. ANB, mandibular body length, facial convexity was statistically highly significant whereas condylion to point A, nasal airway and total airway volume were statistically significant. The nasal airway volume and the superior pharyngeal airway volume had a positive correlation, nasal airway was correlated to middle and total airway superior had a relation with middle, inferior and total airway, middle was related to all other airways, inferior was also related to all the airways except nasal. Lateral cephalometric values were positively correlated with the airway volume with Frankfurt Mandibular Plane Angle and facial convexity showed significant correlations with total airway volume. Additionally, ANB angle was significantly correlated with total airway volume and superior airway.

Research conclusions

Position of the mandible has positive correlation with the airway volume. Retrognathic mandible showed decreased overall airway in patients. Facial convexity and length of the mandible also influence the airway.

Research perspectives

The current study gives direction for future research on a larger cohort related to mandibular position and airway, linking the two for timely maxillo-facial orthopedic treatment interventions.

REFERENCES

1 **Gholinia F**, Habibi L, Amrollahi Boyouki M. Cephalometric Evaluation of the Upper Airway in Different Skeletal Classifications of Jaws. *J Craniofac Surg* 2019; **30**: e469-e474 [PMID: 31299819 DOI: 10.1097/SCS.0000000000005637]

2 **Angle E**. Treatment of malocclusion of the teeth. Philadelphia: SS White Manufacturing Company. 1907

3 **Ricketts RM**. Respiratory obstruction syndrome. *Am J Orthod* 1968; **54**: 495-507 [PMID: 5240645 DOI: 10.1016/0002-9416(68)90218-2]

4 **Martin O**, Muelas L, Viñas MJ. Nasopharyngeal cephalometric study of ideal occlusions. *Am J Orthod Dentofacial Orthop* 2006; **130**: 436.e1-436. e9 [PMID: 17045141 DOI: 10.1016/j.ajodo.2006.03.022]

5 **Uslu-Akcam O**. Pharyngeal airway dimensions in skeletal class II: A cephalometric growth study. *Imaging Sci Dent* 2017; **47**: 1-9 [PMID: 28361023 DOI: 10.5624/isd.2017.47.1.1]

6 **Bollhalder J**, Hänggi MP, Schätzle M, Markic G, Roos M, Peltomäki TA. Dentofacial and upper airway characteristics of mild and severe class II division 1 subjects. *Eur J Orthod* 2013; **35**: 447-453 [PMID: 22427406 DOI: 10.1093/ejo/cjs010]

7 **Arun T**, Isik F, Sayinsu K. Vertical growth changes after adenoidectomy. *Angle Orthod* 2003; **73**: 146-150 [PMID: 12725370]

8 **Kirjavainen M**, Kirjavainen T. Upper airway dimensions in Class II malocclusion. Effects of headgear treatment. *Angle Orthod* 2007; **77**: 1046-1053 [PMID: 18004913 DOI: 10.2319/081406-332]

9 **Joy A**, Park J, Chambers DW, Oh H. Airway and cephalometric changes in adult orthodontic patients after premolar extractions. *Angle Orthod* 2020; **90**: 39-46 [PMID: 31403835 DOI: 10.2319/021019-92.1]

10 **Barrera JE**, Pau CY, Forest VI, Holbrook AB, Popelka GR. Anatomic measures of upper airway structures in obstructive sleep apnea. *World J Otorhinolaryngol Head Neck Surg* 2017; **3**: 85-91 [PMID: 29204584 DOI: 10.1016/j.wjorl.2017.05.002]

11 **Ayoub N**, Eble P, Kniha K, Peters F, Möhlhenrich SC, Goloborodko E, Hölzle F, Modabber A. Three-dimensional evaluation of the posterior airway space: differences in computed tomography and cone beam computed tomography. *Clin Oral Investig* 2019; **23**: 603-609 [PMID: 29725852 DOI: 10.1007/s00784-018-2478-y]

12 **Hofmann E**, Schmid M, Lell M, Hirschfelder U. Cone beam computed tomography and low-dose multislice computed tomography in orthodontics and dentistry: a comparative evaluation on image quality and radiation exposure. *J Orofac Orthop* 2014; **75**: 384-398 [PMID: 25158951 DOI: 10.1007/s00056-014-0232-x]

13 **Kim KB**. How has our interest in the airway changed over 100 years? *Am J Orthod Dentofacial Orthop* 2015; **148**: 740-747 [PMID: 26522033 DOI: 10.1016/j.ajodo.2015.08.002]

14 **Torres HM**, Evangelista K, Torres EM, Estrela C, Leite AF, Valladares-Neto J, Silva MAG. Reliability and validity of two software systems used to measure the pharyngeal airway space in three-dimensional analysis. *Int J Oral Maxillofac Surg* 2020; **49**: 602-613 [PMID: 31564477 DOI: 10.1016/j.ijom.2019.09.008]

15 **Major MP**, Flores-Mir C, Major PW. Assessment of lateral cephalometric diagnosis of adenoid hypertrophy and posterior upper airway obstruction: a systematic review. *Am J Orthod Dentofacial Orthop* 2006; **130**: 700-708 [PMID: 17169731 DOI: 10.1016/j.ajodo.2005.05.050]

16 **Neelapu BC**, Kharbanda OP, Sardana HK, Balachandran R, Sardana V, Kapoor P, Gupta A, Vasamsetti S. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: A systematic review and meta-analysis of cephalometric studies. *Sleep Med Rev* 2017; **31**: 79-90 [PMID: 27039222 DOI: 10.1016/j.smrv.2016.01.007]

17 **Hsu WE**, Wu TY. Comparison of upper airway measurement by lateral cephalogram in upright position and CBCT in supine position. *J Dent Sci* 2019; **14**: 185-191 [PMID: 31205607 DOI: 10.1016/j.jds.2019.01.007]

18 **Laine-Alava MT**, Minkkinen UK. Should a history of nasal symptoms be considered when estimating nasal patency? *Angle Orthod* 1999; **69**: 126-132 [PMID: 10227552]

19 **Sam A**, Currie K, Oh H, Flores-Mir C, Lagravére-Vich M. Reliability of different three-dimensional cephalometric landmarks in cone-beam computed tomography : A systematic review. *Angle Orthod*

2019; **89**: 317-332 [PMID: 30423256 DOI: 10.2319/042018-302.1]
20 **Park J**, Baumrind S, Curry S, Carlson SK, Boyd RL, Oh H. Reliability of 3D dental and skeletal landmarks on CBCT images. *Angle Orthod* 2019; **89**: 758-767 [PMID: 30883187 DOI: 10.2319/082018-612.1]
21 **Grewal H**, Sidhu SS, Kharbanda OP. A cephalometric appraisal of dento-facial and soft tissue pattern in Indo-Aryans. *J Pierre Fauchard Acad* 1994; **8**: 87-96 [PMID: 9791249]
22 **Li L**, Liu H, Cheng H, Han Y, Wang C, Chen Y, Song J, Liu D. CBCT evaluation of the upper airway morphological changes in growing patients of class II division 1 malocclusion with mandibular retrusion using twin block appliance: a comparative research. *PLoS One* 2014; **9**: e94378 [PMID: 24705466 DOI: 10.1371/journal.pone.0094378]
23 **Kamaruddin N**, Daud F, Yusof A, Aziz ME, Rajion ZA. Comparison of automatic airway analysis function of Invivo5 and Romexis software. *PeerJ* 2019; **7**: e6319 [PMID: 30697493 DOI: 10.7717/peerj.6319]
24 **Ceylan I**, Oktay H. A study on the pharyngeal size in different skeletal patterns. *Am J Orthod Dentofacial Orthop* 1995; **108**: 69-75 [PMID: 7598107 DOI: 10.1016/s0889-5406(95)70068-4]
25 **de Freitas MR**, Alcazar NM, Janson G, de Freitas KM, Henriques JF. Upper and lower pharyngeal airways in subjects with Class I and Class II malocclusions and different growth patterns. *Am J Orthod Dentofacial Orthop* 2006; **130**: 742-745 [PMID: 17169736 DOI: 10.1016/j.ajodo.2005.01.033]
26 **Xu J**, Sun R, Wang L, Hu X. Cone-beam evaluation of pharyngeal airway space in adult skeletal Class II patients with different condylar positions. *Angle Orthod* 2019; **89**: 312-316 [PMID: 30457352 DOI: 10.2319/040518-253.1]
27 **Di Carlo G**, Polimeni A, Melsen B, Cattaneo PM. The relationship between upper airways and craniofacial morphology studied in 3D. A CBCT study. *Orthod Craniofac Res* 2015; **18**: 1-11 [PMID: 25237711 DOI: 10.1111/ocr.12053]
28 **Dunn GF**, Green LJ, Cunat JJ. Relationships between variation of mandibular morphology and variation of nasopharyngeal airway size in monozygotic twins. *Angle Orthod* 1973; **43**: 129-135 [PMID: 4511991]
29 **Lopatienė K**, Dabkutė A, Juškevičiūtė V. Vertical and sagittal morphology of the facial skeleton and the pharyngeal airway. *Stomatologija* 2016; **18**: 21-25 [PMID: 27649613]
30 **Alhammadi MS**, Almashraqi AA, Helboub E, Almahdi S, Jali T, Atafi A, Alomar F. Pharyngeal airway spaces in different skeletal malocclusions: a CBCT 3D assessment. *Cranio*2019: 1-10 [PMID: 30821659 DOI: 10.1080/08869634.2019.1583301]
31 **Hwang YI**, Lee KH, Lee KJ, Kim SC, Cho HJ, Cheon SH, et al Effect of airway and tongue in facial morphology of prepubertal Class I, II children.
Korean J Orthod 2008; 38: 74-82 [DOI: 10.4041/kjod.2008.38.2.74]
32 **Shokri A**, Mollabashi V, Zahedi F, Tapak L. Position of the hyoid bone and its correlation with airway dimensions in different classes of skeletal malocclusion using cone-beam computed tomography. *Imaging Sci Dent* 2020; **50**: 105-115 [PMID: 32601585 DOI: 10.5624/isd.2020.50.2.105]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 March 28; 13(3): 53-74

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 3 March 28, 2021

MINIREVIEWS

World Journal of Radiology

Monthly Volume 13 Number 3 March 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Gaurav Malhotra, MBBS, DRM, DNB, FICNM, MNAMS (Nuclear Medicine), Professor, Homi Bhabha National Institute, Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Jerbai Wadia Road, Parel, Mumbai 400012, India. maloonucmed@yahoo.com

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
March 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 March 28; 13(3): 53-63

DOI: 10.4329/wjr.v13.i3.53

ISSN 1949-8470 (online)

MINIREVIEWS

Radiological and clinical spectrum of COVID-19: A major concern for public health

Henu Kumar Verma

ORCID number: Henu Kumar Verma 0000-0003-1130-8783.

Author contributions: Verma HK contributed to the manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B, B

Henu Kumar Verma, Developmental and Stem Cell Biology Lab, Institute of Experimental Endocrinology and Oncology CNR, Naples 80131, Campania, Italy

Corresponding author: Henu Kumar Verma, PhD, Research Scientist, Developmental and Stem Cell Biology Lab, Institute of Experimental Endocrinology and Oncology CNR, Via Pansini 5, Naples 80131, Campania, Italy. henu.verma@yahoo.com

Abstract

The pandemic of novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by +ve strand RNA virus (SARS-CoV-2, severe acute respiratory syndrome coronavirus 2) that belongs to the corona viridae family. In March, the World Health Organization declared the outbreak of novel coronavirus for the public health emergency. Although SARS-CoV-2 infection presents with respiratory symptoms, it affects other organs such as the kidneys, liver, heart and brain. Early-stage laboratory disease testing shows many false positive or negative outcomes such as less white blood cell count and a low number of lymphocyte count. However, radiological examination and diagnosis are among the main components of the diagnosis and treatment of COVID-19. In particular, for COVID-19, chest computed tomography developed vigorous initial diagnosis and disease progression assessment. However, the accuracy is limited. Although real-time reverse transcription-polymerase chain reaction is the gold standard method for the diagnosis of COVID-19, sometimes it may give false-negative results. Due to the consequences of the missing diagnosis. This resulted in a discrepancy between the two means of examination. Conversely, based on currently available evidence, we summarized the possible understanding of the various patho-physiology, radio diagnostic methods in severe COVID-19 patients. As the information on COVID-19 evolves rapidly, this review will provide vital information for scientists and clinicians to consider novel perceptions for the comprehensive knowledge of the diagnostic approaches based on current experience.

Key Words: COVID-19; Diagnosis; Therapeutic; Radio diagnostics; Imaging

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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

Received: November 3, 2020
Peer-review started: November 3, 2020
First decision: November 16, 2020
Revised: December 7, 2020
Accepted: March 12, 2021
Article in press: March 12, 2021
Published online: March 28, 2021

P-Reviewer: Wang DW
S-Editor: Gao CC
L-Editor: A
P-Editor: Yuan YY

Core Tip: Computed tomography has played an important auxiliary role in diagnosing coronavirus disease 2019 (COVID-19) patients with higher sensitivity but lower specificity. Ground glass opacities pattern is the most common finding in COVID-19 infections. Recognizing the manifestations of COVID-19 on chest X-ray may be used as first-line imaging in hospitals, especially in high prevalence areas. COVID-19 classically appears as a bilateral, peripheral and patchy consolidation on imaging. It is important to remember that there may be no radiological changes in positive COVID-19 patients. In this perspective, a diagnosis of real-time reverse transcription-polymerase chain reaction is needed.

Citation: Verma HK. Radiological and clinical spectrum of COVID-19: A major concern for public health. *World J Radiol* 2021; 13(3): 53-63
URL: https://www.wjgnet.com/1949-8470/full/v13/i3/53.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i3.53

INTRODUCTION

In December 2019, pneumonia with unknown aetiology officially reported by local hospitals in Wuhan, and it is severely impending around the world[1]. Later on January 7, 2020, the World Health Organization (WHO) declared a public health emergency named the novel coronavirus disease 2019 (COVID-19). The official classification of the International Committee on Taxonomy of Viruses is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2].

COVID-19 is spreading to more than 200 countries around the world, especially the United States, India, Germany, and Russia[3,4]. Past evidence suggests that the likelihood of a pandemic has increased over the last century. Previous to COVID-19, many infections affected world populations, such as cholera (1817-1824)[5], the plague of 1855[6], Spanish flu (1918-1920)[7], Swine Flu (2009-2010) (H1N1)[8], and the SARS-CoV (2003)[9]. The transmission rate of SARS-CoV-2 is higher than SARS-CoV due to the protein structure[10].

The most common signs and symptoms of COVID-19 among people hospitalized include fever, dry cough, or shortness of breath. It might be spread by the asymptomatic, presymptomatic, and symptomatic conditions. However, the lungs are the main organs involved in the disease. Also, patients infected with COVID-19 may potentially suffer from myocardial, renal, gastrointestinal, and nervous systems damage[11-14].

Till now, No vaccine, specific drug against coronavirus. Several clinical trials of vaccines or medicines are underway and have not been completed. Further, it was showed that convalescent plasma transfusion has the effectiveness to reduce the mortality of severe COVID-19 patients[15,16]. Due to the high rate of diagnostic tests and updated content on COVID-19 is emerging every day. As radiological examination and diagnosis are among the critical components of the diagnosis and treatment of COVID-19, clinical imaging plays a unique role in the COVID-19 pandemic situation.

Since radiographers working in medical imaging on ground zero for patients often care under ever-more difficult specific working circumstances. Although attention is required to staff mental health. While the chest computed tomography (CT) has limited accuracy, in COVID-19 patients, it plays a vital role in the initial diagnosis and disease progression assessment. Further, real-time reverse transcription polymerase chain reaction (RT-PCR) is standard for the precise information of COVID-19. Due to its low detection rates and low sensitivity, sometimes it shows false-negative results. Still, they are vital resources within healthcare systems.

In this critical situation, depth work is needed the improve early diagnosis and clinical management. In this report, we seek to address the vital elements that may improve patient experiences to date on COVID-19 and the role of the radiological aspect in the diagnosis for better management have been summarised. This review may assist researchers and clinicians in understanding this disease accurately.

PATHOPHYSIOLOGY OF COVID-19

CoVs are non-segmented positive-sense RNA viruses belonging to the corona viridae; typically, viruses have infected many different animals, including humans and other host species[17]. Studies have shown that COVID-19 patients have several events, including systemic inflammation, thrombosis, microvascular dysfunction and hematological symptoms[18,19]. The genome sequence analysis shows that the length of SARS-CoV-2 ranges from 26 kb to 32 kb with a 5′-capping site and 3′ polyadenylation stimulates host genome transcription and translation[20]. The human SARS-CoV and SARS-CoV-2 show variable degrees of pathogenicity, but it has 82% identical to code for structural proteins (sps) and non-structural proteins (nsps)[21].

The SARS-CoV-2 genomes contain many open reading frames (ORFs), serving as a template for subgenomic mRNAs' biosynthesis. Among these are 16 nsps encoded by ORF1a and ORF1b, code for viral protein synthesis[9,22]. The spike (S) protein of SARS-CoV-2, composed of two subunits, S1 and S2, among S1, plays a crucial role in the binding of angiotensin-converting enzyme 2 (ACE2) receptor that allows the entry of virus and highly expressed in host lung epithelial cells. The transmembrane S2 domain contains heptad repeat protein that facilitates the fusion of viral and host cell membranes. Therefore, researchers are considering the S2 domain as a promising target for COVID-19[23,24].

The transmembrane protease serine 2 (TMPRSS2) and cathepsin L also facilitate the cell surface entry into the host genome[1,25]. During COVID-19 infection, these specialized structural cells activate immune system events expressed by antigen-presenting cells (APCs). APCs trigger a defence system containing $CD4^+$-T-helper (Th1) designed to interact with foreign cells. After the activation of Th1 cells, it triggers the $CD8^+$-T-killer cells, which recognize massive Th1 and Th2 cytokine to activate B-cells to produce selected viral-specific antibodies. ACE2 found on the apical surface of nasal and larynx mucosa, then targets lung epithelial cells[26,27]. Elevated white blood cells (WBCs) stimulate the cytokines, including pro-inflammatory interleukin (IL)-6. However, a higher IL-6 level increases the aggressiveness and viral spread.

DIFFERENTIAL DIAGNOSTIC APPROACH OF COVID-19

Laboratory findings

A nucleic acid-based test confirms the diagnosis of COVID19 with respiratory samples[28]. Although quantitative RT-PCR is a specific method for diagnosing COVID-19, it can give false-negative and false-positive results. Yang *et al*[29] noticed that about 11% of sputum, 27% of nasal, and 40% of throat samples were known to be false negative after RT-PCR tests. A study has shown that the current rate of false-positive operation in the preliminary estimates shows that it could be between 0.8% and 4.0%[30]. Similarly, Katz *et al*[31] has shown a 7.1% false-positive result in RT-PCR with a low detection rate. This situation may lead to severe outcomes from a missed diagnosis[32]. The quantitative RT-PCR method can only result in positive outcomes, but it has not been possible to analyze the severity of COVID-19 and its development in the organs.

The symptoms of COVID-19 are nonspecific for an accurate diagnosis. In the initial stage of the onset, patients had normal or decreased WBC count and lymphocytopenia. Some patients had elevated liver enzymes, lactate dehydrogenase and myoglobin. Increased troponin was seen in some severe cases[33]. Patients with severe disease had respiratory difficulties, including shortness of breath, chest pain or tightness with breathing, fever diminished vocal fremitus on palpation of the chest[34].

Most patients had normal procalcitonin levels but increased C-reactive protein and erythrocyte sedimentation rate at the time of admission. In severe cases, the D-dimer level was higher, and the peripheral blood T-cell phenotype of patients gradually decreased[35].

RADIOLOGICAL FEATURES OF COVID-19

Medical imaging plays a significant role in the diagnosis and therapeutic interventions of COVID-19 patients. The recommended procedure is shown in Figure 1.

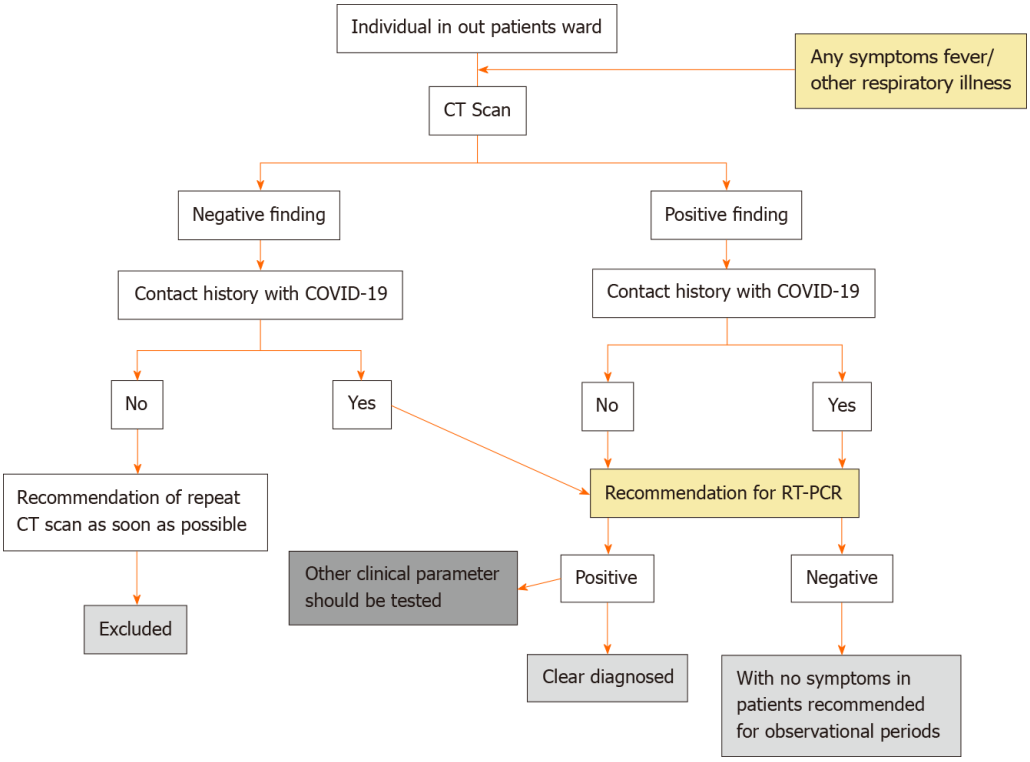


Figure 1 Overview of screening process for coronavirus disease 2019 in outpatient department. COVID-19: Coronavirus disease 2019; CT: Computed tomography; RT-PCR: Real-time reverse transcription polymerase chain reaction.

Imaging

Considering that clinical ultrasound images support vital roles in early screening, diagnosis and monitoring of response to COVID-19 treatment. Across the world, the preference for radiological approaches is the same for COVID-19 as they managed in the other respiratory symptoms. The high load of the virus could be detected by chest X-ray, chest CT, lung ultrasound (LUS), and magnetic resonance imaging (MRI), that each has strengths and weakness. All of these roles have to be seen as a best-practice option.

Chest radiographs

Chest radiographs (CXR) can provide rapid and valuable information in diagnosing COVID-19 pneumonia[36]. Preliminary clinical assessment by radiologists at the time of imaging is the expected competence of professionals in many countries. As radiologists are the first consultants to check and diagnose disease, it follows that the PCE clinical report plays a crucial role in recognizing the potential COVID-19 infection. Radiologists and referral health professionals need to know that CXR or CT does not exclude COVID-19 in high-risk patients[37]. Initial CXR report of two female COVID-19 patients showed bilateral consolidation in the lower lung areas after follow-up with patchy consolidation in Wuhan[38]. The hallmark of COVID-19 is the classical CXR patterns. Almost half of the patients with COVID-19 have an abnormal chest X-ray. The presence of ground-glass opacities (GGO), associated consolidation and crazy paving pattern linked with COVID-19 infection[39,40].

There are no abnormal results in positive COVID-19 patients on CXRs during an early or moderate stage. Pneumothorax or lung cavitation are rare complications. In severe COVID-19 cases during disease progression, the number of nodes may increase significantly and spread to central areas where the lower left lobe is more often involved than the upper and right lobes in young and middle-aged adult COVID-19 patients[41]. Imaging appearances may vary from patient to patient with the disease stages and the severity of the disease[42]. However, the existing information on the reliability of CXR in COVID-19 is limited, with fewer cases than CT in the chest and often without specific criteria for the inclusion of healthy or non-COVID-19 issues.

The sensitivity of CXRs depends on the progression of COVID-19 infection. The sensitivity (69%) of CXRs imaging is higher in mild to moderate COVID-19 patients was reported[43]. Another single-centre study found that 27 patients had a bilateral or unilateral distribution of 32 patients, and 84% had a sensitivity[44]. Besides,

asymptomatic and minimally symptomatic quarantine patients' CXR results showed 58.8% sensitivity in patients positive for COVID-19, but RT-PCR confirmation was not performed[45].

X-ray findings

Chest X-rays are the most widely used for investigating COVID-19 suspected cases due to rapid results with low sensitivity. No abnormal findings have been observed in early-stage positive COVID-19 patients. A classic picture of patchy or diffuse reticular nodule opacities and consolidation has been found in most patients with positive RT-PCR results. However, the routine chest radiography does not exclude COVID-19 pneumonia. Radiologists will be recommended for severe cases to allow quick initiation of treatments currently available for COVID-19 infection. However, there is no fixed definition for COVID-19 pneumonia to date. Radiologists may consider other respiratory symptoms when diagnosing patients[46-48].

CT

CT, as a non-invasive imaging approach, can identify specific trademark indications in the lung related to COVID-19 pneumonia. For the precise diagnosis of COVID-19 epidemiological evidence, common symptoms and tests are crucial. Imaging will be the first choice for the diagnosis. Suspected COVID-19 patients will undergo chest X-ray as soon as possible and an urgent CT scan based on severity, also follow routine protocol[49].

Hence, CT could serve as an effective way for early screening and determination of COVID-19. The sensitivity of the CT in a present pandemic situation is the gold standard at the beginning staging with RT-PCR, which recognizes viral load and is the current reference standard in the identification of COVID-19 infection. Several researchers proposed the sensitivity of without contrast chest CT for identifying COVID-19 disease is 98% compared with initial results with 71% sensitivity in RT-PCR[50-52]. Another study has shown the chest CT has a high sensitivity of (97%). Still, a low specificity was recorded (25%), with an accuracy of 68% for the diagnosis of COVID-19, and it may be considered as a primary tool for the current pandemic situation in positively affected areas[53]. No abnormal CT findings have been observed at an early and during disease progression stage. Later on, it could appear atypical CT report, including GGO, consolidation, nodule. Further, fibrosis, predominantly in the peripheral, basal lungs, and a small amount of pleural effusion may occur[54,55].

CT staging system

Till-date, there is no systematic comparison study between imaging findings and clinical case-control data. There is no significant research on the imaging stage and the rating of COVID-19. Based on abnormal findings in the CT, the stages of the COVID-19 manifestation may deviate into the four categories of early-stage, progressive stage, severe stage and pneumonia-determined stage (Table 1).

LUS

LUS has several benefits over chest radiography and chest CT in the diagnosis of COVID-19 patients. LUS has good diagnosis efficiency, is ergonomically favourable and has less impact on preventing infections. Therefore, it is used in intensive care, cardiology and nephrology, and may also be useful in diagnosing and monitoring pneumonia. LUS may allow clinicians to assess where a patient has clinical symptoms of COVID-19 related lung damage, particularly in an intensive care setting. Although its full diagnostic role in COVID-19 patient care has not yet been identified, LUS may show alveolar damage, subpleural consolidation, white lung regions, thick irregular pleural lines and abnormal B-lines. According to LUS, the severity of COVID-19 disease is divided into moderate, severe and critical. Irregular B-lines develop and their number and distribution gradually increase across the upper and anterior areas of the lungs. However, alveolar injury, sub pleural consolidation, thick distinctive pleural lines and abnormal B-lines are not very specific to COVID-19 and can be seen in other viral pneumonia and acute respiratory distress syndrome. However, when these results are combined, they may help to diagnose during the COVID-19 pandemic. However, at present, no precise data show enhanced patient outcomes; future work should focus on further multi-center studies and the integration of LUS into clinical care pathways[59-62].

MRI

Although MRI plays a crucial role in oncology, although it is not related to evaluating

Table 1 Disease progression and its associated radiological changes[56-58]

Stages	Periods	Clinical findings
Early-stage	< 2 d	(1) More than half of the patients have a negative chest result; (2) It shows single or multiple GGO, nodule small patchy GGO, or large patchy GGO; (3) The lesions are located predominately in the middle and lower lung lobes with subpleural, peri-fissure, or peri-bronchovascular distribution; (4) The thickening of the bronchial wall, thickening of small vessels, air bronchogram sign and the thickening of adjacent interlobular pleura are common; (5) Some large patchy GGO with subsegmental distribution and increased small vessels seems like the fine grid shadow or "crazy paving" sign; And (6) Some GGO shows "reversed halo" sign
Intermediate stage	3-5 d	(1) Multiple new lesions similar to those in the early stage appeared; (2) Most of the original lesions would enlarge, with the presence of consolidation varying sizes and density; (3) Nodular, halo sign and air bronchogram sign in the consolidation could be seen; (4) Fusion or partial absorption of the original GGOs or consolidation could be seen; And (5) The scope and shape of lesions often changed after the fusion, which might not distribute along with the bronchovascular bundle thoroughly
Late or severe stage	6-12 d	(1) Progression of the disease, diffuse consolidation with increased density would occur; (2) The bronchiectasis and air bronchogram sign appeared; (3) Patchy GGOs were shown in non-consolidated regions; (4) "White lung" appeared when most of the lungs were involved in the severe stage; And (5) Thickened interlobular and bilateral pleura were commonly seen with a small amount of pleural effusion
Resolved stage	> 14 d	(1) After the treatment, most COVID-19 patients tend to be stable and improved, showing that the range of lesions diminished, the density gradually decreased, the number of lesions reduced; (2) The GGO can be fully absorbed; And (3) In some cases, the lesions can evolve into a fibrous cord in a relatively short period

GGO: Ground-glass opacities; COVID-19: Coronavirus disease 2019.

lung infection, it can contribute to the defining brain and spine targets of COVID-19 positive patients. The first report of the *in vivo* human brain involved in a COVID-19 patient has been shown by Politi *et al*[63] demonstrated that a signal alteration compatible with a viral brain invasion in a cortical region. Kamishima *et al*[64] observed that respiratory-gated MRI is highly effective in reducing respiratory artefacts and these may use in various neurological manifestations of severe COVID-19 patients. Gulko *et al*[65] found that acute and sub-acute infarctions were the most common diagnosis of brain MRI imaging and leukoencephalopathy, microhemorrhage constellation, leptomeningeal contrast enhancement, and cortical fluid-attenuated inversion recovery (FLAIR) signal abnormality are common features in COVID-19 patients. In the current situation, MRI is in the diagnosis of secondary manifestations, including cardiac complications or persistent myositis. At present COVID-19 is still being explored and the use of MRI is likely to expand as we know much about this disease.

GUIDELINE AND SCREENING FOR COVID-19

Initial screening of COVID-19 is based on clinical features, travel history in recent days, and exposure to someone confirmed to have COVID-19. Based on United States practice and WHO guidance, there are two main reasons for being tested for SARS-CoV-2, including symptoms or exposure to an infected person. Although those at higher risk, such as people over 60 years of age or underlying medical conditions, may be considered for testing when others without these high-risk factors are not considered for testing[66]. For symptomatic patients, WHO suggests that chest imaging be used for suspected COVID-19 patients for precise diagnosis even if the following condition: (1) RT-PCR test not performed; (2) RT-PCR testing performed, but results delayed; and (3) The first RT-PCR test result is negative, but patients have a severe clinical feature of COVID-19. For patients with doubted or confirmed COVID-19 who are not present in the hospital and have minor symptoms, the WHO suggests additional clinical and laboratory assessments can be done by the hospital and later maybe discharge[67]. Later on June 16, 2020, the Food and Drug Administration (FDA) took initiatives to strengthen screening tests for asymptomatic patients and recommend pooled testing for all samples. The FDA believes that the pooling of samples may be authorized for use in specific SARS-CoV-2 tests with appropriate mitigation and validation (https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/pooled-sample-testing-and-screening-testing-covid-19).

The sample may be taken from the upper (nasopharyngeal or pharyngeal) or lower respiratory tract for diagnosis of SARS-CoV-2. Accumulating data indicates that the RT-PCR tests' accuracy is more sensitive and may vary depending on the specimen[68]. Preliminary results suggested that sputum is the most accurate sample for SARS-CoV-

2 diagnosis, followed by nasal and throat swabs when comparing different types of specimens[26]. Some reports have shown that nasopharyngeal or pharyngeal swab samples are more sensitive to the SARS-CoV-2diagnosis, which varies based on viral load[69-71].

ADVANTAGES AND LIMITATIONS

Medical imaging plays a vital role in the diagnosis, management and treatment of COVID-19 patients. CXR are the most commonly used imaging method for suspected and reported COVID-19 cases, although their sensitivity is very low. On the other hand, CT in the chest is highly sensitive (97%), although not entirely specific. There are some major challenges in terms of infection control. LUS shows the benefits of chest X-rays and chests CT in the diagnosis of COVID-19 patients. It can be easily performed without the exposure of harmful radiation to patients and can be easily repeated at the bedside only. It also has more sensitivity than CXR and CT in the chest. MRI may lead to patients' diagnosis with symptoms of the central nervous system, even if it is not relevant to lung disease assessment. At present, the role of MRI is only used in the diagnosis of secondary complications of COVID-19, including cardiac complications or chronic myositis, and the use of MRI in this field is likely to increase because patients are more frequently affected by this disease[72-75].

CONCLUSION

COVID-19 is extremely infectious and people are highly vulnerable to infection in general. Medical imaging plays a crucial role in the COVID-19 pandemic, providing the benefit of additional evaluation and follow-up to critically ill patients. Based on the epidemiological evidence and clinical features, a descriptive radiological diagnosis is needed and the final diagnosis needs to be confirmed by RT-PCR testing. Even though radiological findings may be dramatic, it is not necessary to the image of all patients with suspected or confirmed COVID-19. Thus, a thorough review of the patient's epidemiological history, laboratory test results, clinical symptoms, and imaging indications are essential for early intervention, early identification, early diagnosis, first isolation, and early treatment.

REFERENCES

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

2 **Xiao C**, Li X, Liu S, Sang Y, Gao SJ, Gao F. HIV-1 did not contribute to the 2019-nCoV genome. *Emerg Microbes Infect* 2020; **9**: 378-381 [PMID: 32056509 DOI: 10.1080/22221751.2020.1727299]

3 **Cucinotta D**, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed* 2020; **91**: 157-160 [PMID: 32191675 DOI: 10.23750/abm.v91i1.9397]

4 **Mahase E**. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. *BMJ* 2020; **368**: m1036 [PMID: 32165426 DOI: 10.1136/bmj.m1036]

5 **Chowdhury FR**, Nur Z, Hassan N, von Seidlein L, Dunachie S. Pandemics, pathogenicity and changing molecular epidemiology of cholera in the era of global warming. *Ann Clin Microbiol Antimicrob* 2017; **16**: 10 [PMID: 28270154 DOI: 10.1186/s12941-017-0185-1]

6 **Bramanti B**, Dean KR, Walløe L, Chr Stenseth N. The Third Plague Pandemic in Europe. *Proc Biol Sci* 2019; **286**: 20182429 [PMID: 30991930 DOI: 10.1098/rspb.2018.2429]

7 **Taubenberger JK**, Morens DM. 1918 Influenza: the mother of all pandemics. *Emerg Infect Dis* 2006; **12**: 15-22 [PMID: 16494711 DOI: 10.3201/eid1201.050979]

8 **Ratre YK**, Vishvakarma NK, Bhaskar LVKS, Verma HK. Dynamic Propagation and Impact of Pandemic Influenza A (2009 H1N1) in Children: A Detailed Review. *Curr Microbiol* 2020; **77**: 3809-3820 [PMID: 32959089 DOI: 10.1007/s00284-020-02213-x]

9 **Luk HKH**, Li X, Fung J, Lau SKP, Woo PCY. Molecular epidemiology, evolution and phylogeny of SARS coronavirus. *Infect Genet Evol* 2019; **71**: 21-30 [PMID: 30844511 DOI: 10.1016/j.meegid.2019.03.001]

10 **Lima CMAO**. Information about the new coronavirus disease (COVID-19). *Radiol Bras* 2020; **53**: V-VI [PMID: 32336833 DOI: 10.1590/0100-3984.2020.53.2e1]

11 **Gavriatopoulou M**, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E,

Terpos E, Dimopoulos MA. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med* 2020; **20**: 493-506 [PMID: 32720223 DOI: 10.1007/s10238-020-00648-x]

12 **Merad M**, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020; **20**: 355-362 [PMID: 32376901 DOI: 10.1038/s41577-020-0331-4]

13 **Valizadeh R**, Baradaran A, Mirzazadeh A, Bhaskar LVKS. Coronavirus-nephropathy; renal involvement in COVID-19. *J Renal Inj Prev* 2020; **9** [DOI: 10.34172/jrip.2020.18]

14 **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]

15 **Verma HK**, Merchant N, Verma MK, Kuru Cİ, Singh AN, Ulucan F, Verma P, Bhattacharya A, Bhaskar LVKS. Current updates on the European and WHO registered clinical trials of coronavirus disease 2019 (COVID-19). *Biomed J* 2020; 424-433 [PMID: 32792167 DOI: 10.1016/j.bj.2020.07.008]

16 **Verma HK**, Farran B, Bhaskar LVKS. Convalescent plasma transfusion a promising therapy for coronavirus diseases 2019 (COVID-19): current updates. *Antib Therapeut* 2020; **3**: 115-125 [DOI: 10.1093/abt/tbaa010]

17 **Pal M**, Berhanu G, Desalegn C, Kandi V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. *Cureus* 2020; **12**: e7423 [PMID: 32337143 DOI: 10.7759/cureus.7423]

18 **Słomka A**, Kowalewski M, Żekanowska E. Coronavirus Disease 2019 (COVID-19): A Short Review on Hematological Manifestations. *Pathogens* 2020; **9** [PMID: 32575786 DOI: 10.3390/pathogens9060493]

19 **Gencer S**, Lacy M, Atzler D, van der Vorst EPC, Döring Y, Weber C. Immunoinflammatory, Thrombohaemostatic, and Cardiovascular Mechanisms in COVID-19. *Thromb Haemost* 2020; **120**: 1629-1641 [PMID: 33124029 DOI: 10.1055/s-0040-1718735]

20 **Rabi FA**, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. *Pathogens* 2020; **9** [PMID: 32245083 DOI: 10.3390/pathogens9030231]

21 **Chan JF**, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* 2020; **9**: 221-236 [PMID: 31987001 DOI: 10.1080/22221751.2020.1719902]

22 **Snijder EJ**, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL, Guan Y, Rozanov M, Spaan WJ, Gorbalenya AE. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 Lineage. *J Mol Biol* 2003; **331**: 991-1004 [PMID: 12927536 DOI: 10.1016/s0022-2836(03)00865-9]

23 **Kirchdoerfer RN**, Cottrell CA, Wang N, Pallesen J, Yassine HM, Turner HL, Corbett KS, Graham BS, McLellan JS, Ward AB. Pre-fusion structure of a human coronavirus spike protein. *Nature* 2016; **531**: 118-121 [PMID: 26935699 DOI: 10.1038/nature17200]

24 **Xu X**, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020; **63**: 457-460 [PMID: 32009228 DOI: 10.1007/s11427-020-1637-5]

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

26 **Chen C**, Zhang XR, Ju ZY, He WF. [Advances in the research of mechanism and related immunotherapy on the cytokine storm induced by coronavirus disease 2019]. *Zhonghua Shao Shang Za Zhi* 2020; **36**: 471-475 [PMID: 32114747 DOI: 10.3760/cma.j.cn501120-20200224-00088]

27 **Bennardo F**, Buffone C, Giudice A. New therapeutic opportunities for COVID-19 patients with Tocilizumab: Possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws. *Oral Oncol* 2020; **106**: 104659 [PMID: 32209313 DOI: 10.1016/j.oraloncology.2020.104659]

28 **Xie C**, Jiang L, Huang G, Pu H, Gong B, Lin H, Ma S, Chen X, Long B, Si G, Yu H, Yang X, Shi Y, Yang Z. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. *Int J Infect Dis* 2020; **93**: 264-267 [PMID: 32114193 DOI: 10.1016/j.ijid.2020.02.050]

29 **Yang Y**, Yang M, Yuan J, Wang F, Wang Z, Li J, Zhang M, Xing L, Wei J, Peng L, Wong G, Zheng H, Wu W, Shen C, Liao M, Feng K, Yang Q, Zhao J, Liu L, Liu Y. Comparative Sensitivity of Different Respiratory Specimen Types for Molecular Diagnosis and Monitoring of SARS-CoV-2 Shedding. *Innovation (N Y)* 2020; **1**: 100061 [PMID: 33169119 DOI: 10.1016/j.xinn.2020.100061]

30 **Cohen AN**, Kessel B, Milgroom MG. False positives in reverse transcription PCR testing for SARS-CoV-2. 2020 Preprint. Available from: medRxiv:2020.04.26.200809 [DOI: 10.1101/2020.04.26.20080911]

31 **Katz AP**, Civantos FJ, Sargi Z, Leibowitz JM, Nicolli EA, Weed D, Moskovitz AE, Civantos AM, Andrews DM, Martinez O, Thomas GR. False-positive reverse transcriptase polymerase chain reaction screening for SARS-CoV-2 in the setting of urgent head and neck surgery and otolaryngologic emergencies during the pandemic: Clinical implications. *Head Neck* 2020; **42**: 1621-1628 [PMID: 32530131 DOI: 10.1002/hed.26317]

32 **Coleman JJ**, Manavi K, Marson EJ, Botkai AH, Sapey E. COVID-19: to be or not to be; that is the

diagnostic question. *Postgrad Med J* 2020; **96**: 392-398 [PMID: 32522844 DOI: 10.1136/postgradmedj-2020-137979]

33 **Kermali M**, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci* 2020; **254**: 117788 [PMID: 32475810 DOI: 10.1016/j.lfs.2020.117788]

34 **Xie J**, Tong Z, Guan X, Du B, Qiu H. Clinical Characteristics of Patients Who Died of Coronavirus Disease 2019 in China. *JAMA Netw Open* 2020; **3**: e205619 [PMID: 32275319 DOI: 10.1001/jamanetworkopen.2020.5619]

35 **Yuan X**, Huang W, Ye B, Chen C, Huang R, Wu F, Wei Q, Zhang W, Hu J. Changes of hematological and immunological parameters in COVID-19 patients. *Int J Hematol* 2020; **112**: 553-559 [PMID: 32656638 DOI: 10.1007/s12185-020-02930-w]

36 **Jacobi A**, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. *Clin Imaging* 2020; **64**: 35-42 [PMID: 32302927 DOI: 10.1016/j.clinimag.2020.04.001]

37 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

38 **Huang WH**, Teng LC, Yeh TK, Chen YJ, Lo WJ, Wu MJ, Chin CS, Tsan YT, Lin TC, Chai JW, Lin CF, Tseng CH, Liu CW, Wu CM, Chen PY, Shi ZY, Liu PY. 2019 novel coronavirus disease (COVID-19) in Taiwan: Reports of two cases from Wuhan, China. *J Microbiol Immunol Infect* 2020; **53**: 481-484 [PMID: 32111449 DOI: 10.1016/j.jmii.2020.02.009]

39 **Carotti M**, Salaffi F, Sarzi-Puttini P, Agostini A, Borgheresi A, Minorati D, Galli M, Marotto D, Giovagnoni A. Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med* 2020; **125**: 636-646 [PMID: 32500509 DOI: 10.1007/s11547-020-01237-4]

40 **Ye Z**, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* 2020; **30**: 4381-4389 [PMID: 32193638 DOI: 10.1007/s00330-020-06801-0]

41 **Toussie D**, Voutsinas N, Finkelstein M, Cedillo MA, Manna S, Maron SZ, Jacobi A, Chung M, Bernheim A, Eber C, Concepcion J, Fayad ZA, Gupta YS. Clinical and Chest Radiography Features Determine Patient Outcomes in Young and Middle-aged Adults with COVID-19. *Radiology* 2020; **297**: E197-E206 [PMID: 32407255 DOI: 10.1148/radiol.2020201754]

42 **Feng Z**, Yu Q, Yao S, Luo L, Zhou W, Mao X, Li J, Duan J, Yan Z, Yang M, Tan H, Ma M, Li T, Yi D, Mi Z, Zhao H, Jiang Y, He Z, Li H, Nie W, Liu Y, Zhao J, Luo M, Liu X, Rong P, Wang W. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. *Nat Commun* 2020; **11**: 4968 [PMID: 33009413 DOI: 10.1038/s41467-020-18786-x]

43 **Stephanie S**, Shum T, Cleveland H, Challa SR, Herring A, Jacobson FL, Hatabu H, Byrne SC, Shashi K, Araki T, Hernandez JA, White CS, Hossain R, Hunsaker AR, Hammer MM. Determinants of Chest X-Ray Sensitivity for COVID- 19: A Multi-Institutional Study in the United States. *Radiology: Cardiothoracic Imag* 2020; **2**: e200337 [DOI: 10.1148/ryct.2020200337]

44 **Lomoro P**, Verde F, Zerboni F, Simonetti I, Borghi C, Fachinetti C, Natalizi A, Martegani A. COVID-19 pneumonia manifestations at the admission on chest ultrasound, radiographs, and CT: single-center study and comprehensive radiologic literature review. *Eur J Radiol Open* 2020; **7**: 100231 [PMID: 32289051 DOI: 10.1016/j.ejro.2020.100231]

45 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]

46 **Durrani M**, Haq IU, Kalsoom U, Yousaf A. Chest X-rays findings in COVID 19 patients at a University Teaching Hospital - A descriptive study. *Pak J Med Sci* 2020; **36**: S22-S26 [PMID: 32582309 DOI: 10.12669/pjms.36.COVID19-S4.2778]

47 **Cozzi D**, Albanesi M, Cavigli E, Moroni C, Bindi A, Luvarà S, Lucarini S, Busoni S, Mazzoni LN, Miele V. Chest X-ray in new Coronavirus Disease 2019 (COVID-19) infection: findings and correlation with clinical outcome. *Radiol Med* 2020; **125**: 730-737 [PMID: 32519256 DOI: 10.1007/s11547-020-01232-9]

48 **Cleverley J**, Piper J, Jones MM. The role of chest radiography in confirming covid-19 pneumonia. *BMJ* 2020; **370**: m2426 [PMID: 32675083 DOI: 10.1136/bmj.m2426]

49 **Shen K**, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, Zheng Y, Xu B, Xie Z, Lin L, Shang Y, Lu X, Shu S, Bai Y, Deng J, Lu M, Ye L, Wang X, Wang Y, Gao L; China National Clinical Research Center for Respiratory Diseases; National Center for Children's Health, Beijing, China; Group of Respirology, Chinese Pediatric Society, Chinese Medical Association; Chinese Medical Doctor Association Committee on Respirology Pediatrics; China Medicine Education Association Committee on Pediatrics; Chinese Research Hospital Association Committee on Pediatrics; Chinese Non-government Medical Institutions Association Committee on Pediatrics; China Association of Traditional Chinese Medicine, Committee on Children's Health and Medicine Research; China News of Drug Information Association, Committee on Children's Safety Medication; Global Pediatric Pulmonology Alliance. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. *World J Pediatr* 2020; **16**: 223-231 [PMID: 32034659 DOI: 10.1007/s12519-020-00343-7]

50 **Udugama B**, Kadhiresan P, Kozlowski HN, Malekjahani A, Osborne M, Li VYC, Chen H, Mubareka S, Gubbay JB, Chan WCW. Diagnosing COVID-19: The Disease and Tools for Detection. *ACS Nano* 2020; **14**: 3822-3835 [PMID: 32223179 DOI: 10.1021/acsnano.0c02624]

51 **Chen Z**, Fan H, Cai J, Li Y, Wu B, Hou Y, Xu S, Zhou F, Liu Y, Xuan W, Hu H, Sun J. High-resolution computed tomography manifestations of COVID-19 infections in patients of different ages. *Eur J Radiol* 2020; **126**: 108972 [PMID: 32240913 DOI: 10.1016/j.ejrad.2020.108972]

52 **Jiang Y**, Guo D, Li C, Chen T, Li R. High-resolution CT features of the COVID-19 infection in Nanchong City: Initial and follow-up changes among different clinical types. *Radiol Infect Dis* 2020; **7**: 71-77 [PMID: 32406420 DOI: 10.1016/j.jrid.2020.05.001]

53 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

54 **Pan Y**, Guan H, Zhou S, Wang Y, Li Q, Zhu T, Hu Q, Xia L. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol* 2020; **30**: 3306-3309 [PMID: 32055945 DOI: 10.1007/s00330-020-06731-x]

55 **Xie X**, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* 2020; **296**: E41-E45 [PMID: 32049601 DOI: 10.1148/radiol.2020200343]

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

57 **Zhen-Dong Y**, Gao-Jun Z, Run-Ming J, Zhi-Sheng L, Zong-Qi D, Xiong X, Guo-Wei S. Clinical and transmission dynamics characteristics of 406 children with coronavirus disease 2019 in China: A review. *J Infect* 2020; **81**: e11-e15 [PMID: 32360500 DOI: 10.1016/j.jinf.2020.04.030]

58 **Zou L**, Dai L, Zhang Y, Fu W, Gao Y, Zhang Z. Clinical Characteristics and Risk Factors for Disease Severity and Death in Patients With Coronavirus Disease 2019 in Wuhan, China. *Front Med (Lausanne)* 2020; **7**: 532 [PMID: 32903644 DOI: 10.3389/fmed.2020.00532]

59 **Jackson K**, Butler R, Aujayeb A. Lung ultrasound in the COVID-19 pandemic. *Postgrad Med J* 2021; **97**: 34-39 [PMID: 32895294 DOI: 10.1136/postgradmedj-2020-138137]

60 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? *J Ultrasound Med* 2020; **39**: 1459-1462 [PMID: 32198775 DOI: 10.1002/jum.15284]

61 **Kulkarni S**, Down B, Jha S. Point-of-care lung ultrasound in intensive care during the COVID-19 pandemic. *Clin Radiol* 2020; **75**: 710.e1-710. e4 [PMID: 32405081 DOI: 10.1016/j.crad.2020.05.001]

62 **Brachini G**, Sapienza P, Cirillo B, Fonsi GB, Crocetti D, Mingoli A. Role of lung ultrasound in patients requiring emergency surgery during COVID-19 Pandemic. *Br J Surg* 2020 [PMID: 33090478]

63 **Politi LS**, Salsano E, Grimaldi M. Magnetic Resonance Imaging Alteration of the Brain in a Patient With Coronavirus Disease 2019 (COVID-19) and Anosmia. *JAMA Neurol* 2020; **77**: 1028-1029 [PMID: 32469400 DOI: 10.1001/jamaneurol.2020.2125]

64 **Kamishima T**, An Y, Fang W, Lu Y. Editorial for "Clinical Potential of UTE-MRI for Assessing the COVID-19: Patient- and Lesion-Based Comparative Analysis". *J Magn Reson Imaging* 2020; **52**: 956-957 [PMID: 32652680 DOI: 10.1002/jmri.27291]

65 **Gulko E**, Oleksk ML, Gomes W, Ali S, Mehta H, Overby P, Al-Mufti F, Rozenshtein A. MRI Brain Findings in 126 Patients with COVID-19: Initial Observations from a Descriptive Literature Review. *AJNR Am J Neuroradiol* 2020; **41**: 2199-2203 [PMID: 32883670 DOI: 10.3174/ajnr.A6805]

66 **Mossa-Basha M**, Medverd J, Linnau KF, Lynch JB, Wener MH, Kicska G, Staiger T, Sahani DV. Policies and Guidelines for COVID-19 Preparedness: Experiences from the University of Washington. *Radiology* 2020; **296**: E26-E31 [PMID: 32267209 DOI: 10.1148/radiol.2020201326]

67 **Chou R**, Pappas M, Buckley D, McDonagh M, Totten A, Flor N, Sardanelli F, Dana T, Hart E, Wasson N, Nelson H. Use of chest imaging in COVID-19: a rapid advice guide. 2nd ed. Geneva: World Health Organization; 2020

68 **COVID-19 Investigation Team**. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med* 2020; **26**: 861-868 [PMID: 32327757 DOI: 10.1038/s41591-020-0877-5]

69 **Pan Y**, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis* 2020; **20**: 411-412 [PMID: 32105638 DOI: 10.1016/S1473-3099(20)30113-4]

70 **Yan Y**, Chang L, Wang L. Laboratory testing of SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV): Current status, challenges, and countermeasures. *Rev Med Virol* 2020; **30**: e2106 [PMID: 32302058 DOI: 10.1002/rmv.2106]

71 **Mawaddah A**, Gendeh HS, Lum SG, Marina MB. Upper respiratory tract sampling in COVID-19. *Malays J Pathol* 2020; **42**: 23-35 [PMID: 32342928]

72 **Antúnez-Montes OY**, Buonsenso D. Routine use of Point-of-Care lung ultrasound during the COVID-19 pandemic. *Med Intensiva* 2020 [PMID: 32386997 DOI: 10.1016/j.medin.2020.04.010]

73 **Kooraki S**, Hosseiny M, Myers L, Gholamrezanezhad A. Coronavirus (COVID-19) Outbreak: What the Department of Radiology Should Know. *J Am Coll Radiol* 2020; **17**: 447-451 [PMID: 32092296 DOI: 10.1016/j.jacr.2020.02.008]

74 **Kok SSX**, Mohamed Shah MTB, Cheong WK, Cheng AKC, Sng LH, Salkade PR, Wong SBS. Dealing with COVID-19: initial perspectives of a small radiology department. *Singapore Med J* 2020; **61**: 375-377 [PMID: 32227793 DOI: 10.11622/smedj.2020043]

75 **Ding J**, Fu H, Liu Y, Gao J, Li Z, Zhao X, Zheng J, Sun W, Ni H, Ma X, Feng J, Wu A, Liu J, Wang Y, Geng P, Chen Y. Prevention and control measures in radiology department for COVID-19. *Eur Radiol* 2020; **30**: 3603-3608 [PMID: 32300968 DOI: 10.1007/s00330-020-06850-5]

World Journal of Radiology

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

World J Radiol 2021 March 28; 13(3): 64-74

DOI: 10.4329/wjr.v13.i3.64

ISSN 1949-8470 (online)

MINIREVIEWS

COVID-19 and venous thromboembolism: Known and unknown for imaging decisions

Love Patel, Darshan Gandhi, Emily Westergard, Michael Ornes, Matthew Lillyblad, Nedaa Skeik

ORCID number: Love Patel 0000-0002-6271-6376; Darshan Gandhi 0000-0002-7079-450X; Emily Westergard 0000-0002-9302-9085; Michael Ornes 0000-0002-1252-5635; Matthew Lillyblad 0000-0002-7657-9237; Nedaa Skeik 0000-0003-2284-1938.

Author contributions: Patel L conceived the idea of this article and contributed to writing the manuscript substantially; Gandhi D contributed to the discussion of the manuscript substantially with the contribution of imaging; Westergard E contributed to the manuscript formatting and revision; Ornes M contributed to reference numbering and designing the algorithm; Lillyblad M contributed to the design and revision of the manuscript; Skeik N contributed to the discussion of the manuscript substantially and editing.

Conflict-of-interest statement: The authors declare that they have no competing or conflicts of interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to

Love Patel, Michael Ornes, Division of Hospital Medicine, Abbott Northwestern Hospital, Allina Health, Minneapolis, MN 55407, United States

Darshan Gandhi, Department of Radiology, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, United States

Emily Westergard, Department of Graduate Medical Education, Abbott Northwestern Hospital, Minneapolis, MN 55408, United States

Matthew Lillyblad, Department of Pharmacy, Abbott Northwestern Hospital, Allina Health, Minneapolis, MN 55407, United States

Nedaa Skeik, Minneapolis Heart Institute, Abbott Northwestern Hospital, Allina Health, Minneapolis, MN 55407, United States

Corresponding author: Darshan Gandhi, MD, Academic Fellow, Doctor, Department of Radiology, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, 676 N St. Clair St, Suite 800, Chicago, IL 60611, United States.
darshan.gandhi@northwestern.edu

Abstract

As we continue to fight against the current coronavirus disease-2019 (COVID-19) pandemic, healthcare professionals across the globe are trying to answer questions surrounding how to best help patients with the up-to-date available science while awaiting the development of new therapies and mass vaccination. Since early in the pandemic, studies indicated a heightened risk of venous thromboembolism (VTE) in COVID-19 infected patients. There have been differing expert opinions about how to assess pretest probability of VTE in this patient population. This has been partly due to the high prevalence of respiratory failure in this patient population and the use of D-dimer as a prognostic test which is also frequently elevated in patients with COVID-19 in absence of VTE. Some experts have argued for an approach similar to usual care with testing if clinical suspicion is high enough. Some have argued for more routine screening at different points of care. Others have even suggested empiric therapeutic anti-coagulation in moderate to severely ill COVID-19 patients. In the following article, we review and summarize the most current literature in hopes of assisting clinicians in decision making and guidance for when to be concerned for VTE in COVID-19 patients. We also discuss research gaps and share pathways currently being used within our institution.

distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Respiratory system

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: January 29, 2021
Peer-review started: January 29, 2021
First decision: March 1, 2021
Revised: March 2, 2021
Accepted: March 22, 2021
Article in press: March 22, 2021
Published online: March 28, 2021

P-Reviewer: Alberca RW
S-Editor: Zhang H
L-Editor: A
P-Editor: Yuan YY

Key Words: COVID-19; Venous thromboembolism; Computed tomography scan; Anticoagulation; Point of care ultrasound

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: As we continue to fight against the current coronavirus disease-2019 (COVID-19) pandemic, healthcare professionals across the globe are trying to answer questions surrounding how to best help patients with the up-to-date available science while awaiting the development of new therapies and mass vaccination. Since early in the pandemic, studies indicated a heightened risk of venous thromboembolism (VTE) in COVID-19 infected patients. There have been differing expert opinions about how to assess pretest probability of VTE in this patient population. This has been partly due to the high prevalence of respiratory failure in this patient population and the use of D-dimer as a prognostic test which is also frequently elevated in patients with COVID-19 in absence of VTE. Some experts have argued for an approach similar to usual care with testing if clinical suspicion is high enough. Some have argued for more routine screening at different points of care. Others have even suggested empiric therapeutic anticoagulation in moderate to severely ill COVID-19 patients. In the following paper we review and summarize the most current literature in hopes of assisting clinicians in decision making and guidance for when to be concerned for VTE in COVID-19 patients. We also discuss research gaps and share pathways currently being used within our institution.

Citation: Patel L, Gandhi D, Westergard E, Ornes M, Lillyblad M, Skeik N. COVID-19 and venous thromboembolism: Known and unknown for imaging decisions. *World J Radiol* 2021; 13(3): 64-74
URL: https://www.wjgnet.com/1949-8470/full/v13/i3/64.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i3.64

INTRODUCTION

At the time this paper was written, globally there are over 100 million patients who have tested positive for coronavirus disease-2019 (COVID-19) infection, with around 2.1 million patients having lost their lives due to this disease[1]. COVID-19 is caused by the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Though COVID-19 infections have a tendency to involve multiple organ systems, the respiratory system is primarily affected resulting in inflammatory infiltrates, and in severe cases leading to hypoxemia and respiratory failure. High risk of venous thromboembolism (VTE) in COVID-19 patients was recognized early on in the pandemic, with one study suggesting enoxaparin prophylaxis was associated with lower mortality[2]. However, despite thromboprophylaxis, the risk for VTE remains high[3]. Timely identification of deep vein thrombosis (DVT) and pulmonary embolism (PE) is critical in making clinical decisions regarding therapeutic anticoagulation. Computed tomography pulmonary angiography (CTPA) is considered the gold standard test for diagnosis of pulmonary artery clot. In patients presenting with COVID-19 infection, deciding when to screen or rule out pulmonary artery thromboembolism remains a challenge for physicians due to frequently fluctuating oxygenation requirements. Different approaches have been suggested and debated by experts including use of clinical decision-making tools, the use of D-dimer testing, universal CTPA or lower extremity ultrasound screening on admission to the hospital or at the time of admission to critical care units, and empiric higher than prophylactic anticoagulation. In the following review, we will explore current literature regarding clinical decision-making for imaging in the diagnosis of VTE in COVID-19 patients in the form of common clinical questions. We will also share our institution's pathway for diagnosing VTE in this patient population.

WHAT IS THE RISK OF VTE IN COVID-19?

Since the beginning of the pandemic, studies have indicated increased risk of both venous and arterial thromboembolism in COVID-19 patients, including DVT, PE, ischemic stroke, myocardial infarction and peripheral arterial thromboembolism[4]. One study, which compared national databases of viral pneumonias, showed COVID-19 was associated with higher incidences of thrombotic complications compared to other viral pneumonias[5]. The reported frequency of pulmonary embolism in critically ill COVID-19 patients is approximately 20%-30%[6,7]. Evidence suggests that small vessel pulmonary thrombi are more common than large pulmonary vessel involvement in COVID-19[8,9]. Pulmonary embolism is a serious thrombotic complication of COVID-19 pneumonia, with mortality rates for patients with COVID-19 and PE estimated at approximately 45%[10]. With available literature it is clear that risk of VTE is very high in patients with COVID-19, especially those requiring intensive care during hospitalization. Patients with COVID-19 and VTE have high risk of mortality.

WHAT IS THE MECHANISM BEHIND VTE IN COVID-19 PATIENTS?

The pathway for clot formation in acutely ill patients is Virchow's Triad, which includes the predisposing factors of venous stasis, hypercoagulability and endothelial damage. All critically ill patients, despite underlying etiology, usually face a combination of the above factors and are therefore considered high risk for VTE. Post-mortem studies have raised significant concerns regarding microvascular thrombosis, as well as macrovascular involvement in COVID-19 patients[11,12]. Data suggests SARS-CoV-2 can infect pulmonary endothelial cells, triggering a cascade of local immune response involving leukocyte activation, complement deposition and platelet aggregation[13]. In a small study of 25 patients with COVID-19 who were admitted to the intensive care unit, screening bilateral lower extremity venous ultrasounds between days 5 and 10 of admission showed an overall incidence of proximal DVT of 24%, indicating lower extremity thrombosis is also a major contributor for pulmonary embolism in COVID-19 patients[14]. Apart from known factors that put critically ill patients at high risk of VTE, direct injury to the endothelium by the virus and strong local immune response seems to play a large role, especially in small pulmonary vessel in-situ thromboses' in patients with COVID-19. Several studies also reported other hemostatic abnormalities in COVID-19 patients, including positive antiphospholipid antibodies, abnormal platelet function and abnormal coagulation parameters that likely add a complex interplay further increasing risk of thromboembolism[15].

WHAT IS THE ROLE OF CLINICAL PROBABILITY SCORES IN DIRECTING EVALUATION FOR VTE IN COVID-19 PATIENTS?

Clinical probability scores have been shown to assist in determining pretest probability of pulmonary embolism with more accuracy than clinician gestalt[16,17]. The Well's criteria are the most popular and commonly used tool internationally used to aid in clinical decision making for diagnosis of VTE. Studies on the use of clinical probability scoring in COVID-19 patients is thus far very limited. One study indicated a Wells score > 2 had a higher correlation for VTE on imaging in critically ill COVID-19 patients[18]. Despite the limited evidence, use of a clinical prediction scoring tool should be considered in conjunction with clinical judgement when defining pretest probability of VTE in COVID-19 patients.

WHAT IS THE ROLE OF D-DIMER IN DECISION MAKING FOR EVALUATION OF VTE IN COVID-19 PATIENTS?

D-dimer is a soluble fibrin degradation product resulting from fibrinolysis of thrombi. It is frequently elevated in acute VTE, but is non-specific, being frequently elevated in many other non-thrombotic conditions including pregnancy, cancer and inflammation[19,20]. Cochrane review suggests D-dimer sensitivity ranging from 80%-100% and specificity from 23%-63% in prediction for VTE[21]. Due to lack of specificity and high false positive results, D-dimer is a good test to rule out VTE in low pretest probability

patients if D-dimer results are normal, but should not be used to establish diagnosis of VTTE when levels are elevated[22].

In multiple studies D-dimer has shown to be frequently elevated in COVID-19 positive patients in the absence of VTE. Studies indicate up to 40%-50% of patients with COVID-19 will have elevated D-dimer during hospitalization[23,24]. In one study, admission D-dimer was found to be the same in those patients who were found to have VTE during hospitalization *vs* those without evidence of VTE[25]. Many retrospective studies suggest significantly higher D-dimer levels in patients with confirmed pulmonary embolism on CTPA *vs* patients without pulmonary embolism on CTPA[26,27]. Though data clearly indicates higher D-dimer values are associated with higher probability for pulmonary embolism on CTPA, there is ongoing debate about serial D-dimer testing and the cut-off value for D-dimer at which imaging to evaluate for VTE should be performed. Based on available studies, we think absolute D-dimer levels and changes over time should be taken into account in decision making on when to obtain imaging to evaluate for VTE despite the absence of significant clinical suspicion, but exact cut off values or percentage of change from initial D-dimer at which imaging should be performed remains controversial.

SHOULD ALL PATIENTS PRESENTING TO THE EMERGENCY DEPARTMENT WITH SUSPECTED COVID-19 INFECTION UNDERGO LOWER EXTREMITY VENOUS ULTRASOUND OR CTPA FOR EVALUATION OF VTE?

Currently, CTPA is considered the gold standard for diagnosis of pulmonary embolism and venous duplex ultrasound is considered standard for diagnosis of DVT. Pulmonary embolism is seen as a hypodense filling defect on CTPA (Figure 1). A normal CTPA effectively rules out pulmonary embolism with high negative predictive values of around 99%[28]. However, like any other testing modality, CTPA carries risks including exposure to ionizing radiation and use of intravenous iodinated contrast, placing the patient at risk for renal toxicity especially in patients with existing kidney disease and hypersensitivity reactions. Overtreatment of clinically insignificant pulmonary emboli also comes with significant risk given the need for therapeutic anticoagulation medications and resulting risk of bleeding[16].

High resolution CT of lungs can identify ground glass opacities with significant accuracy. In the early part of pandemic there was concern regarding accuracy of reverse transcriptase- polymerase chain reaction (RT-PCR) which led to studies suggesting lung CT scan as a more sensitive modality for diagnosing COVID-19 pneumonia[29]. Though RT-PCR remains the gold standard for confirmation of COVID-19 diagnosis, it has been advised to consider CT chest as a primary modality for diagnosis, especially if RT-PCR availability is limited or there is a delay in testing results[30]. Many institutions use CT modalities over chest x-ray due to the poor sensitivity of chest x-ray in diagnosing COVID-19 pneumonia. Questions naturally arise if one should consider CTPA as a triage test due to the potential added value of evaluating for pulmonary embolism in addition to imaging the lung parenchyma, especially in patients presenting to the emergency department.

Studies evaluating the role of CTPA as a triage and universal evaluation strategy in emergency departments are limited. In a single center retrospective study in the United Kingdom, 48 patients with COVID-19 like symptoms, but without clinical concern for PE, were screened with non-contrast CT. All patients who had findings concerning for COVID-19 or RT-PCR confirmed COVID-19 underwent CTPA. Overall, there was only one positive CTPA (2%) for pulmonary embolism[31]. On the other side in one retrospective study, emergency department clinicians referred COVID-19 patients for CTPA based on clinical suspicion for PE with results showing detection of PE on CTPA in 18% of patients[32]. Of note, data from early in the pandemic in France suggested that PE's in COVID-19 positive patients typically occurred around day 6 of infection (median)[33]. Currently there are no studies to our knowledge evaluating venous ultrasound as mandatory screening in emergency room in patients with COVID-19.

Though there are many studies indicating high prevalence of VTE in COVID-19 patients, most studies were performed involving patients in the intensive care setting. Data suggests that critically ill patients are at high risk for VTE despite primary cause of that illness[34,35].

Due to the risk associated with intravenous contrast exposure, the role of CTPA as

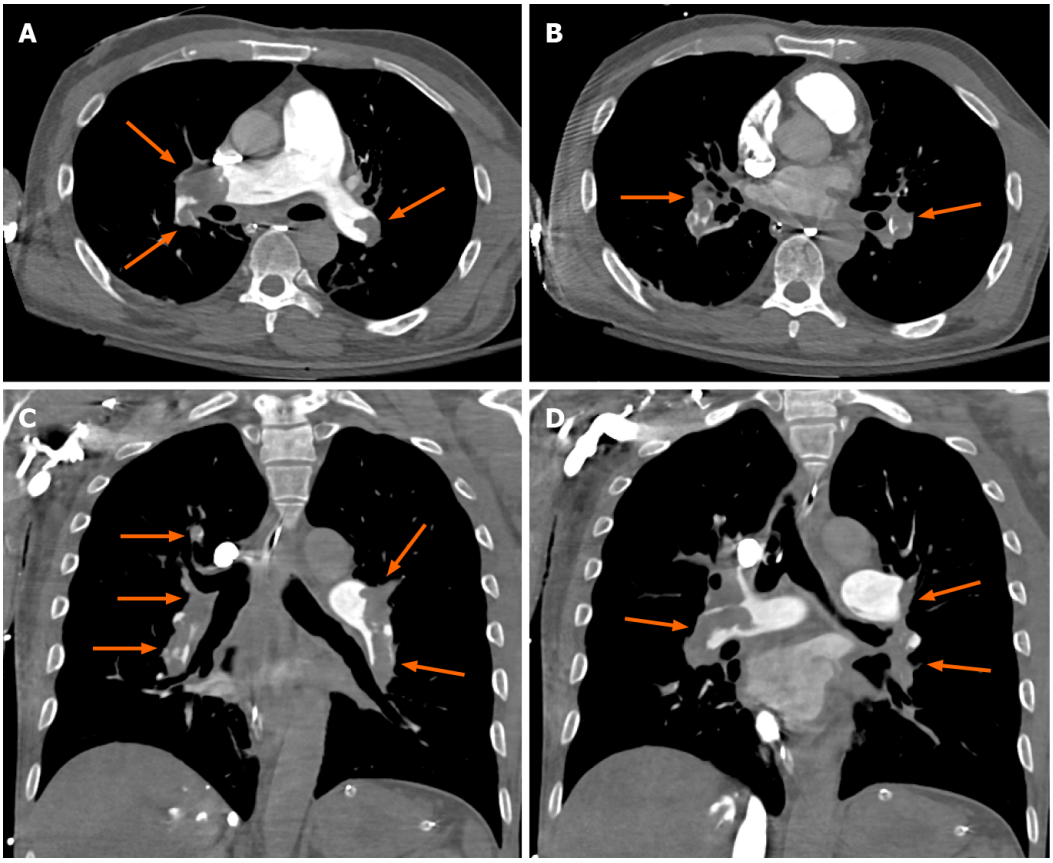


Figure 1 Computed tomography angiography images. A and B: Chest axial views; C and D: Chest coronal views. Computed tomography angiography chest axial and coronal views soft tissue window shows large hypodense filling defects in distal right and left main pulmonary arteries and all segmental pulmonary branches in both lungs (orange arrows) in a 58-year male patient with shortness of breath. Findings are compatible with bilateral extensive pulmonary embolisms.

universal testing for all emergency room or hospitalized patients with COVID-19 is not advisable. Similarly routine lower extremity ultrasound of all COVID-19 patients in emergency department does not have cost benefits and is also associated with risks, especially in regards to detecting small distal DVTs with unknown clinical significance.

A high index of clinical suspicion especially in patients with significant hypoxemia along with the use of clinical probability scores and D-dimer should be the driving factors in determining when to obtain CTPA or lower extremity ultrasound in COVID-19 patients.

SHOULD ALL PATIENTS ADMITTED TO THE HOSPITAL OR CRITICAL CARE UNITS WITH COVID-19 BE SCREENED FOR VTE?

Hospitalization due to medical illness is associated with increased risk of VTE. Critically ill patients have an even higher risk of VTE despite underlying diagnosis, with many critically ill patients unable to express their symptoms. Physical diagnosis can be challenging and usually not very high yield in diagnosis of DVT[36].

In Prophylaxis for Thromboembolism in Critical Care Trial study pre-COVID 3764 intensive care unit (ICU) patients were randomized to receive either prophylactic low molecular weight heparin, dalteparin or unfractionated heparin. Patients underwent mandatory twice weekly lower extremity ultrasound. The overall VTE rate in the study was 9.1% and DVT rate was 5.5%[37]. In a study published recently involving medical-surgical critically ill patients, twice weekly surveillance with lower extremity ultrasonography lead to 9.6% rate of DVT and was associated with higher detection of DVT compared to non-surveillance standard care group and a lower 90 d mortality (adjusted HR: 0.75, 95%CI: 0.57 to 0.98)[38].

To date, there are not many studies involving systematic screening ultrasound for detection of DVT in COVID-19 patients. In a study involving 26 critically ill patients with COVID-19, when surveillance ultrasonography was mandated, DVT rate was

close to 50%. In this study, all patients were mechanically ventilated and about 90% of patients were on vasopressor therapy[39]. Based on limited available data, some institutes and expert groups recommend screening lower extremity ultrasound for patients with COVID-19 who need ICU level care[40,41]. Factors such as size of the hospital, as well as location and local treatment cultures can play a role in which patients are cared for in ICU settings. Smaller hospitals may treat patients on high oxygen or noninvasive mechanical ventilation in intensive care units. Flow management can lead to patients spending some time in intensive care beds due to lack of availability of beds on medical wards. These factors should all be considered when making surveillance imaging decisions.

SHOULD CTPA BE PERFORMED TO EVALUATE FOR PULMONARY THROMBOEMBOLISM IF OXYGEN REQUIREMENTS SEEM OUT OF PROPORTION TO LUNG INFILTRATES OR OXYGEN REQUIREMENTS ARE INCREASING IN COVID-19 PATIENTS WITH STABLE LUNG INFILTRATES?

This is one area where there is agreement amongst most experts and professional societies. The European Society of Radiology, European Society of Thoracic Imaging and European Society of Cardiology suggested that CTPA should be performed to evaluate for pulmonary embolism in COVID-19 patients with limited extent of disease on non-contrast imaging and significant supplemental oxygen needs[42,43].

SHOULD WE GIVE THERAPEUTIC ANTICOAGULATION TO ALL MODERATE TO SEVERELY ILL PATIENTS WITH COVID-19 WITHOUT IMAGING CONFIRMATION OF VTE?

Given the prevalence of VTE in COVID-19 patients, many physicians and professional societies have contemplated the role of empiric therapeutic anticoagulation for all hospitalized COVID-19 patients. Currently, randomized data is lacking to support the use of empiric therapeutic anticoagulation even amongst critically ill patients. One recent randomized controlled trial comparing therapeutic and prophylactic enoxaparin showed therapeutic enoxaparin improved gas exchange and need for mechanical ventilation in severe COVID-19 patients[44], Many institutions have created alternate guidelines supporting the use of " intermediate" or full therapeutic anticoagulation[6]. Of course, the use of higher intensity anticoagulation comes with its own set of risks, with several small retrospective studies showing major bleeding events and even fatalities associated with its use[45]. Current guidelines recommend prophylactic dose anticoagulation for hospitalized adults with COVID-19[46]. In addition, guidelines recommend empiric treatment of suspected PE if imaging is expected to take > 4 h or for DVT if imaging is expected to take > 24 h[47]. Currently optimal dosing of intermediate anticoagulation with goal of pharmacoprophylaxis in COVID-19 patients remains unknown[48]. Randomized controlled trials are underway to answer these questions. Results of these trials will help clarify more precise use of anticoagulation strategy in near future[49]. At this point, at our institution, we do not recommend universal intermediate or therapeutic anticoagulation for all patients with COVID-19. We suggest universal pharmacologic prophylactic anticoagulation (if bleeding risk is acceptable) and maintaining a high index of clinical suspicion to help in early diagnosis of VTE events and escalation to appropriate therapeutic dosing when indicated.

WHAT IS THE ROLE OF POINT OF CARE ULTRASOUND IMAGING IN EVALUATION OF VTE IN COVID-19?

Point of care ultrasound (POCUS) in care of all patients is rapidly evolving. Currently, training in POCUS is variable across different medical institutions. Availability of good quality ultrasound machines for point of care use is an additional challenge. Evaluation of the lower extremity deep veins with POCUS for evaluation of deep

venous thrombosis is reasonable if the provider has the skills for acquisition and interpretation of images. At our institute, bedside clinicians are not trained and do not use venous ultrasound for thrombosis evaluation. Although periodic screening for deep venous thromboses in medical patients was performed in previous VTE prophylaxis efficacy trials, it has not been studied as an intervention, and, therefore, cannot be recommended[49-55]. For providers with this set of skills, however, lower extremity venous POCUS can be considered in critically ill patients with COVID-19. For patients with moderate to severe COVID-19 with hemodynamic worsening or sudden instability, POCUS use is recommended for rapid evaluation of cor pulmonale[41].

OUR APPROACH

Due to the coronavirus pandemic, a disaster preparedness group of health system experts came together to form the COVID Clinical Content Group. A new webpage on COVID care was created on the health systems website to assist providers with current evidence and local expert guidance. Evidence on risk of thrombosis and management is routinely evaluated panel of experts which include hospitalists, intensivist, vascular medicine specialist, hematologist and anticoagulation pharmacist. Consensus recommendations are posted on this webpage, and periodic educational webinars are hosted. Our current algorithm is described below (Figure 2).

CONCLUSION

VTE remains a concerning complication in patients with COVID-19 infections. Currently, there remain many unanswered questions related to imaging and anticoagulation strategies. Maintaining a high index of suspicion and use of imaging for early diagnosis of VTE without universal screening appears to be the most logical method in managing this issue until further research can be completed and validated.

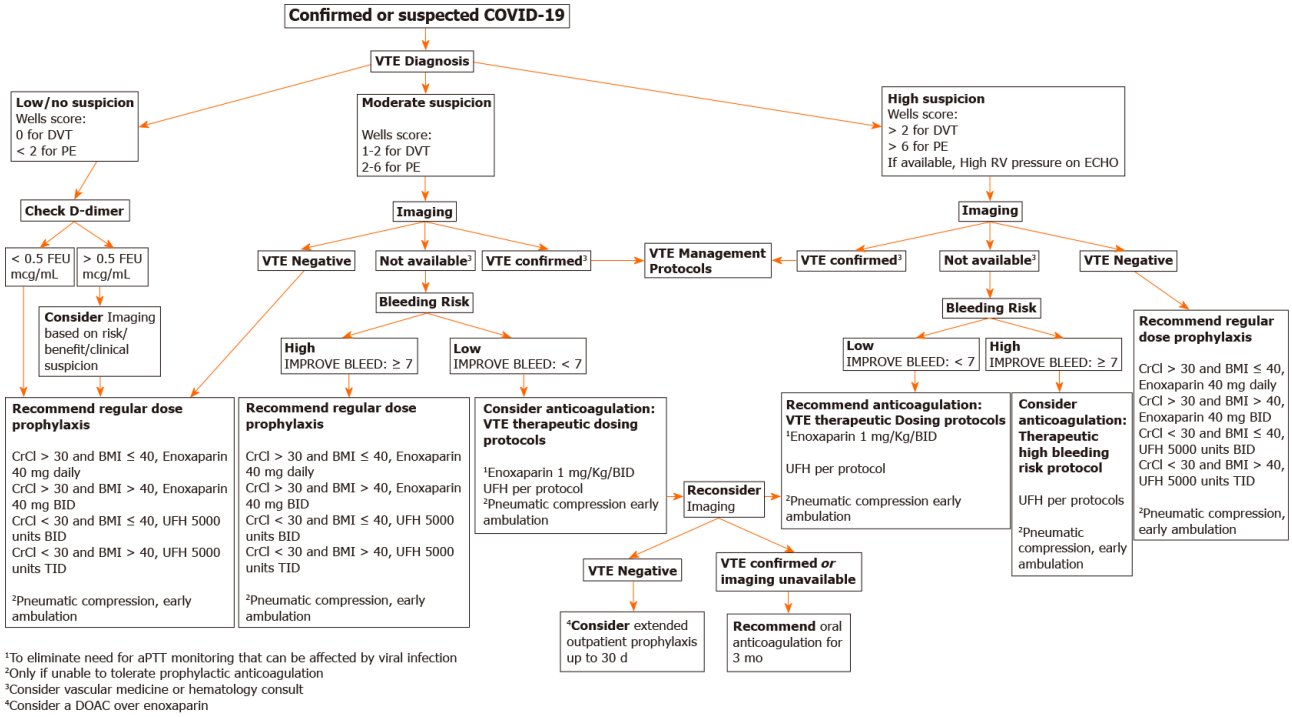


Figure 2 Diagnosis and management of venous thromboembolism in hospitalized patients with coronavirus disease-2019. COVID-19: Coronavirus disease-2019; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism.

REFERENCES

1 **COVID-19 Map - Johns Hopkins Coronavirus Resource Center**. [cited January 21, 2021]. Available from: https://coronavirus.jhu.edu

2 **Tang N**, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; **18**: 1094-1099 [PMID: 32220112 DOI: 10.1111/jth.14817]

3 **Chi G**, Lee JJ, Jamil A, Gunnam V, Najafi H, Memar Montazerin S, Shojaei F, Marszalek J. Venous Thromboembolism among Hospitalized Patients with COVID-19 Undergoing Thromboprophylaxis: A Systematic Review and Meta-Analysis. *J Clin Med* 2020; **9** [PMID: 32756383 DOI: 10.3390/jcm9082489]

4 **Poggiali E**, Bastoni D, Ioannilli E, Vercelli A, Magnacavallo A. Deep Vein Thrombosis and Pulmonary Embolism: Two Complications of COVID-19 Pneumonia? *Eur J Case Rep Intern Med* 2020; **7**: 001646 [PMID: 32399449 DOI: 10.12890/2020_001646]

5 **Smilowitz NR**, Subashchandran V, Yuriditsky E, Horowitz JM, Reynolds HR, Hochman JS, Berger JS. Thrombosis in hospitalized patients with viral respiratory infections versus COVID-19. *Am Heart J* 2021; **231**: 93-95 [PMID: 33181067 DOI: 10.1016/j.ahj.2020.10.075]

6 **Klok FA**, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; **191**: 145-147 [PMID: 32291094 DOI: 10.1016/j.thromres.2020.04.013]

7 **Cui S**, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020; **18**: 1421-1424 [PMID: 32271988 DOI: 10.1111/jth.14830]

8 **Ooi MWX**, Rajai A, Patel R, Gerova N, Godhamgaonkar V, Liong SY. Pulmonary thromboembolic disease in COVID-19 patients on CT pulmonary angiography - Prevalence, pattern of disease and relationship to D-dimer. *Eur J Radiol* 2020; **132**: 109336 [PMID: 33069986 DOI: 10.1016/j.ejrad.2020.109336]

9 **Alonso-Fernández A**, Toledo-Pons N, Cosío BG, Millán A, Calvo N, Ramón L, de Mendoza SH, Morell-García D, Bauça-Rossello JM, Núñez B, Pons J, Palmer JA, Martín L, Peñaranda M, Pou JA, Sauleda J, Sala-Llinas E. Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study. *PLoS One* 2020; **15**: e0238216 [PMID: 32841275 DOI: 10.1371/journal.pone.0238216]

10 **Liao SC**, Shao SC, Chen YT, Chen YC, Hung MJ. Incidence and mortality of pulmonary embolism in COVID-19: a systematic review and meta-analysis. *Crit Care* 2020; **24**: 464 [PMID: 32718343 DOI: 10.1186/s13054-020-03175-z]

11 **Wichmann D**, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S,

Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med* 2020; **173**: 268-277 [PMID: 32374815 DOI: 10.7326/M20-2003]

12 **Ackermann M**, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; **383**: 120-128 [PMID: 32437596 DOI: 10.1056/NEJMoa2015432]

13 **McFadyen JD**, Stevens H, Peter K. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. *Circ Res* 2020; **127**: 571-587 [PMID: 32586214 DOI: 10.1161/CIRCRESAHA.120.317447]

14 **Longchamp A**, Longchamp J, Manzocchi-Besson S, Whiting L, Haller C, Jeanneret S, Godio M, Garcia Martinez JJ, Bonjour T, Caillat M, Maitre G, Thaler JM, Pantet R, Donner V, Dumoulin A, Emonet S, Greub G, Friolet R, Robert-Ebadi H, Righini M, Sanchez B, Delaloye J. Venous thromboembolism in critically Ill patients with COVID-19: Results of a screening study for deep vein thrombosis. *Res Pract Thromb Haemost* 2020; **4**: 842-847 [PMID: 32685893 DOI: 10.1002/rth2.12376]

15 **Skeik N**, Smith JE, Patel L, Mirza AK, Manunga JM, Beddow D. Risk and Management of Venous Thromboembolism in Patients with COVID-19. *Ann Vasc Surg* 2021 [PMID: 33333197 DOI: 10.1016/j.avsg.2020.11.007]

16 **Duffett L**, Castellucci LA, Forgie MA. Pulmonary embolism: update on management and controversies. *BMJ* 2020; **370**: m2177 [PMID: 32759284 DOI: 10.1136/bmj.m2177]

17 **Ceriani E**, Combescure C, Le Gal G, Nendaz M, Perneger T, Bounameaux H, Perrier A, Righini M. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. *J Thromb Haemost* 2010; **8**: 957-970 [PMID: 20149072 DOI: 10.1111/j.1538-7836.2010.03801.x]

18 **Zotzmann V**, Lang CN, Wengenmayer T, Bemtgen X, Schmid B, Mueller-Peltzer K, Supady A, Bode C, Duerschmied D, Staudacher DL. Combining lung ultrasound and Wells score for diagnosing pulmonary embolism in critically ill COVID-19 patients. *J Thromb Thrombolysis* 2020 [PMID: 33145663 DOI: 10.1007/s11239-020-02323-0]

19 **Weitz JI**, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. *J Am Coll Cardiol* 2017; **70**: 2411-2420 [PMID: 29096812 DOI: 10.1016/j.jacc.2017.09.024]

20 **Johnson ED**, Schell JC, Rodgers GM. The D-dimer assay. *Am J Hematol* 2019; **94**: 833-839 [PMID: 30945756 DOI: 10.1002/ajh.25482]

21 **Crawford F**, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst Rev*2016: CD010864 [PMID: 27494075 DOI: 10.1002/14651858.CD010864.pub2]

22 **Wells PS**, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; **349**: 1227-1235 [PMID: 14507948 DOI: 10.1056/NEJMoa023153]

23 **Zhang JJ**, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730-1741 [PMID: 32077115 DOI: 10.1111/all.14238]

24 **Zhang L**, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020; **18**: 1324-1329 [PMID: 32306492 DOI: 10.1111/jth.14859]

25 **Rodriguez-Sevilla JJ**, Rodó-Pin A, Espallargas I, Villar-García J, Molina L, Pérez Terán P, Vázquez Sanchez A, Masclans JR, Jiménez C, Millan Segovia R, Zuccarino F, Salar A, Rodriguez-Chiaradía DA. Pulmonary Embolism in Patients With Covid-19 Pneumonia: The Utility of D-dimer. *Arch Bronconeumol* 2020; **56**: 758-759 [PMID: 32773301 DOI: 10.1016/j.arbres.2020.06.013]

26 **Artifoni M**, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, Néel A, Lecomte R. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis* 2020; **50**: 211-216 [PMID: 32451823 DOI: 10.1007/s11239-020-02146-z]

27 **Garcia-Olivé I**, Sintes H, Radua J, Abad Capa J, Rosell A. D-dimer in patients infected with COVID-19 and suspected pulmonary embolism. *Respir Med* 2020; **169**: 106023 [PMID: 32454268 DOI: 10.1016/j.rmed.2020.106023]

28 **Mos IC**, Klok FA, Kroft LJ, DE Roos A, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. *J Thromb Haemost* 2009; **7**: 1491-1498 [PMID: 19552684 DOI: 10.1111/j.1538-7836.2009.03518.x]

29 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

30 **Gandhi D**, Jain N, Khanna K, Li S, Patel L, Gupta N. Current role of imaging in COVID-19 infection with recent recommendations of point of care ultrasound in the contagion: a narrative review. *Ann Transl Med* 2020; **8**: 1094 [PMID: 33145313 DOI: 10.21037/atm-20-3043]

31 **Birk R**, Shaw D, Kennedy C, Higashi Y, Patel R, Gupta A, Au-Yong I. Low Detection Rate of Pulmonary Embolism in Patients Presenting to the Emergency Department With Suspected Coronavirus Disease 2019 (COVID-19): A Single-Centre UK Study. *Curr Probl Diagn Radiol* 2020

[PMID: 33036814 DOI: 10.1067/j.cpradiol.2020.09.014]

32 **Gervaise A**, Bouzad C, Peroux E, Helissey C. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. *Eur Radiol* 2020; **30**: 6170-6177 [PMID: 32518989 DOI: 10.1007/s00330-020-06977-5]

33 **Poissy J**, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S; Lille ICU Haemostasis COVID-19 Group. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation* 2020; B: 184-186 [PMID: 32330083 DOI: 10.1161/CIRCULATIONAHA.120.047430]

34 **Helms J**, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; **46**: 1089-1098 [PMID: 32367170 DOI: 10.1007/s00134-020-06062-x]

35 **Bompard F**, Monnier H, Saab I, Tordjman M, Abdoul H, Fournier L, Sanchez O, Lorut C, Chassagnon G, Revel MP. Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J* 2020; **56** [PMID: 32398297 DOI: 10.1183/13993003.01365-2020]

36 **Ambesh P**, Obiagwu C, Shetty V. Homan's sign for deep vein thrombosis: A grain of salt? *Indian Heart J* 2017; **69**: 418-419 [PMID: 28648447 DOI: 10.1016/j.ihj.2017.01.013]

37 **PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group**, Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, Vallance S, Qushmaq I, Rocha M, Berwanger O, Vlahakis NE. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011; **364**: 1305-1314 [PMID: 21417952 DOI: 10.1056/NEJMoa1014475]

38 **Arabi YM**, Burns KEA, Alsolamy SJ, Alshahrani MS, Al-Hameed FM, Arshad Z, Almaani M, Hawa H, Mandourah Y, Almekhlafi GA, Al Aithan A, Khalid I, Rifai J, Rasool G, Abdukahil SAI, Jose J, Afesh LY, Al-Dawood A; Saudi Critical Care Trials Group. Surveillance or no surveillance ultrasonography for deep vein thrombosis and outcomes of critically ill patients: a pre-planned sub-study of the PREVENT trial. *Intensive Care Med* 2020; **46**: 737-746 [PMID: 32095845 DOI: 10.1007/s00134-019-05899-1]

39 **Llitjos JF**, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020; **18**: 1743-1746 [PMID: 32320517 DOI: 10.1111/jth.14869]

40 **McBane RD 2nd**, Torres Roldan VD, Niven AS, Pruthi RK, Franco PM, Linderbaum JA, Casanegra AI, Oyen LJ, Houghton DE, Marshall AL, Ou NN, Siegel JL, Wysokinski WE, Padrnos LJ, Rivera CE, Flo GL, Shamoun FE, Silvers SM, Nayfeh T, Urtecho M, Shah S, Benkhadra R, Saadi SM, Firwana M, Jawaid T, Amin M, Prokop LJ, Murad MH. Anticoagulation in COVID-19: A Systematic Review, Meta-analysis, and Rapid Guidance From Mayo Clinic. *Mayo Clin Proc* 2020; **95**: 2467-2486 [PMID: 33153635 DOI: 10.1016/j.mayocp.2020.08.030]

41 **Hussain A**, Via G, Melniker L, Goffi A, Tavazzi G, Neri L, Villen T, Hoppmann R, Mojoli F, Noble V, Zieleskiewicz L, Blanco P, Ma IWY, Wahab MA, Alsaawi A, Al Salamah M, Balik M, Barca D, Bendjelid K, Bouhemad B, Bravo-Figueroa P, Breitkreutz R, Calderon J, Connolly J, Copetti R, Corradi F, Dean AJ, Denault A, Govil D, Graci C, Ha YR, Hurtado L, Kameda T, Lanspa M, Laursen CB, Lee F, Liu R, Meineri M, Montorfano M, Nazerian P, Nelson BP, Neskovic AN, Nogue R, Osman A, Pazeli J, Pereira-Junior E, Petrovic T, Pivetta E, Poelaert J, Price S, Prosen G, Rodriguez S, Rola P, Royse C, Chen YT, Wells M, Wong A, Xiaoting W, Zhen W, Arabi Y. Multi-organ point-of-care ultrasound for COVID-19 (PoCUS4COVID): international expert consensus. *Crit Care* 2020; **24**: 702 [PMID: 33357240 DOI: 10.1186/s13054-020-03369-5]

42 **The European Society for Cardiology**. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. [cited January 21, 2021]. Available from: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESCCOVID-19-Guidance

43 **Revel MP**, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A; European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; **30**: 4903-4909 [PMID: 32314058 DOI: 10.1007/s00330-020-06865-y]

44 **Lemos ACB**, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, Miranda CH. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thromb Res* 2020; **196**: 359-366 [PMID: 32977137 DOI: 10.1016/j.thromres.2020.09.026]

45 **Al-Samkari H**, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020; **136**: 489-500 [PMID: 32492712 DOI: 10.1182/blood.2020006520]

46 **NIH**. COVID-19 Treatment Guidelines. [cited January 21, 2021]. Available from: http://www.covid19treatmentguidelines.nih.gov

47 **Obi AT**, Barnes GD, Wakefield TW, Brown S, Eliason JL, Arndt E, Henke PK. Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. *J Vasc Surg*

Venous Lymphat Disord 2020; **8**: 526-534 [PMID: 32305585 DOI: 10.1016/j.jvsv.2020.04.009]

48 **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]

49 **Talasaz AH**, Sadeghipour P, Kakavand H, Aghakouchakzadeh M, Kordzadeh-Kermani E, Van Tassell BW, Gheymati A, Ariannejad, Hosseini SH, Jamalkhani S, Sholzberg M, Monreal M, Jimenez D, Piazza G, Parikh SA, Kirtane A, Eikelboom JW, Connors JM, Hunt BJ, Konstantinides SV, Cushman M, Weitz JI, Stone GW, Krumholz PM, Lip GYH, Goldhaber SZ, Bikdeli B. Antithrombotic Therapy in COVID-19: Systematic Summary of Ongoing or Completed Randomized Trials. *medRxiv* 2021.01.04. 21249227 [DOI: 10.1101/2021.01.04.21249227]

50 **Cook D**, Crowther M, Meade M, Rabbat C, Griffith L, Schiff D, Geerts W, Guyatt G. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Crit Care Med* 2005; 33: 1565-1571 [PMID: 16003063 DOI: 10.1097/01.ccm.0000171207.95319.b2]

51 **Samama MM**, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weisslinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999; **341**: 793-800 [PMID: 10477777 DOI: 10.1056/NEJM199909093411103]

52 **Khouli H**, Shapiro J, Pham VP, Arfaei A, Esan O, Jean R, Homel P. Efficacy of deep venous thrombosis prophylaxis in the medical intensive care unit. *J Intensive Care Med* 2006; **21**: 352-358 [PMID: 17095499 DOI: 10.1177/0885066606292880]

53 **Leizorovicz A**, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ; PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; **110**: 874-879 [PMID: 15289368 DOI: 10.1161/01.CIR.0000138928.83266.24]

54 **Cohen AT**, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, Turpie AG, Egberts JF, Lensing AW; ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006; **332**: 325-329 [PMID: 16439370 DOI: 10.1136/bmj.38733.466748.7C]

55 **Goldhaber SZ**, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JI; ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011; **365**: 2167-2177 [PMID: 22077144 DOI: 10.1056/NEJMoa1110899]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 April 28; 13(4): 75-101

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 4 April 28, 2021

EVIDENCE REVIEW

MINIREVIEWS

World Journal of Radiology

Monthly Volume 13 Number 4 April 28, 2021

Contents

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
April 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 April 28; 13(4): 75-93

DOI: 10.4329/wjr.v13.i4.75

ISSN 1949-8470 (online)

EVIDENCE REVIEW

Discrepancies in the clinical and radiological profiles of COVID-19: A case-based discussion and review of literature

Hemant Kumar, Cornelius James Fernandez, Sangeetha Kolpattil, Mohamed Munavvar, Joseph M Pappachan

ORCID number: Hemant Kumar 0000-0001-9689-7235; Cornelius James Fernandez 0000-0003-0886-5222; Sangheetha Kolpattil 0000-0003-0886-5223; Mohamed Munavvar 0000-0003-0886-5234; Joseph M Pappachan 0000-0003-0886-5255.

Author contributions: Kumar H and Fernandez CJ performed majority of the initial drafting, prepared the figures and tables, and share the first authorship of the paper; Kolpattil S and Munavvar M did additional literature search, and made critical revisions in the write up; Pappachan JM conceived the idea, made critical revisions, and provided final approval of the final version of the manuscript to be published.

Conflict-of-interest statement: Dr. Pappachan and coauthors have nothing to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the

Hemant Kumar, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TH, United Kingdom

Cornelius James Fernandez, Department of Medicine & Endocrinology, Pilgrim Hospital, Boston PE21 9QS, United Kingdom

Sangeetha Kolpattil, Department of Radiology, University Hospitals of Morecambe Bay NHS Trust, Lancaster LA1 4RP, United Kingdom

Mohamed Munavvar, Department of Pulmonology & Chest Diseases, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9HT, United Kingdom

Joseph M Pappachan, Department of Medicine & Endocrinology, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9HT, United Kingdom

Joseph M Pappachan, Faculty of Science, Manchester Metropolitan University, Manchester M15 6BH, United Kingdom

Joseph M Pappachan, Faculty of Biology, Medicine & Health, The University of Manchester, Manchester M13 9PL, United Kingdom

Corresponding author: Joseph M Pappachan, MD, FRCP, Consultant Physician-Scientist, Honorary Professor, Senior Researcher, Department of Medicine & Endocrinology, Lancashire Teaching Hospitals NHS Trust, Sharoe Green Lane, Preston PR2 9HT, United Kingdom. drpappachan@yahoo.co.in

Abstract

The current gold standard for the diagnosis of coronavirus disease-19 (COVID-19) is a positive reverse transcriptase polymerase chain reaction (RT-PCR) test, on the background of clinical suspicion. However, RT-PCR has its limitations; this includes issues of low sensitivity, sampling errors and appropriate timing of specimen collection. As pulmonary involvement is the most common manifestation of severe COVID-19, early and appropriate lung imaging is important to aid diagnosis. However, gross discrepancies can occur between the clinical and imaging findings in patients with COVID-19, which can mislead clinicians in their decision making. Although chest X-ray (CXR) has a low sensitivity for the diagnosis of COVID-19 associated lung disease, especially in the earlier stages, a positive CXR increases the pre-test probability of COVID-19. CXR scoring systems have shown to be useful, such as the COVID-19 opacification rating score which

original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: United Kingdom

Peer-review report's scientific quality classification

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

Received: December 16, 2020
Peer-review started: December 16, 2020
First decision: March 31, 2021
Revised: April 3, 2021
Accepted: April 13, 2021
Article in press: April 13, 2021
Published online: April 28, 2021

P-Reviewer: Wang X
S-Editor: Zhang H
L-Editor: A
P-Editor: Yuan YY

helps to predict the need of tracheal intubation. Furthermore, artificial intelligence-based algorithms have also shown promise in differentiating COVID-19 pneumonia on CXR from other lung diseases. Although costlier than CXR, unenhanced computed tomographic (CT) chest scans have a higher sensitivity, but lesser specificity compared to RT-PCR for the diagnosis of COVID-19 pneumonia. A semi-quantitative CT scoring system has been shown to predict short-term mortality. The routine use of CT pulmonary angiography as a first-line imaging modality in patients with suspected COVID-19 is not justifiable due to the risk of contrast nephropathy. Scoring systems similar to those pioneered in CXR and CT can be used to effectively plan and manage hospital resources such as ventilators. Lung ultrasound is useful in the assessment of critically ill COVID-19 patients in the hands of an experienced operator. Moreover, it is a convenient tool to monitor disease progression, as it is cheap, non-invasive, easily accessible and easy to sterilise. Newer lung imaging modalities such as magnetic resonance imaging (MRI) for safe imaging among children, adolescents and pregnant women are rapidly evolving. Imaging modalities are also essential for evaluating the extra-pulmonary manifestations of COVID-19: these include cranial imaging with CT or MRI; cardiac imaging with ultrasonography (US), CT and MRI; and abdominal imaging with US or CT. This review critically analyses the utility of each imaging modality to empower clinicians to use them appropriately in the management of patients with COVID-19 infection.

Key Words: COVID-19; Pneumonia; Lung imaging; Chest X-ray; Computed tomography; Lung ultrasound

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The coronavirus disease-19 (COVID-19) pandemic has had a devastating impact on the human race, with the current death toll exceeding 2.8 million. Although a positive reverse transcriptase polymerase chain reaction test is the gold standard for diagnosing a COVID-19 infection, the reported sensitivity of the test is < 90%, and clinicians often need to rely upon various imaging studies for definitive diagnoses and prognostication. However, discrepancies between the clinical and imaging profiles of patients with the disease can often pose challenges in therapeutic decision making. Therefore, it is imperative to understand the diagnostic sensitivity, specificity, and positive and negative predictive values of each imaging modality for the rational management of patients with this enigmatic disease. This evidence-based review is a clinical update to empower clinicians across the world who is involved in combatting COVID-19.

Citation: Kumar H, Fernandez CJ, Kolpattil S, Munavvar M, Pappachan JM. Discrepancies in the clinical and radiological profiles of COVID-19: A case-based discussion and review of literature. *World J Radiol* 2021; 13(4): 75-93
URL: https://www.wjgnet.com/1949-8470/full/v13/i4/75.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i4.75

INTRODUCTION

The mega-pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more commonly referred to as coronavirus disease-2019 (COVID-19), continues to hit the global population even after 16 mo of its first report from China in December 2019. As of April 2021, the total death toll exceeds 2.84 million worldwide. Although COVID-19 can affect any organ system in the human body, the most clinically severe cases often have a constellation of pneumonia, acute respiratory distress syndrome (ARDS), septic shock, acute kidney injury, diarrhoea, rhabdomyolysis, and disseminated intravascular coagulation[1]. Because of the mild nature of COVID-19 in most patients, the early diagnosis of severe illness is important for optimal treatment and appropriate utilisation of resources to prevent overstrain on the

global healthcare systems. Since dyspnoea and pulmonary involvement are the most common manifestations of severe COVID-19, appropriate and early lung imaging is important not only for diagnostic evaluation, but also for prognostication[2,3]. In addition, the imaging of other visceral organs may also become necessary for the diagnosis of extra-pulmonary diseases and complications related to COVID-19[4-6].

However, many of the imaging findings in COVID-19 can be nonspecific, and there can be occasional discrepancies between the imaging and clinical features seen in these patients[7,8]. Moreover, on occasions, extrapulmonary disease may dominate in some patients, and pre-existing major illnesses (such as heart failure, liver diseases, chronic kidney disease and malignancies) with the acquisition of COVID-19 illness may pose additional diagnostic dilemmas[9-14]. Therefore, it is important to review the sensitivity, specificity, positive and negative predictive values of each imaging technique used for the diagnosis of COVID-19 cases, and to identify the discordance that can exist between clinical and imaging features for the optimal care of patients with the disease. In this evidence-based review, we discuss these discrepancies that clinicians should be aware of, in order to manage patients with COVID-19, with the aid of three clinical case scenarios.

Case 1

A 46-year-old male without any major past medical illness attends the emergency department (ED) with history of fever, dry cough, and intermittent dyspnoea over the past three days. His pulse oximetry showed an oxygen saturation of 92% while breathing ambient air, with an arterial blood gas analysis showing mild hypoxaemia (PaO_2 9.3 kPa, $PaCO_2$ 3.82 kPa and pH 7.47). A chest X-ray (CXR) showed bilateral extensive airspace disease (Figure 1A). His full blood count showed neutrophilic leucocytosis with lymphopenia and the C-reactive protein (CRP) was elevated (232 units/L; normal < 7). The reverse transcriptase polymerase chain reaction (RT-PCR) test was positive for SARS-CoV-2 RNA confirming COVID-19 pneumonia. Management with oxygen at 2 L/minute through nasal cannula and oral dexamethasone 6 mg daily was commenced, as per the hospital protocol. This resulted in a rapid resolution of his hypoxaemia and he was discharged home on the third day of admission. A subsequent chest radiograph after 8 wk showed complete resolution of the pulmonary findings (Figure 1B).

Case 2

A 62-year-old lady with poorly controlled type 2 diabetes mellitus and hypertension presents at the ED with fever, loss of smell and taste, dry cough, and progressive dyspnoea in the past 2 d. Her pulse oximetry showed an oxygen saturation of 84% while breathing ambient air with an arterial gas analysis showing type 1 respiratory failure (PaO_2 6.3 kPa, $PaCO_2$ 5.12 kPa and pH 7.38). A CXR was unremarkable (Figure 2A). Her full blood count showed lymphopenia without neutrophilia and CRP was 86 units/L. The RT-PCR was positive for SARS-CoV-2 RNA confirming COVID-19 infection. As the D-dimer was high (8.3 μg/mL; normal < 0.5 μg/mL) with disproportionate hypoxaemia and a normal CXR, an urgent computed tomography (CT) pulmonary angiogram (CTPA) was done which excluded pulmonary embolism (PE), but CTPA showed evidence of bilateral COVID-19 pneumonia (Figure 2B). The patient was managed with 40% oxygen *via* a Venturi mask, intravenous insulin infusion, and oral dexamethasone 6 mg daily. The patient's hypoxaemia worsened on the next day requiring invasive ventilation and subsequently died in the intensive care unit on the 6th day with multi-organ failure.

Case 3

A 52-year-old lady with a history of well-controlled asthma and hypertension presented to the ED with a productive cough and breathlessness for 2 wk. Her pulse oximetry showed an oxygen saturation of 93% while on 40% oxygen *via* a Venturi mask. The arterial blood gas analysis showed type 1 respiratory failure (pH 7.43, PO_2 7.34 kPa, and PCO_2 5.09 kPa). There was lymphopenia (0.56×10^9/L) without neutrophilia and the CRP was 112 units/L. The RT-PCR test was positive and the CXR showed bilateral lower zone opacities (Figure 3A). She was treated with oxygen, doxycycline, and prophylactic enoxaparin and was discharged in 4 d. One week later she presented with syncope, severe breathlessness, chest tightness, tachycardia, hypoxia, and hypotension. Troponin I was raised at 205 ng/L (5-14 ng/L), along with a raised D-dimer of 6.26 μg/mL. The repeat CXR showed improving bibasilar infiltrates (Figure 3B). The CTPA showed bilateral extensive thromboembolism in the pulmonary arterial branches (Figure 3C), along with evidence of resolving COVID-19

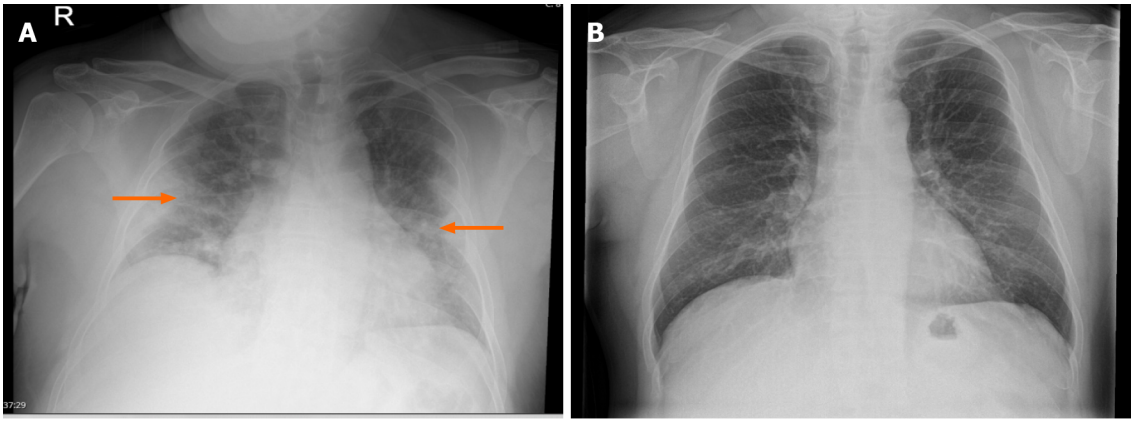


Figure 1 Case 1. A: Chest radiograph (CXR) at the time of admission showing bilateral extensive airspace opacities (arrows); B: The CXR at 8 wk showing complete resolution of pulmonary opacities.

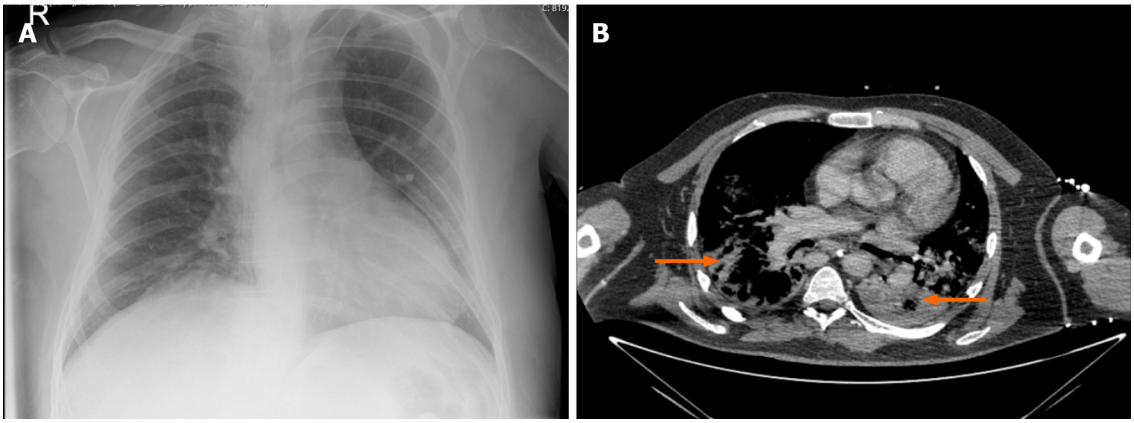


Figure 2 Case 2. A: The unremarkable chest radiograph at the time of admission; B: Computed tomographic pulmonary angiography showing evidence of bilateral coronavirus disease-19 pneumonia (arrows).

pneumonia (Figure 3D; lung window). She underwent thrombolysis with recombinant tissue plasminogen activator, followed by therapeutic enoxaparin for an initial 4 d. She was discharged on rivaroxaban 15 mg twice daily for 21 d, followed by 20 mg once daily for 3 more mo.

These cases illustrate some of the discrepancies between the clinical and imaging features of COVID-19. We aim to update the current evidence on the concordance and discordance between imaging and clinical profiles of the disease to empower clinicians fighting against the pandemic.

INTRODUCTION TO IMAGING STUDIES IN THE DIAGNOSIS OF COVID-19

The current gold standard for the diagnosis of COVID-19 is a positive RT-PCR test on the background of clinical suspicion. The usefulness of RT-PCR as a reference standard is limited due to its low sensitivity, sampling errors and the impact of timing of specimen collection[15]. RT-PCR testing from a single nasopharyngeal swab in a patient with COVID-19 like symptoms has sensitivity of 87%, specificity of 97%, positive predictive value (PPV) of 98% and negative predictive value (NPV) of 80%[16]. Because of the lower sensitivity, or when RT-PCR is unavailable, imaging tests have been used to aid in the diagnosis of COVID-19.

Another major challenge to combating the disease is its unpredictable clinical course. There is a heterogeneity in presentations, ranging from asymptomatic patients to those with critical illness, with no available prognostic biomarker to effectively triage different cohorts[17]. Nearly 40% of transmission is attributed to asymptomatic or pre-symptomatic carriers[18,19]. These asymptomatic infected individuals present unique challenges since they may not seek medical attention, thus leading to a failure of

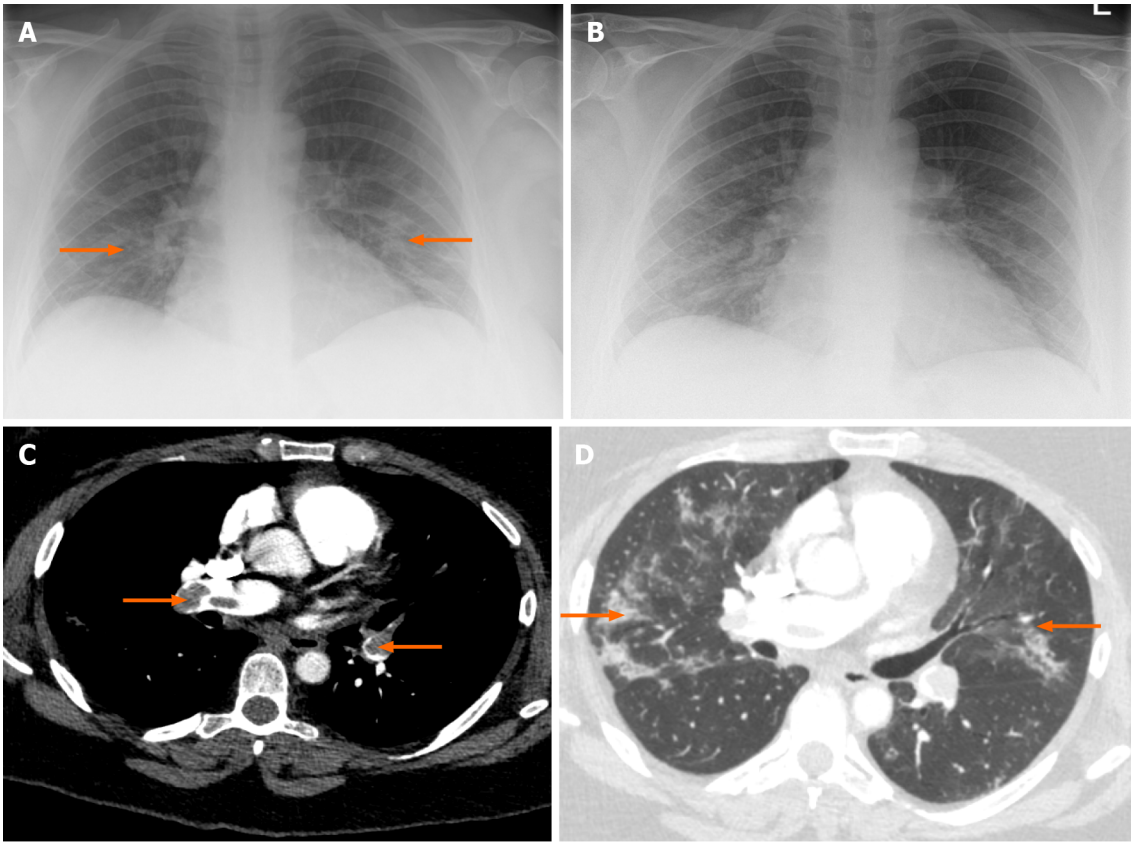


Figure 3 Case 3. A: The chest radiograph (CXR) at the time of admission showing mild bilateral opacities (arrows); B: CXR on 2nd admission with improving bibasilar lung infiltrates; C: Computed tomographic pulmonary angiogram (CTPA) of case 3 showing evidence of extensive pulmonary embolism (arrows); D: The CTPA lung window showing resolving coronavirus disease-19 pneumonia (arrows).

interventions that solely rely on identifying symptomatic cases. There have been some notable studies that investigate imaging in both symptomatic and asymptomatic COVID-19 positive cohorts, to assess any clinically significant findings which may guide appropriate management (discussed below).

Although imaging is often imperative for diagnosing, triaging and guiding management, there are some drawbacks. There may be hazards of radiation exposure, risk of COVID-19 transmission through contaminated equipment and consumption of personal protective equipment (PPE), all in the context of global resource constraints. The following section investigates the appropriate use of imaging in the assessment of different COVID-19 related pathologies, to explore the discrepancies between imaging findings and clinical presentation.

IMAGING FOR PULMONARY MANIFESTATIONS OF COVID-19

Chest X-ray

Chest radiographs are routinely used at the time of initial triage to assess for disease severity in the context of respiratory tract infections. Although systematic reviews have found that CXRs in lower respiratory tract infections do not lead to an improvement in clinical outcome, it is unclear what its role may be in COVID-19 patients[20]. CXRs are more readily accessible than other imaging modalities and are associated with lower costs. It also allows an immediate assessment of more serious pulmonary pathologies such as pneumothorax, pulmonary oedema, pleural effusions, lung collapse and masses, although an accurate interpretation may be confounded by cardiopulmonary co-morbidities. Furthermore, the disinfection protocols for X-Ray machines are more streamlined than other bulkier systems, such as CT, or magnetic resonance imaging (MRI), which is an advantage in the era of COVID-19 disinfection protocols.

Pormohammad *et al*[21], conducted a systematic review to compare the laboratory and radiographic findings along with outcomes of different corona viruses [(COVID-

19, SARS, and Middle East respiratory syndrome (MERS)]. 52251 COVID-19 cases, 10037 SARS cases and 8139 MERS cases were included in the meta-analysis and it was seen that 85.6% of COVID-19 patients, 96% of SARS and 74% of MERS had fever at time of presentation. Cough was the presenting complaint in 63% in COVID-19 cases, 54% in SARS and 61% in MERS. Severe complications such as ARDS were found in 51% of SARS, 29% of MERS and 10.6% of COVID-19 patients. With regards to chest imaging, abnormal findings were seen in a large majority of patients with all corona viruses; 84% in COVID-19, 86% in SARS and 74% in MERS. The most pertinent findings in COVID-19 patients were bilateral distribution of consolidation (76%), ground glass opacities (71%), and bilateral lung involvement (77%). Unilateral lung involvement was comparatively uncommon and was observed in 16.5% of cases. Interestingly, there were no distinguishing imaging features between different corona viruses. Between the three diseases, COVID-19 had been more contagious, thus resulted in a higher number of deaths despite its lower overall mortality rate[21].

As CXR can be normal in up to 63% of patients with COVID-19 related lung disease, a normal CXR does not exclude it[22]. Typical appearances in CXR with high specificity for COVID-19 pneumonia are bilateral lower zone predominance and peripheral multifocal opacities, which could be in the form of ground glass opacities or GGO (68.5%), horizontal coarse linear opacities, or consolidation. The GGOs were shown to occur early in the disease course, and it might later progress to consolidation. The involvement is bilateral in 72.9%. However, it can be unilateral in 25% of patients with COVID-19 pneumonia[22]. However, similar CXR findings can occur in other viral pneumonias like influenza pneumonia, organizing pneumonia or with drug reactions. Non-specific appearances that are not commonly found in COVID-19 pneumonia include unilateral perihilar opacities, diffuse involvement (without zonal preference), upper zone predominance, lymphadenopathy, cavitation, or pleural effusion with Kerley B lines.

An international panel of thoracic imaging experts released a statement during the pandemic for the use of CXR, CT and ultrasound in both suspected and confirmed COVID-19 patients[23]. The consensus on the use of CXR is that it cannot reliably exclude COVID-19 in suspected patients, particularly in the early stages of the disease. Although CXR has a low sensitivity (69%) for the diagnosis of COVID-19 because of the non-specific imaging features, a positive CXR increases the clinical pre-test probability of COVID-19 infection[23]. As mentioned earlier, CXRs are effective at excluding other more sinister diagnoses that may be the cause of the patient's symptoms, which may require more immediate medical attention. CXR is not recommended for patients with mild symptoms, as it is often going to be normal in these patients, leading to a false reassurance. Thus, the timing of investigation is very important, and early investigations will often yield false-negative results. The panel also advocated a standardised reporting structure and terminology for CXRs for those with suspected or confirmed COVID-19 cases, which will be helpful in comparing findings of different studies and between different regions[23].

An Italian study by Schiaffino *et al*[24], observed that in comparison to RT-PCR for the diagnosis of COVID-19 pneumonia, CXR had a sensitivity of 89.0% (95%CI: 85.5%-91.8%), specificity of 60.6% (95%CI: 51.6%-69.2%), PPV of 87.9% (95%CI: 84.4%-90.9%), and NPV of 63.1% (95%CI: 53.9%-71.7%). A Cochrane database systematic review by Salameh *et al*[15] observed that, in patients with confirmed COVID-19, the pooled sensitivity of CXR is 82.1% (95%CI: 62.5%-92.7%). Another Cochrane review by Islam *et al*[25] reported that, in patients with suspected COVID-19, the CXR has a sensitivity ranging from 56.9%-89.0% and specificity ranging from 11.1%-88.9%. However, neither group could perform a meta-analysis due to limited number of studies found[15,25].

Artificial intelligence-based algorithms have also been investigated, which showed that it can be used with higher sensitivity and specificity for the differentiation between COVID-19 pneumonia and non-COVID-19 pneumonia on CXR[26,27]. In one such study by Zhang *et al*[27], a sensitivity of 88% (95%CI: 87%-89%) and specificity of 79% (95%CI: 77%-80%) is achieved using a high sensitivity operating threshold. Similarly, the authors reported a sensitivity of 78% (95%CI: 77%-79%) and specificity of 89% (95%CI: 88%-90%) using a high specificity operating threshold.

A study by Xiao *et al*[28] explored ways to objectively assess CXRs of COVID-19 positive patients at the time of admission. The authors also assessed any correlation of CXR severity and time to intubation. Their methods involved assigning a COVID-19 opacification rating score (CORS) by dividing the lung fields on the CXR into 12 zones and counting the total number of zones showing opacity. Out of the 140 patients included in the study, 48% of patients had a CORS ≥ 6, and this was a statistically significant predictor of higher rates of intubation (OR 6.1, 95%CI: 2.1-18.1, $P < 0.001$). Patients with CORS ≥ 6 had an intubation rate of 46%, whereas only 14% were

intubated with CORS < 6. There were no significant correlations between a higher CORS and age, sex, body mass index or underlying cardiopulmonary comorbidities. Inter-rater agreement in cases of CORS ≥ 6 was noted to be moderate/substantial (κ = 0.65), suggesting the scoring system was reproducible between radiographers. The findings of this study show a reliable predictor of early intubation using an objective scoring method[28]. CORS or similar scoring criteria could have a role in reliably triaging patients with regards to planned intubation to make effective use of hospital resources such as ventilators. Although this may not correlate with clinical symptoms, it is a useful prognostic tool for risk of intubation.

Chest CT

CT scans have been shown to be a useful first-line screening method since their sensitivity has been reported as high as 98%, as opposed to the relatively low sensitivity of the RT-PCR test (can be as low as 71%)[29,30]. Consequently, patients are seen to exhibit positive CT findings even with negative RT-PCR tests, thus highlighting a role in addressing the RT-PCR false-negative cohort[31]. CT chest scans have also shown to add value in prognostic information; reports show that asymptomatic cases with normal chest CTs have shorter periods from diagnosis to being COVID-negative, than cases with positive CT findings[32]. The limitation with this modality includes an increased exposure to radiation, higher costs, nephrotoxic contrast media, and a more time-consuming disinfection protocol.

A review into the imaging findings of COVID-19 found that CT was more sensitive than chest radiographs, and offers more unique findings which allows it to be useful even in the early disease stages[33]. The typical findings observed include multifocal GGOs in the subpleural regions, patchy consolidation in the posterior and lower lobes which can develop into a crazy-paving pattern in later disease stages due to thickening of the interlobular or intralobular septum, and reverse CT halo sign (which are characteristic of the organizing pneumonia). Atypical findings include lung nodules, cavitation, pleural effusions, and lymphadenopathy[33-36]. There have also been reports that findings of GGO are more common than consolidation in asymptomatic cases, whereas the opposite was observed in symptomatic patients[37]. The sensitivity and specificity for the diagnosis of COVID-19 using CT scans is highest if GGO is observed simultaneously to one or more of the other aforementioned CT features (specificity: 89%, sensitivity: 90%)[38]. The diagnostic odds ratio of GGO with at least one other feature is reported as 20, and is significantly higher than any sign in singularity.

Unenhanced CT chest scans may be considered as the best imaging modality to assess the extent of pulmonary involvement in patients with suspected COVID-19 pneumonia[39,40]. The COVID-19 Reporting And Data System is a categorical CT assessment scheme based on unenhanced CT chest in patients with suspected COVID-19 infection, where the level of suspicion increases from very low to very high. A summary of CT observations and their interpretation, as well as classifications into various categories, is given in Table 1[41].

However, some suggest that CT imaging findings may not correlate with symptomatology. Nearly 54% patients showed a normal CT scan within 2 d of symptom onset, indicating that a negative CT scan should not exclude COVID-19 in patients that have relevant symptoms and exposure[42]. In some cases, an initially negative CT scan within 2 d of symptom onset would become positive when repeated at a later stage[33]. Another review that investigated the CT findings in asymptomatic COVID-19 positive cases showed that among 63% of patients who had positive CT findings, 58% remained asymptomatic, however the remainder developed the symptoms[43]. Out of those who developed symptoms, 90% had previously shown positive CT scans. This important study proves the need for close clinical monitoring of asymptomatic cases with radiographic findings since a significant percentage will become symptomatic.

Although CT scans are more effective in identifying COVID-19 related changes than CXR in the early disease stages, it still has limited sensitivity and negative predicative value for ruling out COVID-19 infection. A Cochrane database systematic review by Salameh *et al*[15], observed that, in patients with confirmed COVID-19, the CT chest has a pooled sensitivity of 93.1% (95%CI: 90.2-95.0), though the studies had considerable heterogeneity. However, in suspected cases where CT scans were used as a first-line diagnostic test, the sensitivity was 86.2% (95%CI: 71.9-93.8), and the specificity was only 18.1% (95%CI: 3.71-55.8) with a high degree of heterogeneity. A subsequent Cochrane review by the same group observed similar findings with a pooled sensitivity of 89.9% (95%CI: 85.7-92.9), and a pooled specificity of 61.1% (95%CI: 42.3-77.1), in patients with suspected COVID-19[25]. These systematic reviews indicate that, in suspected patients, CT chest may not be able to differentiate COVID-19 from other respiratory illnesses. Therefore, CT chest should not be used as a stand-alone tool for

Table 1 Coronavirus disease-19 Reporting and Data System category of computed tomography reporting and the level of suspicion for coronavirus disease-19[41]

Category	Level of suspicion	Summary of CT observation and interpretation
CO-RADS 0	Cannot interpret	Due to technically insufficient CT scan
CO-RADS 1	Very low	Normal CT chest or non-infectious CT chest
CO-RADS 2	Low	Typical for other infections like lobar consolidation
CO-RADS 3	Equivocal	Features compatible with COVID-19 & other infections
CO-RADS 4	High	Suspicious CT features of COVID-19
CO-RADS 5	Very high	Typical CT features of COVID-19
CO-RADS 6	Proven (RT-PCR)	RT-PCT positive for SARS-CoV-2 RNA

CT: Computed tomography; CO-RADS: Coronavirus disease-19 Reporting and Data System; COVID-19: Coronavirus disease-19; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Reverse transcriptase polymerase chain reaction.

an early assessment of COVID-19 status and, in an ideal setting, may be best used in combination with RT-PCR. This would accommodate for the low sensitivity of RT-PCR, thus giving a more holistic approach for COVID-19 diagnoses. Similarly, CT chest scans can also be used in those patients with negative RT-PCR, but with typical symptoms of COVID-19, to address the false-negative cohort.

The reduced specificity of the CT scans could partly be due to the lower sensitivity of the reference standard (RT-PCR). A systematic review by Kovács *et al*[44], observed that CT chest has a high sensitivity (67%-100%), and low specificity (25%-80%), whereas the RT-PCR has only a modest sensitivity (53%-88%). They applied a reverse calculation approach, after considering CT chest as a hypothetical gold standard. The reverse calculation approach showed that CT could have a higher specificity (83%-100%), once the modest sensitivity of RT-PCR is considered. Similarly, an Italian study by Falaschi *et al*[45], observed that, when compared to RT-PCR, CT chest has a sensitivity, specificity, PPV, NPV, and accuracy of 90.7%, 78.8%, 86.4%, 85.1% and 85.9%, respectively. A recent French study by Herpe *et al*[46], observed that CT chest has a sensitivity of 90% (95%CI: 89%-91%), specificity of 91% (95%CI: 91%-92%), PPV of 89% (95%CI: 87%-90%), and NPV of 92% (95%CI: 91%-93%), when compared to RT-PCR.

Furthermore, CT scans can be utilised to closely monitor disease progression since imaging features have been observed to follow a predictable time course. Following symptom onset, the severity of CT findings progresses rapidly to peak at 6-11 d, from which it shows slow resolution, and the disease course can be classified into four stages[33]. In the early stage (0-4 d), GGOs are seen in the subpleural lower lobes. This is followed by a progressive stage (5-8 d) where multiple, diffuse GGOs are seen in bilateral lobes with crazy-paving and /or consolidation. In the next peak stage (9-13 d), there are extensive GGOs with dense consolidation and crazy paving pattern with or without parenchymal bands. Lastly, the absorption stage (over 14 d) shows gradual resolution with an absence of crazy paving. These stages have been echoed by other studies as well[47].

In addition to the four similar temporal stages of CT findings, Kong *et al*[48], noted the presence of fibrosis-like strips in the lower lobes and their median time of appearance was 4.5 d after disease onset. Among 88% of the cases, these strips disappeared within 9-20 d. This study also noted a correlation between symptomatology and CT findings. Nearly 14/22 patients had resolution of fever during the progressive stage, and all patients that had cough showed resolution during the last 'dissipation stage' (akin to the above absorption stage). Since this was a small study, correlations between clinical and imaging findings cannot be conclusively stated.

A semi-quantitative scoring system was developed to correlate the extent of pulmonary involvement with the clinical stage of the disease and laboratory findings to assess the role of CT in predicting short-term outcomes including mortality[49]. The scoring system involved considering the extent of anatomical involvement to each of the 5 lung lobes, with each lobe involvement being visually scored from 0 to 5, as given in Table 2. This was then combined to get a sum for a total CT score that ranged from 0 (no involvement) to 25 (maximum involvement). Francone *et al*[50], observed that the CT score to be significantly higher in critical and severe cases compared to other groups. Moreover, the CT score was significantly correlated with CRP and D-dimer levels. A total CT score of over 18 was associated with an increased mortality risk and

Table 2 Extent of lung involvement and the corresponding computed tomography scores[47,49]

CT score	Extent of lung involvement
Score 0	No lung involvement
Score 1	< 5% lung involvement
Score 2	5%-25% lung involvement
Score 3	26%-50% lung involvement
Score 4	51%-75% lung involvement

CT: Computed tomography.

was predictive of death in univariate analysis and multivariate analysis [HR 8.33 (95%CI: 3.19-21.73; $P < 0.0001$), and 3.74 (95%CI: 1.10-12.77; $P = 0.0348$) respectively]. This system, although reliant on subjective CT reporting, shows how CT can be used for prognostication. Inter-rater agreement should be measured in future studies to understand the reliability between different reporters and institutions.

Pan *et al*[47], studied the extent of lung involvement using the total CT score in various stages of the diseases and they observed that the total CT score peaked at the 10th day of illness. In their study the total CT score in stage 1 (early stage) was 2 ± 2, in stage 2 (progressive stage) it was 6 ± 4, in stage 3 (peak stage) it was 7 ± 4, and in stage 4 (absorption stage) it was 6 ± 4. Moreover, the lung involvement increased, and consolidation was observed up to 2 wk after the onset of the disease. Thereafter, consolidation was absorbed, leaving extensive GGO and sub-pleural parenchymal bands.

Patients with severe COVID-19 infections requiring hospitalization (even those who are not critically ill) are at high risk of venous thromboembolism (VTE), and a significant proportion would develop VTEs even while on standard prophylactic anticoagulation therapy[51]. The incidence of VTE in patients admitted to the intensive care unit, even after receiving standard prophylactic anticoagulation therapy with low molecular weight heparin (LMWH), is nearly 25%[52]. A recent study by Jalaber *et al*[53], observed that the prevalence of acute pulmonary embolism at initial presentation in unselected (severe and non-severe) COVID-19 patients is less than 6%. They observed that most patients who developed acute pulmonary embolism had D-dimer levels above 5000 ng/mL. Moreover, the median interval between symptoms onset and pulmonary embolism was 7 d. Thus, acute PE occurred in the second stage of COVID-19 illness corresponding to the cytokine storm[54]. Current explanations for the pathogenesis of COVID-19-associated hypercoagulability include hypoxia and systemic inflammation secondary to COVID-19 that may lead to high levels of inflammatory cytokines and the consequent activation of the coagulation pathway. However, the exact mechanisms causing thromboembolic episodes remain elusive. Though disseminated intravascular coagulation was suggested as one of the pathogenic mechanisms, a recent study by Martín-Rojas *et al*[55], has not shown an evidence for consumption coagulopathy in these patients.

A recent National Institute for Health and Clinical Excellence guideline recommends initiating standard prophylactic anticoagulation with LMWH, fondaparinux, or unfractionated heparin, and to continue them for the duration of hospitalisation or 7 d, whichever is longer[56]. Patients requiring advanced respiratory support in the form of invasive mechanical ventilation, bi-level positive airway pressure, continuous positive airway pressure or extracorporeal membrane oxy-genation can be considered for doubling the standard prophylactic dose of LMWH, which is also known as intermediate-prophylactic dose (off-label indication).

Routine use of CTPA as the first-line imaging modality in patients with suspected COVID-19 pneumonia is not justifiable due to the deleterious effects of contrast administration in patients at high risk of developing acute kidney injury (particularly those that are elderly and those with diabetes). Artificial intelligence-based algorithms have been developed to evaluate diagnostic test accuracy of CT chest in diagnosing COVID-19 lung disease[57]. A recent study using multinational database found that artificial intelligence-based algorithms exhibited 90.8% accuracy, 84% sensitivity and 93% specificity in the detection of COVID-19 pneumonia in the CT chest, indicating that these algorithms can readily identify COVID-19 pneumonia in CT chest imaging, and can distinguish non-COVID-19 related pneumonias with high specificity[58].

Lung ultrasound

The use of lung ultrasound (LUS) is gaining interest in the context of COVID-19. However, its usefulness in diagnosis is still uncertain[23]. The modality has unique advantages since it is quick and cheap to use, non-invasive, easily accessible, easily sterilised, and it does not involve radiation. It also allows an immediate exclusion of other causes of symptomatology, including myocardial injury and pneumothoraces[59]. This bedside test also negates having to move infected patients from their isolated hospital areas (*e.g.*, into CT scanners), and offers a rapid assessment of lung infection, and also offers an alternative investigation to those who cannot accept CT scans (*i.e.*, in pregnant patients). However, it is reliant on an operator with sufficient expertise, and it is difficult to gain useful information about deeper structures. As with CT scans, the sensitivity and specificity are thought to increase with severity of infection[60]. In a Cochrane Database systematic review, it was observed that in suspected COVID-19 patients, the LUS has a sensitivity of 96.8% and a specificity of 62.3%[25].

It is reported that the evaluation of respiratory failure in critically ill patients is better done with LUS than CT or CXR, especially in the context of ARDS and pneumonia[33,61,62]. LUS can also be used to define severity and progression of COVID-19 associated lung changes, with different stages of the disease being characterised by typical findings. On US scans, normal reverberation artifacts of pleural lines show as motionless and regularly spaced lines perpendicular to the pleura – these are A-lines. From the pleural lines, vertical linear artifacts which arise from thickened interlobular septa and other subpleural structures represent B-lines. The number of B-lines increases as the lung density increases and with reduced air content, which indicates pulmonary interstitial pathology. Mild-moderate disease will show scattered B lines, thickened pleural lines, skip lesions (alternating areas of B lines with A lines), along with small consolidations (around 1 cm). In severe disease, B lines become confluent, and consolidation increases. Furthermore, in critically ill COVID-19 patients, extensive coalescent and disappearing B lines affecting upper and anterior lungs, with corresponding consolidation are observed[33,63,64]. Apart from the physiological A lines, and pathological B lines, other artifacts such as C, E and Z lines, have been described[65]. Moreover, as consolidation increases, the echogenicity of the lung changes to resemble that of the liver ('hepatic pattern'), while also demonstrating changes to the bronchi morphology. The 'shred sign' denotes the shredded appearance at the interface between consolidation and normal lung; this is thought to be the most specific sign of pneumonia in LUS[66,67].

According to most studies, these findings are non-specific and there are no pathognomonic LUS signs of COVID-19 that can be used to establish a definitive diagnosis. In some studies, however, point of care ultrasound (POCUS) of the lungs done in the emergency department exhibited a strong correlation with CT scan findings in COVID-19 patients[68]. A recently published study by Haak *et al*[69], showed that the POCUS has an overall sensitivity of 89% (95%CI: 70%-97%), specificity of 59% (95%CI: 46%-71%), PPV of 47% (95%CI: 33%-61%), and NPV of 93% (95%CI: 79%-98%). In patients without past medical history of cardiopulmonary disease, POCUS has a sensitivity of 100% (95%CI: 70%-100%), specificity of 76% (95%CI: 54%-90%), PPV of 67% (95%CI: 41%-86%), and NPV of 100% (95%CI: 79%-100%).

In addition, Millington *et al*. established four probabilities of disease manifestations on LUS. High probability LUS patterns include bilateral and multifocal clusters of B-lines, alternating with normal lung, with some peripheral consolidation[63]. Intermediate LUS patterns involve unilateral clusters of B lines with or without peripheral consolidations. Alternate LUS patterns are observed with large consolidation or effusions and symmetrical B-lines. This may suggest alternative diagnosis such as cardiogenic pulmonary oedema. Low probability LUS patterns is characterised by generalised bilateral A-line pattern and may also indicate an alternative diagnosis. LUS is observed to have positive findings in early stages of pneumonia, and before disease symptomatology[64]. Extrapolating this further, US may have a role in early diagnosis and monitoring of COVID-19 positive patients, especially in the critical care setting and in pregnant women, where there is a high threshold for the use of other modalities. Table 3 compares the sensitivity, specificity, PPV and NPV of various lung investigations that were used in the diagnosis of COVID-19 infection, where RT-PCR is considered as the gold-standard and the other modalities are compared to it.

MRI

Thoracic MRI can be used as a radiation-free tool for the evaluation of lung parenchyma in high-risk patients with COVID-19 infection including pregnant women and children, in whom ionizing radiation should be avoided. Movement artfacts and the

Table 3 Efficacy of reverse transcriptase polymerase chain reaction, chest X-ray, computed tomography chest, and lung ultrasound in the diagnosis is of coronavirus disease-19 [16,24,43,44,69]

	Sensitivity	Specificity	PPV	NPV
RT-PCR	87.0%	97.0%	98.0%	80.0%
CXR	89.0%	60.6%	87.9%	63.1%
CT-chest	90.0%-90.7%	78.8%-91.0%	86.4%-89.0%	85.1%-92.0%
Lung US	89.0%	59.0%	47.0%	93.0%

CT: Computed tomography; RT-PCR: Reverse transcriptase polymerase chain reaction; CXR: Chest X-ray; US: Ultrasonography; PPV: Positive predictive value; NPV: Negative predictive value.

low proton content of normal lungs make its evaluation by MRI difficult[70]. However, the consolidation and ground-glass opacities occurring in patients with COVID-19 pneumonia cause an increase in proton content and signal intensity of the lungs. Moreover, advanced technologies such as T2-weighted spin-echo PROPELLER MRI sequences provide rapid acquisition of images, with better quality and with lesser artefacts, in as quick as 3 min.

A study that compared the findings on CT chest and MRI chest in patients with COVID-19 infection revealed that 90% of patients had ground-glass opacities in CT and MRI[71]. Consolidation was observed in nearly 45% of patients in both CT and MRI. Moreover, nodules were detected in 37.5% by CT and in 34.4% by MRI. In summary, when compared to CT chest, in the detection of lung nodules, MRI chest has a sensitivity of 91.7%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 95.2%. Another study, in which ultrashort echo time MRI was compared with conventional CT imaging in patients with COVID-19 infection, showed that there is substantial agreement for detecting the typical lesions of COVID-19 pneumonia, including pure GGOs, pure consolidation, and GGOs with consolidation[72].

Myocardial injury characterized by troponin elevation is seen in nearly 17% of patients with COVID-19 infection[73]. Many of these patients might develop new onset left ventricular systolic dysfunction of uncertain aetiology, as observed on fast bedside echocardiography. The cardiovascular magnetic resonance (CMR) done in these patients might also show interstitial myocardial oedema, contractile dysfunction, cardiomyocyte necrosis, or myocardial fibrosis[74]. The pulmonary magnetic resonance angiography (MRA) might facilitate direct visualisation of filling defects in the pulmonary arteries and/or as parenchymal perfusion defects. The CMR protocol for the cardiovascular structures can be combined with the MRI protocol for the pulmonary arterial tree and lung parenchyma; this combined cardiothoracic-MRI protocol might save precious time in these critically unwell patients[75]. Cranial MRI is a useful investigation in the evaluation of anosmia[76].

Positron emission tomography

The positron emission tomography (PET) scan is not considered as one of the primary diagnostic modalities in patients with COVID-19 infection, even though it possesses high sensitivity to detect subclinical infection. The disadvantages of PET include low specificity, high cost, prolonged exposure time, and time-consuming decontamination process. However, prompt detection of COVID-19 infection and early initiation of supportive treatment in patients undergoing PET for other indications including malignancies and other immunocompromised states could improve survival[77].

IMAGING FOR THE EXTRA-PULMONARY MANIFESTATIONS

Neuroimaging

COVID-19 infection also has impacts on the nervous system. Patients often present with anosmia, ageusia, headache, stroke, impairment of consciousness, seizures, and encephalopathy. These nonspecific manifestations warrant cranial imaging with CT or MRI to exclude severe acute manifestations including intracranial haemorrhage, cerebral venous sinus thrombosis, stroke, and encephalomyelitis[78]. A systematic review of five observational studies found that 24% of COVID-19 positive patients

presented with neurological features, while not suffering from any respiratory symptoms[79]. The pooled incidence of acute stroke was estimated to be 1.2% with a high mortality rate of 38% in these patients. The mean age of patients considered was 63.4 years and it was thought to be difficult to establish a causal relationship between COVID-19 and cerebrovascular stroke due to co-existent cardiovascular comorbidities. In addition, clinicians need to be aware of immune mediated complications such as Guillain-Barre syndrome and acute disseminated encephalomyelitis. Mood disorders and psychosis are also some of the documented neuropsychiatric disorders associated with COVID-19[80].

Although the neurological symptoms may be quite dramatic, the imaging may not show any positive findings[81]. If present, positive findings on cranial imaging include evidence of cerebrovascular diseases with haemorrhagic or non-haemorrhagic infarction, cerebral venous thrombosis, thrombotic microangiopathy, infectious and inflammatory diseases, acute disseminated encephalomyelitis and other demyelinating diseases including white matter demyelinating diseases[82]. Patients with severe COVID-19 infection and subsequent intensive care unit admission may develop neurological sequalae; this is thought to be due to brain ischaemia, however, one must rule out the possibility of chronic neuro-inflammation and demyelination during follow up appointments of recovered patients. Hence, neuro imaging should be organised to exclude demyelinating diseases including multiple sclerosis[83].

Cardiovascular imaging

Cardiovascular complications were demonstrated in various studies in patients affected by COVID-19. Appropriate multi-modality imaging should be considered depending on the clinical manifestations of the disease, which are all part of a nonspecific spectrum of symptoms. Considering the easy availability and feasibility of bedside US scans, any patients with suspected cardiovascular symptoms should be directed to a preliminary echocardiography to assess for ischaemic or non-ischaemic myocardial injury and pericardial pathologies[84]. The clinical severity of cardiovascular symptoms helps to determine the appropriate imaging and interventions, with consideration to the laboratory investigation results. Mild symptoms warrant bedside US scans which have the advantage of being radiation free, portable, repeatable, quick, and inexpensive and can be performed in isolation with minimal risk of spread of infection[85].

In an acute clinical set up, the role of cardiac CT and MRI are reserved for patients with more serious or inconclusive symptomatology and the evidence for their use is still mounting. Although chest CT scan provides detailed information on the mediastinum and the lungs, early changes of myocardial oedema is best appreciated on cardiac MRI. The use of cardiac imaging by CT and MRI are limited by their availability, time, cost, and patient factors. It is also recognised that comorbid cardiac pathologies complicate the clinical picture of COVID-19 positive patients. In addition to worsening the pre-existing cardiovascular disease, COVID-19 infection can cause primary infective/inflammatory changes in myocardium and pericardium with possible myocarditis, myopericarditis, myocardial ischaemia and pulmonary emboli[59].

Abdominal imaging

Approximately 16% of COVID-19 patients present with gastrointestinal symptoms with or without respiratory symptoms[86]. In one study by Behzad *et al*[87], 0.5%-19% of patients showed some form of renal dysfunction, and it is observed that renal dysfunction in COVID-19 can be caused by a direct endothelial invasion of the glomerular capillaries (endotheliitis)[88]. The knowledge of this is particularly important when planning a contrast enhanced CT scan or MRI due to the risk of inducing contrast nephropathy[89]. Several COVID-19 patients demonstrated abnormal liver function but there are no specific diagnostic features. Imaging by US scan and CT showed hepatic steatosis, which is also a nonspecific finding, which could be attributed to pre-existing changes or even due to drug induced pathologies[81]. In more severe COVID-19 infection, multi organ disease can also manifest as septic shock, refractory metabolic acidosis, and coagulation dysfunction[90].

It was also observed that COVID-19 infected patients shed detectable traces of virus in faeces. It is found that the stool samples remain positive for viral RNA after respiratory samples became negative[91]. This implies that the health care workers dealing with suspected or confirmed COVID-19 patients requiring endoscopy and collecting faecal samples during patient recovery should be done with proper use of PPEs. On CT imaging of the abdomen in COVID-19 positive patients, the nonspecific findings include small and large bowel wall thickening, fluid filled colon, pneumatosis intestinalis, pneumoperitoneum, intussusceptions, and ascites[86]. A small study in

COVID-19 infected pregnant ladies showed that there are no specifically different aspects of the disease and the findings are just as nonspecific as in the general population[92].

DISCUSSION

Why can there be clinical and imaging discrepancies among COVID-19 patients?

CT chest images of some COVID-19 patients showed apparent lesions in the lungs, yet the RT-PCR repeatedly showed negative results until eventually turning positive[93]. This discrepancy is due to the increased sensitivity of CT chest compared to RT-PCR[45]. Among imaging studies themselves, there exist discrepancies in the diagnostic yield, especially when imaging is done in the early stages and in patients with mild COVID-19 infections[94]. Moreover, interstitial pneumonia is one of the most common features of COVID-19[95]. The CXR is less sensitive in detecting interstitial pneumonia, in comparison to high resolution CT chest. There is a high thromboembolic risk associated with COVID-19. Many of these patients may present simply with dyspnoea and type 1 respiratory failure where a normal CXR or non-contrast CT chest often would not exclude pulmonary thromboembolism. Prompt evaluation with CTPA or MRA should be considered when such clinic-imaging discrepancy is present.

Certain patients with extensive pneumonic changes in CXR will come off oxygen and could be discharged soon after admission, whereas some other patients without extensive pneumonic changes succumb to the disease. This is mostly related to the varied propensity to develop the cytokine storm syndrome, which is responsible for acute respiratory distress syndrome, multiorgan failure and death[96].

Discrepancies among children and young adults

The clinical and imaging features of COVID-19 can be different from that of middle- and old-age adults. This is often related to milder course of the clinical illness in most of these patients. Consolidations with surrounding halo signs were peculiar to paediatric COVID-19 pulmonary disease, probably resulting from underlying coinfections[97] whereas the imaging features were different among older adults as described earlier. Paediatric cases less commonly show a peculiar presentation of COVID-19 known as multisystem inflammatory syndrome in children (MIS-C). The chest radiographic features of MIS-C include pleural effusions and opacifications of lower lung zones[98].

Young adults and adolescents are usually affected by less severe attack of SARS-CoV-2 virus compared to middle aged and older adults. Therefore, the clinico-radiological features of such patients are expected to be different from those among older adults. This discrepancy could be explained by more profound virus-related immune dysfunction in the latter age-groups and the associated co-morbidities[99]. There seems even a gender preponderance in the severity of COVID-19, with males affected more than the females, necessitating longer periods of hospitalisation, intensive care unit admissions, and mortality[100].

CONCLUSION

Although the advent of RT-PCR testing for COVID-19 has undoubtedly been crucial in combating the disease, its diagnostic utility remains limited due to its relatively low sensitivity. For this reason, imaging tests are now gaining focus to aid the diagnosis in clinical scenarios where the RT-PCR result is inconclusive. Since most symptoms relate to the respiratory system, the use of chest imaging plays a crucial role in diagnosis. CXRs are a quick and useful tool for an immediate assessment of thoracic pathology. However, it must be noted that its sensitivity for diagnostic purposes is far from perfect, owing to the lack of specificity in findings seen in COVID-19. It must be noted, however, that chest radiographs with COVID-19 opacification rating score is a significant predictor of the need for intubation, while exhibiting reproducibility between reviewers.

CT scans, on the other hand, show good sensitivity compared to RT-PCR, however its specificity is less. Combined observation of GGO and one other sign of pneumonia (septal thickening, consolidation, or pleural effusions) is the most specific and sensitive sign for COVID-19. CT has been shown to be useful for disease monitoring as it is can be used to map the disease in its temporal stages. The advantage of CT chest is that it

gives both diagnostic and prognostic information. However, the limitations with CT chest (either unenhanced or CTPA) includes the cost, increased radiation exposure, and the difficult as well as time-consuming disinfection protocols. LUS has been proven to be superior to CT and CXR in the assessment of critically ill patients, especially with ARDS and pneumonia and can be used to monitor disease progression, severity, and resolution. Again, the findings are non-specific and there are no pathognomonic findings to indicate a COVID-19 diagnosis. MRI of lungs has recently emerged as a highly sensitive and specific imaging tool for diagnosis of COVID-19 lung disease especially when CT scans pose higher radiation risk among children, adolescents and pregnant women.

With regards to extra-pulmonary manifestations of COVID-19, imaging plays a key role in identifying and monitoring these impacts. Neurological sequelae are common and range from ischaemic injury to demyelinating conditions. Thus, neurological imaging is paramount in those with symptoms, and it is equally important to use them during follow up. Cardiac imaging can be in the form of echo, or cardiac CT/MRI, and the symptom severity and clinical suspicion of an underlying cardiac diagnosis will guide clinicians to use a specific modality. Abdominal symptoms are often present in COVID-19 patients and require monitoring. A significant proportion of patients may also suffer from renal impairment. Thus, imaging and laboratory tests are needed to monitor this, especially since contrast enhanced imaging is often required for those that are most ill.

In summary, there have been lots of studies to inform imaging practices in COVID-19 patients, and the evidence is being gathered to highlight their usefulness in the context of this diagnosis. This review highlights the appropriate uses of imaging in COVID-19, and how it may guide clinical management. Despite there being data on what imaging findings are to be typically expected, there seems to be a paucity of literature in correlating imaging findings with clinical symptomatology. Further research is needed to elucidate this, since it could have significant clinical implications in patient management.

REFERENCES

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

2 **Berlin DA**, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020; **383**: 2451-2460 [PMID: 32412710 DOI: 10.1056/NEJMcp2009575]

3 **Reeves RA**, Pomeranz C, Gomella AA, Gulati A, Metra B, Hage A, Lange S, Parekh M, Donuru A, Lakhani P, Sundaram B. Performance of a Severity Score on Admission Chest Radiograph in Predicting Clinical Outcomes in Hospitalized Patients with Coronavirus Disease (COVID-19). *AJR Am J Roentgenol* 2020 [PMID: 33112201 DOI: 10.2214/AJR.20.24801]

4 **Espinosa PS**, Rizvi Z, Sharma P, Hindi F, Filatov A. Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy, MRI Brain and Cerebrospinal Fluid Findings: Case 2. *Cureus* 2020; **12**: e7930 [PMID: 32499974 DOI: 10.7759/cureus.7930]

5 **Lei P**, Zhang L, Han P, Zheng C, Tong Q, Shang H, Yang F, Hu Y, Li X, Song Y. Liver injury in patients with COVID-19: clinical profiles, CT findings, the correlation of the severity with liver injury. *Hepatol Int* 2020; **14**: 733-742 [PMID: 32886333 DOI: 10.1007/s12072-020-10087-1]

6 **Shiralkar K**, Chinapuvvula N, Ocazionez D. Cross-Sectional Abdominal Imaging Findings in Patients With COVID-19. *Cureus* 2020; **12**: e9538 [PMID: 32905406 DOI: 10.7759/cureus.9538]

7 **Kerpel A**, Apter S, Nissan N, Houri-Levi E, Klug M, Amit S, Konen E, Marom EM. Diagnostic and Prognostic Value of Chest Radiographs for COVID-19 at Presentation. *West J Emerg Med* 2020; **21**: 1067-1075 [PMID: 32970556 DOI: 10.5811/westjem.2020.7.48842]

8 **Kaufman AE**, Naidu S, Ramachandran S, Kaufman DS, Fayad ZA, Mani V. Review of radiographic findings in COVID-19. *World J Radiol* 2020; **12**: 142-155 [PMID: 32913561 DOI: 10.4329/wjr.v12.i8.142]

9 **Yazdanpanah F**, Asmarz HY, Shadman S. Literature Review of COVID-19, Pulmonary and Extrapulmonary Disease. *Am J Med Sci* 2021 [PMID: 33785204 DOI: 10.1016/j.amjms.2021.01.023]

10 **Ata F**, Montoro-Lopez MN, Awouda S, Elsukkar AMA, Badr AMH, Patel AAAH. COVID-19 and Heart Failure: The Big Challenge. *Heart Views* 2020; **21**: 187-192 [PMID: 33688410 DOI: 10.4103/HEARTVIEWS.HEARTVIEWS_122_20]

11 **Cho SI**, Yoon S, Lee HJ. Impact of comorbidity burden on mortality in patients with COVID-19 using the Korean health insurance database. *Sci Rep* 2021; **11**: 6375 [PMID: 33737679 DOI:

10.1038/s41598-021-85813-2]
12 **Sanchez-Russo L**, Billah M, Chancay J, Hindi J, Cravedi P. COVID-19 and the Kidney: A Worrisome Scenario of Acute and Chronic Consequences. *J Clin Med* 2021; **10** [PMID: 33668833 DOI: 10.3390/jcm10050900]
13 **Giri M**, Puri A, Wang T, Guo S. Comparison of clinical manifestations, pre-existing comorbidities, complications and treatment modalities in severe and non-severe COVID-19 patients: A systemic review and meta-analysis. *Sci Prog* 2021; **104**: 368504211000906 [PMID: 33752530 DOI: 10.1177/00368504211000906]
14 **Yang L**, Chai P, Yu J, Fan X. Effects of cancer on patients with COVID-19: a systematic review and meta-analysis of 63,019 participants. *Cancer Biol Med* 2021; **18**: 298-307 [PMID: 33628602 DOI: 10.20892/j.issn.2095-3941.2020.0559]
15 **Salameh JP**, Leeflang MM, Hooft L, Islam N, McGrath TA, van der Pol CB, Frank RA, Prager R, Hare SS, Dennie C, Spijker R, Deeks JJ, Dinnes J, Jenniskens K, Korevaar DA, Cohen JF, Van den Bruel A, Takwoingi Y, van de Wijgert J, Damen JA, Wang J; Cochrane COVID-19 Diagnostic Test Accuracy Group, McInnes MD. Thoracic imaging tests for the diagnosis of COVID-19. *Cochrane Database Syst Rev* 2020; **9**: CD013639 [PMID: 32997361 DOI: 10.1002/14651858.CD013639.pub2]
16 **George B**, McGee J, Giangrasso E, Finkelstein S, Wu S, Glatt AE. What Is the Predictive Value of a Single Nasopharyngeal SARS-CoV-2 PCR Swab Test in a Patient With COVID-Like Symptoms and/or Significant COVID-19 Exposure? *Open Forum Infect Dis* 2020; **7**: ofaa399 [PMID: 33062799 DOI: 10.1093/ofid/ofaa399]
17 **Yan L**, Zhang H-T, Goncalves J, Xiao Y, Wang M, Guo Y, Sun C, Tang X, Jing L, Zhang M, Huang X, Cao H, Chen Y, Ren T, Wang F, Huang S, Tan S, Huang N, Jiao B, Cheng C, Zhang Y, Luo A, Mombaerts L, Jin J, Cao, Z, Li S, Xu H, Yuan Y. An interpretable mortality prediction model for COVID-19 patients. *Nat Mach Intell* 2020; **2**: 283-288 [DOI: 10.1038/s42256-020-0180-7]
18 **He X**, Lau EHY, Wu P, Deng X, Wang J, Hao X, Lau YC, Wong JY, Guan Y, Tan X, Mo X, Chen Y, Liao B, Chen W, Hu F, Zhang Q, Zhong M, Wu Y, Zhao L, Zhang F, Cowling BJ, Li F, Leung GM. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26**: 672-675 [PMID: 32296168 DOI: 10.1038/s41591-020-0869-5]
19 **Zhou X**, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. *Clin Microbiol Infect* 2020; **26**: 957-959 [PMID: 32234453 DOI: 10.1016/j.cmi.2020.03.024]
20 **Cao AM**, Choy JP, Mohanakrishnan LN, Bain RF, van Driel ML. Chest radiographs for acute lower respiratory tract infections. *Cochrane Database Syst Rev* 2013; CD009119 [PMID: 24369343 DOI: 10.1002/14651858.CD009119.pub2]
21 **Pormohammad A**, Ghorbani S, Khatami A, Farzi R, Baradaran B, Turner DL, Turner RJ, Bahr NC, Idrovo JP. Comparison of confirmed COVID-19 with SARS and MERS cases - Clinical characteristics, laboratory findings, radiographic signs and outcomes: A systematic review and meta-analysis. *Rev Med Virol* 2020; **30**: e2112 [PMID: 32502331 DOI: 10.1002/rmv.2112]
22 **Cleverley J**, Piper J, Jones MM. The role of chest radiography in confirming covid-19 pneumonia. *BMJ* 2020; **370**: m2426 [PMID: 32675083 DOI: 10.1136/bmj.m2426]
23 **Dennie C**, Hague C, Lim RS, Manos D, Memauri BF, Nguyen ET, Taylor J. Canadian Society of Thoracic Radiology/Canadian Association of Radiologists Consensus Statement Regarding Chest Imaging in Suspected and Confirmed COVID-19. *Can Assoc Radiol J* 2020; **71**: 470-481 [PMID: 32380844 DOI: 10.1177/0846537120924606]
24 **Schiaffino S**, Tritella S, Cozzi A, Carriero S, Blandi L, Ferraris L, Sardanelli F. Diagnostic Performance of Chest X-Ray for COVID-19 Pneumonia During the SARS-CoV-2 Pandemic in Lombardy, Italy. *J Thorac Imaging* 2020; **35**: W105-W106 [PMID: 32404797 DOI: 10.1097/RTI.0000000000000533]
25 **Islam N**, Salameh JP, Leeflang MM, Hooft L, McGrath TA, van der Pol CB, Frank RA, Kazi S, Prager R, Hare SS, Dennie C, Spijker R, Deeks JJ, Dinnes J, Jenniskens K, Korevaar DA, Cohen JF, Van den Bruel A, Takwoingi Y, van de Wijgert J, Wang J, McInnes MD; Cochrane COVID-19 Diagnostic Test Accuracy Group. Thoracic imaging tests for the diagnosis of COVID-19. *Cochrane Database Syst Rev* 2020; **11**: CD013639 [PMID: 33242342 DOI: 10.1002/14651858.CD013639.pub3]
26 **Borkowski AA**, Viswanadhan NA, Thomas LB, Guzman RD, Deland LA, Mastorides SM. Using Artificial Intelligence for COVID-19 Chest X-ray Diagnosis. *Fed Pract* 2020; **37**: 398-404 [PMID: 33029064 DOI: 10.12788/fp.0045]
27 **Zhang R**, Tie X, Qi Z, Bevins NB, Zhang C, Griner D, Song TK, Nadig JD, Schiebler ML, Garrett JW, Li K, Reeder SB, Chen GH. Diagnosis of Coronavirus Disease 2019 Pneumonia by Using Chest Radiography: Value of Artificial Intelligence. *Radiology* 2021; **298**: E88-E97 [PMID: 32969761 DOI: 10.1148/radiol.2020202944]
28 **Xiao N**, Cooper JG, Godbe JM, Bechel MA, Scott MB, Nguyen E, McCarthy DM, Abboud S, Allen BD, Parekh ND. Chest radiograph at admission predicts early intubation among inpatient COVID-19 patients. *Eur Radiol* 2020 [PMID: 33051736 DOI: 10.1007/s00330-020-07354-y]
29 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]
30 **Kanne JP**, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for Radiologists on COVID-19:

An Update-*Radiology* Scientific Expert Panel. *Radiology* 2020; **296**: E113-E114 [PMID: 32105562 DOI: 10.1148/radiol.2020200527]

31 **Fang Y**, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296**: E115-E117 [PMID: 32073353 DOI: 10.1148/radiol.2020200432]

32 **Pan Y**, Yu X, Du X, Li Q, Li X, Qin T, Wang M, Jiang M, Li J, Li W, Zhang Q, Xu Z, Zhang L. Epidemiological and Clinical Characteristics of 26 Asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 Carriers. *J Infect Dis* 2020; **221**: 1940-1947 [PMID: 32318703 DOI: 10.1093/infdis/jiaa205]

33 **Gandhi D**, Jain N, Khanna K, Li S, Patel L, Gupta N. Current role of imaging in COVID-19 infection with recent recommendations of point of care ultrasound in the contagion: a narrative review. *Ann Transl Med* 2020; **8**: 1094 [PMID: 33145313 DOI: 10.21037/atm-20-3043]

34 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]

35 **Awulachew E**, Diriba K, Anja A, Getu E, Belayneh F. Computed Tomography (CT) Imaging Features of Patients with COVID-19: Systematic Review and Meta-Analysis. *Radiol Res Pract* 2020; **2020**: 1023506 [PMID: 32733706 DOI: 10.1155/2020/1023506]

36 **Altmayer S**, Zanon M, Pacini GS, Watte G, Barros MC, Mohammed TL, Verma N, Marchiori E, Hochhegger B. Comparison of the computed tomography findings in COVID-19 and other viral pneumonia in immunocompetent adults: a systematic review and meta-analysis. *Eur Radiol* 2020; **30**: 6485-6496 [PMID: 32594211 DOI: 10.1007/s00330-020-07018-x]

37 **Inui S**, Fujikawa A, Jitsu M, Kunishima N, Watanabe S, Suzuki Y, Umeda S, Uwabe Y. Chest CT Findings in Cases from the Cruise Ship *Diamond Princess* with Coronavirus Disease (COVID-19). *Radiol Cardiothorac Imaging* 2020; **2**: e200110 [PMID: 33778566 DOI: 10.1148/ryct.2020200110]

38 **Hossein H**, Ali KM, Hosseini M, Sarveazad A, Safari S, Yousefifard M. Value of chest computed tomography scan in diagnosis of COVID-19; a systematic review and meta-analysis. *Clin Transl Imaging* 2020; 1-13 [PMID: 33072656 DOI: 10.1007/s40336-020-00387-9]

39 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin J, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest* 2020; **158**: 106-116 [PMID: 32275978 DOI: 10.1016/j.chest.2020.04.003]

40 **Revel MP**, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A; European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; **30**: 4903-4909 [PMID: 32314058 DOI: 10.1007/s00330-020-06865-y]

41 **Prokop M**, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**: E97-E104 [PMID: 32339082 DOI: 10.1148/radiol.2020201473]

42 **Bernheim A**, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020; **295**: 200463 [PMID: 32077789 DOI: 10.1148/radiol.2020200463]

43 **Tsikala Vafea M**, Atalla E, Kalligeros M, Mylona EK, Shehadeh F, Mylonakis E. Chest CT findings in asymptomatic cases with COVID-19: a systematic review and meta-analysis. *Clin Radiol* 2020; **75**: 876.e33-876.e39 [PMID: 32861461 DOI: 10.1016/j.crad.2020.07.025]

44 **Kovács A**, Palásti P, Veréb D, Bozsik B, Palkó A, Kincses ZT. The sensitivity and specificity of chest CT in the diagnosis of COVID-19. *Eur Radiol* 2020 [PMID: 33051732 DOI: 10.1007/s00330-020-07347-x]

45 **Falaschi Z**, Danna PSC, Arioli R, Pasché A, Zagaria D, Percivale I, Tricca S, Barini M, Aquilini F, Andreoni S, Carriero A. Chest CT accuracy in diagnosing COVID-19 during the peak of the Italian epidemic: A retrospective correlation with RT-PCR testing and analysis of discordant cases. *Eur J Radiol* 2020; **130**: 109192 [PMID: 32738464 DOI: 10.1016/j.ejrad.2020.109192]

46 **Herpe G**, Lederlin M, Naudin M, Ohana M, Chaumoitre K, Gregory J, Vilgrain V, Freitag CA, De Margerie-Mellon C, Flory V, Ludwig M, Mondot L, Fitton I, Jacquier ARR, Ardilouze P, Petit I, Gervaise A, Bayle O, Crombe A, Mekuko Sokeng M, Thomas C, Henry G, Bliah V, Le Tat T, Guillot MS, Gendrin P, Garetier M, Bertolle E, Montagne C, Langlet B, Kalaaji A, Kayayan H, Desmots F, Dhaene B, Saulnier PJ, Guillevin R, Bartoli JM, Beregi JP, Tasu JP. Efficacy of Chest CT for COVID-19 Pneumonia Diagnosis in France. *Radiology* 2021; **298**: E81-E87 [PMID: 32870139 DOI: 10.1148/radiol.2020202568]

47 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-

19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]
48 **Kong M**, Yang H, Li X, Shen J, Xu X, Lv D. Evolution of chest CT manifestations of COVID-19: a longitudinal study. *J Thorac Dis* 2020; **12**: 4892-4907 [PMID: 33145063 DOI: 10.21037/jtd-20-1363]
49 **Chang YC**, Yu CJ, Chang SC, Galvin JR, Liu HM, Hsiao CH, Kuo PH, Chen KY, Franks TJ, Huang KM, Yang PC. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. *Radiology* 2005; **236**: 1067-1075 [PMID: 16055695 DOI: 10.1148/radiol.2363040958]
50 **Francone M**, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, Panebianco V, Andreoli C, Colaiacomo MC, Zingaropoli MA, Ciardi MR, Mastroianni CM, Pugliese F, Alessandri F, Turriziani O, Ricci P, Catalano C. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. *Eur Radiol* 2020; **30**: 6808-6817 [PMID: 32623505 DOI: 10.1007/s00330-020-07033-y]
51 **Ali S**, Mathew S, Pappachan JM. Acute cor pulmonale from saddle pulmonary embolism in a patient with previous COVID-19: should we prolong prophylactic anticoagulation? *Int J Infect Dis* 2020; **97**: 299-302 [PMID: 32544670 DOI: 10.1016/j.ijid.2020.06.039]
52 **Tal S**, Spectre G, Kornowski R, Perl L. Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? *Acta Haematol* 2020; **143**: 417-424 [PMID: 32396903 DOI: 10.1159/000508233]
53 **Jalaber C**, Revel MP, Chassagnon G, Bajeux E, Lapotre T, Croisille P, Lederlin M. Role of upfront CT pulmonary angiography at admission in COVID-19 patients. *Thromb Res* 2020; **196**: 138-140 [PMID: 32866826 DOI: 10.1016/j.thromres.2020.08.037]
54 **Connors JM**, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost* 2020; **18**: 1559-1561 [PMID: 32302453 DOI: 10.1111/jth.14849]
55 **Martín-Rojas RM**, Pérez-Rus G, Delgado-Pinos VE, Domingo-González A, Regalado-Artamendi I, Alba-Urdiales N, Demelo-Rodríguez P, Monsalvo S, Rodríguez-Macías G, Ballesteros M, Osorio-Prendes S, Díez-Martín JL, Pascual Izquierdo C. COVID-19 coagulopathy: An in-depth analysis of the coagulation system. *Eur J Haematol* 2020; **105**: 741-750 [PMID: 32749010 DOI: 10.1111/ejh.13501]
56 **National Institute for Health and Clinical Excellence**. Reducing the risk of venous thromboembolism (VTE) in over 16s with COVID-19 pneumonia (online). 2020 [cited 9 December 2020]; Available from: https://www.nice.org.uk/guidance/ng186/resources.
57 **Li L**, Qin L, Xu Z, Yin Y, Wang X, Kong B, Bai J, Lu Y, Fang Z, Song Q, Cao K, Liu D, Wang G, Xu Q, Fang X, Zhang S, Xia J. Using Artificial Intelligence to Detect COVID-19 and Community-acquired Pneumonia Based on Pulmonary CT: Evaluation of the Diagnostic Accuracy. *Radiology* 2020; **296**: E65-E71 [PMID: 32191588 DOI: 10.1148/radiol.2020200905]
58 **Harmon SA**, Sanford TH, Xu S, Turkbey EB, Roth H, Xu Z, Yang D, Myronenko A, Anderson V, Amalou A, Blain M, Kassin M, Long D, Varble N, Walker SM, Bagci U, Ierardi AM, Stellato E, Plensich GG, Franceschelli G, Girlando C, Irmici G, Labella D, Hammoud D, Malayeri A, Jones E, Summers RM, Choyke PL, Xu D, Flores M, Tamura K, Obinata H, Mori H, Patella F, Cariati M, Carrafiello G, An P, Wood BJ, Turkbey B. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets. *Nat Commun* 2020; **11**: 4080 [PMID: 32796848 DOI: 10.1038/s41467-020-17971-2]
59 **Agricola E**, Beneduce A, Esposito A, Ingallina G, Palumbo D, Palmisano A, Ancona F, Baldetti L, Pagnesi M, Melisurgo G, Zangrillo A, De Cobelli F. Heart and Lung Multimodality Imaging in COVID-19. *JACC Cardiovasc Imaging* 2020; **13**: 1792-1808 [PMID: 32762885 DOI: 10.1016/j.jcmg.2020.05.017]
60 **Lu W**, Zhang S, Chen B, Chen J, Xian J, Lin Y, Shan H, Su ZZ. A Clinical Study of Noninvasive Assessment of Lung Lesions in Patients with Coronavirus Disease-19 (COVID-19) by Bedside Ultrasound. *Ultraschall Med* 2020; **41**: 300-307 [PMID: 32294796 DOI: 10.1055/a-1154-8795]
61 **Maw AM**, Hassanin A, Ho PM, McInnes MDF, Moss A, Juarez-Colunga E, Soni NJ, Miglioranza MH, Platz E, DeSanto K, Sertich AP, Salame G, Daugherty SL. Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2019; **2**: e190703 [PMID: 30874784 DOI: 10.1001/jamanetworkopen.2019.0703]
62 **Alzahrani SA**, Al-Salamah MA, Al-Madani WH, Elbarbary MA. Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. *Crit Ultrasound J* 2017; **9**: 6 [PMID: 28244009 DOI: 10.1186/s13089-017-0059-y]
63 **Millington SJ**, Koenig S, Mayo P, Volpicelli G. Lung Ultrasound for Patients With Coronavirus Disease 2019 Pulmonary Disease. *Chest* 2021; **159**: 205-211 [PMID: 32835709 DOI: 10.1016/j.chest.2020.08.2054]
64 **Allinovi M**, Parise A, Giacalone M, Amerio A, Delsante M, Odone A, Franci A, Gigliotti F, Amadasi S, Delmonte D, Parri N, Mangia A. Lung Ultrasound May Support Diagnosis and Monitoring of COVID-19 Pneumonia. *Ultrasound Med Biol* 2020; **46**: 2908-2917 [PMID: 32807570 DOI: 10.1016/j.ultrasmedbio.2020.07.018]
65 **Gandhi D**, Ahuja K, Grover H, Sharma P, Solanki S, Gupta N, Patel L. Review of X-ray and computed tomography scan findings with a promising role of point of care ultrasound in COVID-19 pandemic. *World J Radiol* 2020; **12**: 195-203 [PMID: 33033574 DOI: 10.4329/wjr.v12.i9.195]
66 **Lichtenstein DA**, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory

failure: the BLUE protocol. *Chest* 2008; **134**: 117-125 [PMID: 18403664 DOI: 10.1378/chest.07-2800]

67 **Sobh E**, Oraby S, Gamal F. Role of thoracic ultrasound in the diagnosis of pneumonia. *Eur Res J* 2017; **50**: PA4113 [DOI: 10.1183/1393003.congress-2017.PA4113]

68 **Poggiali E**, Dacrema A, Bastoni D, Tinelli V, Demichele E, Mateo Ramos P, Marcianò T, Silva M, Vercelli A, Magnacavallo A. Can Lung US Help Critical Care Clinicians in the Early Diagnosis of Novel Coronavirus (COVID-19) Pneumonia? *Radiology* 2020; **295**: E6 [PMID: 32167853 DOI: 10.1148/radiol.2020200847]

69 **Haak SL**, Renken IJ, Jager LC, Lameijer H, van der Kolk BBY. Diagnostic accuracy of point-of-care lung ultrasound in COVID-19. *Emerg Med J* 2020 [PMID: 33208399 DOI: 10.1136/emermed-2020-210125]

70 **Meier-Schroers M**, Kukuk G, Homsi R, Skowasch D, Schild HH, Thomas D. MRI of the lung using the PROPELLER technique: Artifact reduction, better image quality and improved nodule detection. *Eur J Radiol* 2016; **85**: 707-713 [PMID: 26971412 DOI: 10.1016/j.ejrad.2015.12.016]

71 **Ates OF**, Taydas O, Dheir H. Thorax Magnetic Resonance Imaging Findings in Patients with Coronavirus Disease (COVID-19). *Acad Radiol* 2020; **27**: 1373-1378 [PMID: 32830031 DOI: 10.1016/j.acra.2020.08.009]

72 **Yang S**, Zhang Y, Shen J, Dai Y, Ling Y, Lu H, Zhang R, Ding X, Qi H, Shi Y, Zhang Z, Shan F. Clinical Potential of UTE-MRI for Assessing COVID-19: Patient- and Lesion-Based Comparative Analysis. *J Magn Reson Imaging* 2020; **52**: 397-406 [PMID: 32491257 DOI: 10.1002/jmri.27208]

73 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

74 **Camastra G**, Ciolina F, Arcari L, Danti M, Cacciotti L. Heart and lung involvement detected by native T1 and T2 mapping magnetic resonance imaging in a patient with coronavirus disease-19. *Eur Heart J Cardiovasc Imaging* 2021 [PMID: 33421058 DOI: 10.1093/ehjci/jeaa414]

75 **Galea N**, Catapano F, Marchitelli L, Cundari G, Maestrini V, Panebianco V, Mancone M, Fedele F, Catalano C, Francone M. How to perform a cardio-thoracic magnetic resonance imaging in COVID-19: comprehensive assessment of heart, pulmonary arteries, and lung parenchyma. *Eur Heart J Cardiovasc Imaging* 2020 [PMID: 33325495 DOI: 10.1093/ehjci/jeaa335]

76 **Galougahi MK**, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. Olfactory Bulb Magnetic Resonance Imaging in SARS-CoV-2-Induced Anosmia: The First Report. *Acad Radiol* 2020; **27**: 892-893 [PMID: 32295727 DOI: 10.1016/j.acra.2020.04.002]

77 **Fields BKK**, Demirjian NL, Dadgar H, Gholamrezanezhad A. Imaging of COVID-19: CT, MRI, and PET. *Semin Nucl Med* 2020 [PMID: 33288215 DOI: 10.1053/j.semnuclmed.2020.11.003]

78 **Sharifian-Dorche M**, Huot P, Osherov M, Wen D, Saveriano A, Giacomini PS, Antel JP, Mowla A. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci* 2020; **417**: 117085 [PMID: 32871412 DOI: 10.1016/j.jns.2020.117085]

79 **Tan YK**, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, Tu TM, Sharma VK, Yeo LLL, Chan BPL, Tan BYQ. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis* 2020; **50**: 587-595 [PMID: 32661757 DOI: 10.1007/s11239-020-02228-y]

80 **Almqvist J**, Granberg T, Tzortzakakis A, Klironomos S, Kollia E, Öhberg C, Martin R, Piehl F, Ouellette R, Ineichen BV. Neurological manifestations of coronavirus infections - a systematic review. *Ann Clin Transl Neurol* 2020; **7**: 2057-2071 [PMID: 32853453 DOI: 10.1002/acn3.51166]

81 **Filatov A**, Sharma P, Hindi F, Espinosa PS. Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy. *Cureus* 2020; **12**: e7352 [PMID: 32328364 DOI: 10.7759/cureus.7352]

82 **Goldberg MF**, Goldberg MF. Neuroradiologic manifestations of COVID-19: what the emergency radiologist needs to know. *Emerg Radiol* 2020; **27**: 737-745 [PMID: 32822060 DOI: 10.1007/s10140-020-01840-y]

83 **Ogier M**, Andéol G, Sagui E, Dal Bo G. How to detect and track chronic neurologic sequelae of COVID-19? *Brain Behav Immun Health* 2020; **5**: 100081 [PMID: 32427134 DOI: 10.1016/j.bbih.2020.100081]

84 **Citro R**, Pontone G, Bellino M, Silverio A, Iuliano G, Baggiano A, Manka R, Iesu S, Vecchione C, Asch FM, Ghadri JR, Templin C. Role of multimodality imaging in evaluation of cardiovascular involvement in COVID-19. *Trends Cardiovasc Med* 2021; **31**: 8-16 [PMID: 33065315 DOI: 10.1016/j.tcm.2020.10.001]

85 **Suri JS**, Puvvula A, Biswas M, Majhail M, Saba L, Faa G, Singh IM, Oberleitner R, Turk M, Chadha PS, Johri AM, Sanches JM, Khanna NN, Viskovic K, Mavrogeni S, Laird JR, Pareek G, Miner M, Sobel DW, Balestrieri A, Sfikakis PP, Tsoulfas G, Protogerou A, Misra DP, Agarwal V, Kitas GD, Ahluwalia P, Kolluri R, Teji J, Maini MA, Agbakoba A, Dhanjil SK, Sockalingam M, Saxena A, Nicolaides A, Sharma A, Rathore V, Ajuluchukwu JNA, Fatemi M, Alizad A, Viswanathan V, Krishnan PR, Naidu S. COVID-19 pathways for brain and heart injury in comorbidity patients: A role of medical imaging and artificial intelligence-based COVID severity classification: A review. *Comput Biol Med* 2020; **124**: 103960 [PMID: 32919186 DOI: 10.1016/j.compbiomed.2020.103960]

86 **Lui K**, Wilson MP, Low G. Abdominal imaging findings in patients with SARS-CoV-2 infection: a scoping review. *Abdom Radiol (NY)* 2021; **46**: 1249-1255 [PMID: 32926211 DOI: 10.1007/s00261-020-02739-5]

87 **Behzad S**, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview. *Clin Imaging* 2020; **66**: 35-41 [PMID: 32425338 DOI: 10.1016/j.clinimag.2020.05.013]

88 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

89 **Zaim S**, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. *Curr Probl Cardiol* 2020; **45**: 100618 [PMID: 32439197 DOI: 10.1016/j.cpcardiol.2020.100618]

90 **Rothan HA**, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020; **109**: 102433 [PMID: 32113704 DOI: 10.1016/j.jaut.2020.102433]

91 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]

92 **Chen S**, Huang B, Luo DJ, Li X, Yang F, Zhao Y, Nie X, Huang BX. [Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases]. *Zhonghua Bing Li Xue Za Zhi* 2020; **49**: 418-423 [PMID: 32114744 DOI: 10.3760/cma.j.cn112151-20200225-00138]

93 **Shi HS**, Yu J, Zheng CS. Radiological diagnosis of new coronavirus infected pneumonitis: expert recommendation from the Chinese Society of Radiology. *Zhonghua Fang She Xue Za Zhi* 2020; 279-285

94 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

95 **Gentile F**, Aimo A, Forfori F, Catapano G, Clemente A, Cademartiri F, Emdin M, Giannoni A. COVID-19 and risk of pulmonary fibrosis: the importance of planning ahead. *Eur J Prev Cardiol* 2020; **27**: 1442-1446 [PMID: 32551971 DOI: 10.1177/2047487320932695]

96 **Chen LYC**, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. *Eur Respir J* 2020; **56** [PMID: 32883678 DOI: 10.1183/13993003.03006-2020]

97 **Xia W**, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr Pulmonol* 2020; **55**: 1169-1174 [PMID: 32134205 DOI: 10.1002/ppul.24718]

98 **Rostad BS**, Shah JH, Rostad CA, Jaggi P, Richer EJ, Linam LE, Alazraki AL, Riedesel EL, Milla SS. Chest radiograph features of multisystem inflammatory syndrome in children (MIS-C) compared to pediatric COVID-19. *Pediatr Radiol* 2021; **51**: 231-238 [PMID: 33404786 DOI: 10.1007/s00247-020-04921-9]

99 **Samadizadeh S**, Masoudi M, Rastegar M, Salimi V, Shahbaz MB, Tahamtan A. COVID-19: Why does disease severity vary among individuals? *Respir Med* 2021; **180**: 106356 [PMID: 33713961 DOI: 10.1016/j.rmed.2021.106356]

100 **Percivale I**, Danna PSC, Falaschi Z, Berardo S, Gangi S, Tricca S, Castello LM, Barini M, Airoldi C, Carriero A. Men and women affected by Sars-CoV-2 pneumonia: same CT features but different outcome. *Clin Radiol* 2021; **76**: 235.e25-235. e34 [PMID: 33358500 DOI: 10.1016/j.crad.2020.11.119]

World Journal of Radiology

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

World J Radiol 2021 April 28; 13(4): 94-101

DOI: 10.4329/wjr.v13.i4.94

ISSN 1949-8470 (online)

MINIREVIEWS

Cardio-thoracic imaging and COVID-19 in the pediatric population: A narrative review

Paolo Ferrero, Isabelle Piazza

ORCID number: Paolo Ferrero 0000-0001-7967-7417; Isabelle Piazza 0000-0002-1316-8107.

Author contributions: Ferrero P wrote the paper; Piazza I performed and collected the data.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Paolo Ferrero, ACHD Unit–Pediatric and Adult Congenital Heart Centre, IRCCS-Policlinico San Donato, San Donato Milanese 20097, Milan, Italy

Isabelle Piazza, Department of Emergency Medicine, ASST Papa Giovanni XXIII, Bergamo 24127, Italy

Corresponding author: Paolo Ferrero, FESC, MD, ACHD Unit–Pediatric and Adult Congenital Heart Centre, IRCCS-Policlinico San Donato, Via Morandi 30, San Donato Milanese 20097, Milan, Italy. ferrerop41@gmail.com

Abstract

Worldwide experience about coronavirus disease 2019 (COVID-19) pandemics suggests that symptomatic disease is significantly less frequent in the pediatric age range. Nevertheless, multi-system inflammatory syndrome has been consistently reported in children and has been associated with severe acute respiratory syndrome coronavirus 2 exposure. In this paper we give an overview of the multimodality chest imaging of pediatric patients with suspected COVID-19, focusing on relevant differences with adults.

Key Words: COVID-19; Radiology; Imaging; Chest; Pediatric; SARS-CoV-2

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Although the pattern of lung involvement of coronavirus disease 2019 in children reproduces the pathology described in the general population, traditional imaging modalities have several limitations in this age group. Specific and unique findings are mainly related to the occurrence of multi-system inflammatory syndrome which is a peculiar complication reproducibly reported in the pediatric population. This syndrome is characterized by occurrence of atypical symptoms as compared with presentation in adult and multimodality imaging approach has to be contemplated.

Citation: Ferrero P, Piazza I. Cardio-thoracic imaging and COVID-19 in the pediatric population: A narrative review. *World J Radiol* 2021; 13(4): 94-101

URL: https://www.wjgnet.com/1949-8470/full/v13/i4/94.htm

DOI: https://dx.doi.org/10.4329/wjr.v13.i4.94

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

Received: January 21, 2021
Peer-review started: January 21, 2021
First decision: February 12, 2021
Revised: February 19, 2021
Accepted: April 13, 2021
Article in press: April 13, 2021
Published online: April 28, 2021

P-Reviewer: He YF, Papazafiropoulou A
S-Editor: Fan JR
L-Editor: A
P-Editor: Yuan YY

INTRODUCTION

Coronavirus disease 2019 (COVID-19) in its most frequent clinical manifestation causes a respiratory syndrome, due to a single stranded RNA beta coronavirus infection, that may results in acute respiratory distress syndrome. Due to the clinical association of this new virus with the onset of a respiratory syndrome it has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, it has been shown that many organs and tissues, including heart, vessels, and brain may be involved in SARS-CoV-2. Furthermore COVID-19 has been repeatedly reported in the pediatric population. Among the 962 million people infected worldwide so far, the pediatric age group constitute less than 2%. Overall atypical and asymptomatic infections are more frequent in children. This might be due to a lower exposure or less susceptible lung barrier due to immature angiotensin enzyme-2 receptors[1,2].

Likewise in adults, COVID-19 in infants is characterized by a background of inflammatory activation that may involve different tissues and organs in different phases. In those area particularly hit by the virus during the first pandemic phase, we observed a surge of mucocutaneous inflammatory syndrome resembling Kawasaki disease[3,4]. This condition has been subsequently named multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19[5,6].

The proteus clinical presentation of COVID-19 in children together with the possible occurrence of MIS-C prompt a different diagnostic approach in this age group as compared to adults. (Table 1) Differently from the general population data about image findings in pediatric COVID-19 are scant and sometimes conflictual.

We aim to provide an overview of peculiarity of thoracic diagnostic algorithm in the pediatric age group, focusing relevant differences with adults.

METHODS

For this narrative review the following keywords: COVID-19, SARS-CoV-2, radiology, imaging and pediatric in different combinations. Papers were screened accordingly to the information provided in the abstract. Only manuscripts written in English and focused on the thoracic district were deemed eligible for inclusion. Within the pediatric age group we did not consider any specific limit of range and all papers dealing with patients younger than 18 years were included point of view papers and editorials were also excluded. Additional data were retrieved from the references of individual papers, whenever appropriate.

Pathophysiology

Several pathophysiologic issues have been advocated to explain differences in clinical presentation of pediatric patients. In particular, an association between SARS-CoV-2 infection and a multi systemic inflammatory syndrome has been consistently reported[7-10]. Diagnostic criteria of MIS-C include fever, hypotension, evidence of cardiac or other end-organ injury together with at least two of the following: maculo-papular rash, non purulent conjunctivitis, mucocutaneous inflammation and gas-trointestinal symptoms[6].

This particular presentation, characterized by multi organ inflammation rather than severe respiratory syndrome, may be due to a different immune system reactivity and a more immature and different distribution of angiotensin-converting enzyme II receptor, which is the entry receptor for the virus. The association of syndromes and the degree of lung maturity can further contribute to modulate the clinical presentation. As far as the thoracic involvement is concerned, coronary involvement is a rare peculiar feature of MIS-C sharing the clinical and anatomic presentation with Kawasaki disease[4].

Characteristics of chest X-ray changes in pediatric COVID-19

Although the concept that radiological manifestations of COVID-19 vary among different age group, information about sensitivity, specificity and characteristic findings of chest X-ray in the pediatric population are limited and conflicting[11].

Chest X-ray may be negative in more than 1/3 of patients in the pediatric group age. Reported sensitivity of chest X-ray vary from 25% to 69%[12].

Commonly encountered chest X-ray abnormalities are consolidations and ground glass opacities (GGO), differently from the adult variant, peribronchial thickening is more frequent in this clinical setting (60% to 80%)[13]. Peribronchial thickening is however aspecific and can be seen in other variant of viral pneumonia in children,

Table 1 Differences of coronavirus disease 2019 relevant characteristics between adult and pediatric population

	Adults	Pediatric age group
Epidemiology	97%-98% of 962 million (worldwide)	About 2% < 18 yr
Clinical presentation	Respiratory symptoms frequent	Respiratory symptoms not frequent
	Multisystem inflammatory toxic syndrome not frequent	Multisystem inflammatory toxic syndrome typical (MIS-C)
Pleuro-pericardial involvement	Not frequent	Frequent
Myocardial dysfunction	Not frequent	Frequent in the context of MIS-C
Chest X-RAY	Routinely done, good sensitivity	Low sensitivity
	GGO sub-pleural	GGO sub-pleural basal
	Nodular consolidation	Nodular consolidation not frequent
	Peri-bronchial thickening not frequent	Peri-bronchial thickening frequent
	Pleural effusion rare	Pleural effusion possible
CT	High sensitivity	Good sensitivity, performed inly in selected cases
	GGO sub-pleural	GGO sub-pleural basal
	Nodular consolidation	Nodular consolidation not frequent
	Peri-bronchial thickening not frequent	Peri-bronchial thickening frequent
	Pleural effusion rare	Pleural effusion possible
Suggested screening modality	Low-dose CT	Bed-side echo

MIS-C: Multisystem inflammatory syndrome in children; GGO: Ground glass opacities; CT: Computer tomography.

while hyperinflation, which is another recognized hallmark, was not reported. Reason for chest X-ray low sensitivity is the higher prevalence of lower density, smaller size and basal opacities, obscured by the diaphragm and hepatic dome[11].

Halo sign, which is deemed to be highly specific of COVID-19, has been observed also in 50% of pediatric cases in a published series, while other finding such as crazy paving pattern or organizing pneumonia pattern, which have been reported as typical in adult with COVID-19, were not consistently reported in pediatric series[13,14].

Finally, pleural effusion is a rare manifestation of COVID-19 in adults and is almost uniquely seen in the pediatric age range being associated with involvement of other serous cavities in patients with MIS-C.

Computer tomography

Although computer tomography (CT) has a much higher sensitivity likewise chest X-ray, according to some reports, pediatric patients are three time more likely to have normal CT scan as compared to adult. However, pooling together literature data, percentage of negative CT is very variable, ranging between 10% and 30%[15,16].

In adults, several series have found that COVID-19 typically presents with peripheral and posterior GGO[17,18]. Opacities may present in a confluent fashion or as more delimited scattered round opacities (so called 'crazy paving patter'). Other peculiar findings typical of organizing pneumonia are 'halo sign' or 'reversal halo sign' [19].

It has been hypothesized that the predominant localization of radiological findings at the periphery of the lung and the presence of enlargement of the vessel feeding the involved lung area (feeding vessel sign) may be explained by the inflammatory involvement of small vessels[20]. Based on these pathogenetic models, standardized reporting methodologies have been devised providing also a ranking of suspicious according to the presence of cluster of signs[19]. However application of diagnostic CT scores based on adult cohorts resulted in low probability of the disease in the pediatric population[11]. According to this background, utilization of low dose CT as screening tool in children with laboratory inconclusive findings is controversial.

As compared to adults, pediatric series show a lower total number of pulmonary lesions and smaller size of them. Bilateral GGO confirmed to be the most common finding accounting for almost 90% of the positive scans[16,21]. Likewise general population GGO may present different stage of consolidation (halo sign) in 50% of cases. As previously discussed about chest X-ray, peribronchial and bronco-vascular thickening

are more common in children[22,23].

Role of thoracic ultrasounds

Lung ultrasounds (LUS) is consistently used in the diagnostic process of different lung diseases in both adults and children[24,25].

Among patients with suspected or ascertained COVID-19, elementary ultrasonographic findings in the context of lung injury are: Normal lung sliding, B lines, that are perpendicular hyperechogenic streaks due to loss of aerated space, subpleural nodules, pleural effusion. Clusters of these signs have been described in association with different probability and severity of the disease[26]. Evidences about diagnostic accuracy in patient with COVID-19 in the pediatric age group is limited to small series. According to these data LUS, although less sensitive than CT, is more sensitive than chest X-ray[27]. In the largest multi-center cohort of 40 children with suspected COVID-19 undergoing LUS, the diagnosis of pulmonary involvement was done in 10 out of 12 patients with positive CT findings, in seven of whom chest X-ray was normal[28].

Common findings were: A line in 72%, various pattern of B line in 27%, while parenchymal nodular consolidation were more rare as compared with adults (10%)[28].

As previously mentioned, clusters of inflammatory syndrome associated with SARS-CoV-2 (MIS-C) have been consistently reported. Even though these patients usually present without respiratory symptoms, LUS showed loss of aeration or pleural effusion in all of them in a small case series[29].

Despite these limited data, use of LUS in this clinical setting might be advocated since it allow early and repeated bedside assessment avoiding X-ray exposure and patient transport in the imaging department, which might potentially increase the risk of virus spread.

Additional specific image modalities

Coagulation disorders have been recognized as a major complication of COVID-19 significantly affecting the prognosis[30]. In this context the ventilation/perfusion single photon emission computed tomography, either as single modality or combined with computed tomography (V/Q SPECT) can be used in selected case to diagnose pulmonary embolism in case of iodinated medium allergy or to integrate CT images. In the pediatric population clinically relevant pulmonary embolism are rarely reported therefore the need to exclude this complication is far less compelling[31]. Furthermore radionuclide exposure and the risk of infection spread across different departments, deeply limits the room for this diagnostic resource in the clinical practice.

Multimodal cardiovascular imaging

Since the first COVID-19 outbreak, different degree of myocardial injury have been reported[32-34]. Biomarker evidence of myocardial injury has been associated with a higher mortality risk in COVID-19 patients[35]. Although typical clinical presentation of COVID-19 in the pediatric age group is rare, association of MIS-C with SARS-CoV-2 exposure has been reproducibly observed. This syndrome, originally labelled ad Kawasaky-like, is characterized by various degree of myocardial and coronary inflammatory involvement[3,4,36]. Even-though clinical manifestation of this syndrome is extremely variable abdominal and gastrointestinal symptoms are key diagnostic features, being present in up to 80%, while cardiovascular involvement my go initially unrecognized[37]. Although abdominal imaging is not the focus of this review, it has to be highlighted that ultrasound of this district is usually the first diagnostic exam performed, furthermore cardiovascular involvement and abdominal imaging are strictly related. Abdominal anechoic space and hepatomegaly are the most frequent findings. In one study screening abdominal echo was able to disclose associated pleuro-pericardial effusion and cardiomegalia in almost 37% and 12% of case, respectively[5]. From the practical point of view, given the high incidence of gastrointestinal symptoms in children with COVID-19 related MIS-C, abdominal screening echo may help in differentiate this condition from other abdominal urgencies[31,38,39].

Trans-thoracic echo has a high diagnostic sensitivity in the acute phase by demonstrating ventricular dysfunction and coronary remodeling[40]. Consistently with echocardiografic diagnostic criteria in typical complete Kawasaky syndrome, coronary size is standardized according to the deviation from the median in the general population with the same body surface area (z score)[41]. Cardiac depression, although sometimes severe at presentation, requiring inotropic or even mechanical circulatory support, recovers in around 70% of cases[7]. Nevertheless, given the limited knowledge about the virus pathogenicity and natural history of the disease in the long term, echocar-

diographic follow up at one month and one year, in patients with documented cardiac or coronary involvement (z score > 25), is recommended.

Cardiac CT scan can provide accurate evaluation of the coronary artery anatomy and may be considered in patients with difficult acoustic windows or with extensive coronary involvement. Cardiac magnetic resonance imaging may be useful during the initial hospitalization or approximately 3 mo post-acute illness to evaluate ventricular function and myocardial characteristics including edema, diffuse fibrosis, and scar by myocardial late gadolinium enhancement[42,43].

Differences of COVID-19 crucial characteristics between adult and children

Table 1 summarizes main differences in COVID-19 that are relevant in planning the diagnostic algorithm. We considered the following nosological variables: Epidemiology, pathophysiology, natural history, image sensitivity.

So far about 96 million COVID-19 cases have been reported, of whom only less than 2% occurred in patients less than 18 years old. Furthermore, as compared with adult cohorts, fewer patients have a severe or critical course (6% *vs* 20%)[1].

Distribution of rate of hospitalization displays a cluster in the age group lower than two years and higher than 10 d. Although infants younger than two years rarely present pneumonia, admission is motivated by poor tolerance of fever. As far as the diagnostic algorithm is concerned, although lung involvement in SARS-CoV-2 infection in the pediatric age range may largely reproduce those reported in the general population, sensitivity of chest X-ray is significantly lower. As a consequence tradi-tional chest imaging is a poor screening test in children with suspected COVID-19. On the other hand, fast bedside ultrasound screening has a high diagnostic yield as may easily disclose multi organ involvement consistent with the infection.

CONCLUSION

COVID-19 pandemics has prompted worldwide rapid reorganization of imaging departments. While the incidence of clinically relevant COVID-19 in pediatric population was previously deemed very low, the observation of a late peak of SARS-CoV-2 related disease in this age group prompted the development of specific management algorithms (Figure 1).

Knowledge about imaging diagnostic findings has significant grown, however significant differences in the pathophysiology and clinical presentation in children as compared with adults must be taken into account. Observational data indicate that both chest X-ray and CT have a lower diagnostic yield and can show peculiar findings, such as broncovascular thickening and pleuro-pericardial effusion, in pediatric patients. The thoracic echo may have a relevant role in the diagnostic algorithm in order to screen and monitor lung involvement as well as specific features of MIS-C in this clinical setting. Furthermore, X-ray exposure and risk of virus spread during patient transport should be taken into account when considering repeated traditional imaging.

This review is based mainly on small case series with heterogeneous populations and sometimes contradictory conclusion about findings and appropriateness of the various diagnostic tools. This limitation does not allow to pool together the data and to provide general recommendation with a sufficient grade of evidence.

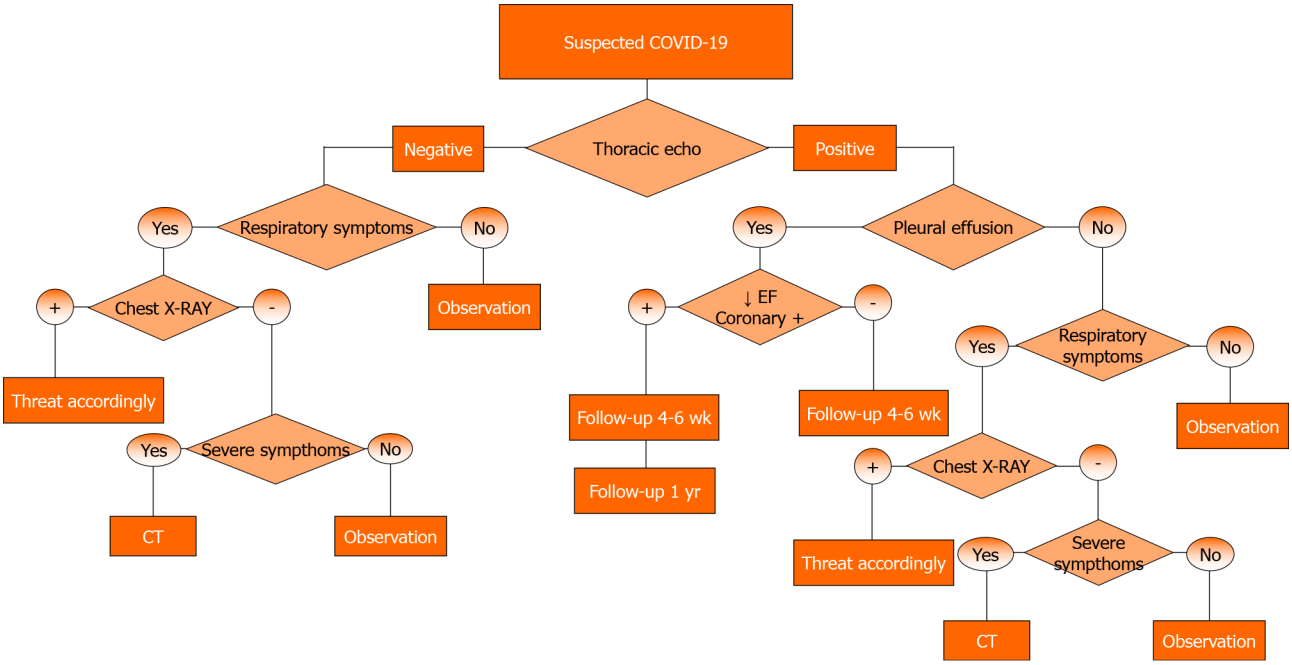


Figure 1 Proposed multimodel diagnostic algorithm. COVID-19: Coronavirus disease 2019; CT: Computer tomography.

REFERENCES

1 **Dong Y**, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020; **145** [PMID: 32179660 DOI: 10.1542/peds.2020-0702]

2 **Chan JF**, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514-523 [PMID: 31986261 DOI: 10.1016/S0140-6736(20)30154-9]

3 **Verdoni L**, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395**: 1771-1778 [PMID: 32410760 DOI: 10.1016/S0140-6736(20)31103-X]

4 **Ferrero P**, Piazza I, Bonino C, Ciuffreda M. Patterns of myocardial involvement in children during COVID-19 pandemic: Early experience from northern Italy. *Ann Pediatr Cardiol* 2020; **13**: 230-233 [PMID: 32863659 DOI: 10.4103/apc.APC_77_20]

5 **Blumfield E**, Levin TL, Kurian J, Lee EY, Liszewski MC. Imaging Findings in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With Coronavirus Disease (COVID-19). *AJR Am J Roentgenol* 2021; **216**: 507-517 [PMID: 32755212 DOI: 10.2214/AJR.20.24032]

6 **New York City Department of Health**. 2020 Health Advisory #16: Updated Reporting. Requirements for Multisystem Inflammatory Syndrome in Children Associated with COVID-19 2020. [cited 27 May 2020]. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/han/advisory/2020/covid-19-providers-mis-c.pdf.

7 **Belhadjer Z**, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, Auriau J, Grimaud M, Oualha M, Beghetti M, Wacker J, Ovaert C, Hascoet S, Selegny M, Malekzadeh-Milani S, Maltret A, Bosser G, Giroux N, Bonnemains L, Bordet J, Di Filippo S, Mauran P, Falcon-Eicher S, Thambo JB, Lefort B, Moceri P, Houyel L, Renolleau S, Bonnet D. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation* 2020; **142**: 429-436 [PMID: 32418446 DOI: 10.1161/CIRCULATIONAHA.120.048360]

8 **Riphagen S**, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395**: 1607-1608 [PMID: 32386565 DOI: 10.1016/S0140-6736(20)31094-1]

9 **Blondiaux E**, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, Schnuriger A, Lorrot M, Guedj R, Ducou le Pointe H. Cardiac MRI in Children with Multisystem Inflammatory Syndrome Associated with COVID-19. *Radiology* 2020; **297**: E283-E288 [PMID: 32515676 DOI: 10.1148/radiol.2020202288]

10 **New York State Department of Health website**. Childhood inflammatory disease relat-ed to COVID-19: overview & stats. 2020. [cited 27 May 2020]. Available from: https://profiles.health.ny.gov/#5.05/42.84/-75.88.

11 **Bayramoglu Z**, Canıpek E, Comert RG, Gasimli N, Kaba O, Sarı Yanartaş M, Hançerli Torun S, Somer A, Erturk SM. Imaging Features of Pediatric COVID-19 on Chest Radiography and Chest CT:

A Retrospective, Single-Center Study. *Acad Radiol* 2021; **28**: 18-27 [PMID: 33067091 DOI: 10.1016/j.acra.2020.10.002]

12 **Choi H**, Qi X, Yoon SH, Park SJ, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, Park CM, Kim YH, Lei J, Hong JH, Kim H, Hwang EJ, Yoo SJ, Nam JG, Lee CH, Goo JM. Erratum: Extension of Coronavirus Disease 2019 (COVID-19) on Chest CT and Implications for Chest Radiograph Interpretation. *Radiol Cardiothorac Imaging* 2020; **2**: e204001 [PMID: 33779627 DOI: 10.1148/ryct.2020204001]

13 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

14 **Oterino Serrano C**, Alonso E, Andrés M, Buitrago NM, Pérez Vigara A, Parrón Pajares M, Cuesta López E, Garzón Moll G, Martin Espin I, Bueno Barriocanal M, De Ceano-Vivas la Calle M, Calvo Rey C, Bret-Zurita M. Pediatric chest x-ray in covid-19 infection. *Eur J Radiol* 2020; **131**: 109236 [PMID: 32932176 DOI: 10.1016/j.ejrad.2020.109236]

15 **Nino G**, Zember J, Sanchez-Jacob R, Gutierrez MJ, Sharma K, Linguraru MG. Pediatric lung imaging features of COVID-19: A systematic review and meta-analysis. *Pediatr Pulmonol* 2021; **56**: 252-263 [PMID: 32926572 DOI: 10.1002/ppul.25070]

16 **Caro-Dominguez P**, Shelmerdine SC, Toso S, Secinaro A, Toma P, Damasio MB, Navallas M, Riaza-Martin L, Gomez-Pastrana D, Ghadimi Mahani M, Desoky SM, Ugas Charcape CF, Almanza-Aranda J, Ucar ME, Lovrenski J, Gorkem SB, Alexopoulou E, Ciet P, van Schuppen J, Ducou le Pointe H, Goo HW, Kellenberger CJ, Raissaki M, Owens CM, Hirsch FW, van Rijn RR; Collaborators of the European Society of Paediatric Radiology Cardiothoracic Task Force. Thoracic imaging of coronavirus disease 2019 (COVID-19) in children: a series of 91 cases. *Pediatr Radiol* 2020; **50**: 1354-1368 [PMID: 32749530 DOI: 10.1007/s00247-020-04747-5]

17 **D'Andrea A**, Radmilovic J, Carbone A, Forni A, Tagliamonte E, Riegler L, Liccardo B, Crescibene F, Sirignano C, Esposito G, Bossone E. Multimodality imaging in COVID-19 patients: A key role from diagnosis to prognosis. *World J Radiol* 2020; **12**: 261-271 [PMID: 33362917 DOI: 10.4329/wjr.v12.i11.261]

18 **Landete P**, Quezada Loaiza CA, Aldave-Orzaiz B, Muñiz SH, Maldonado A, Zamora E, Sam Cerna AC, Del Cerro E, Alonso RC, Couñago F. Clinical features and radiological manifestations of COVID-19 disease. *World J Radiol* 2020; **12**: 247-260 [PMID: 33362916 DOI: 10.4329/wjr.v12.i11.247]

19 **Salehi S**, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *AJR Am J Roentgenol* 2020; **215**: 87-93 [PMID: 32174129 DOI: 10.2214/AJR.20.23034]

20 **Magro C**, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res* 2020; **220**: 1-13 [PMID: 32299776 DOI: 10.1016/j.trsl.2020.04.007]

21 **Steinberger S**, Lin B, Bernheim A, Chung M, Gao Y, Xie Z, Zhao T, Xia J, Mei X, Little BP. CT Features of Coronavirus Disease (COVID-19) in 30 Pediatric Patients. *AJR Am J Roentgenol* 2020; **215**: 1303-1311 [PMID: 32442030 DOI: 10.2214/AJR.20.23145]

22 **Chen A**, Huang J, Liao Y, Liu Z, Chen D, Yang C, Yang R, Wei X. Differences in Clinical and Imaging Presentation of Pediatric Patients with COVID-19 in Comparison with Adults. *Radiol Cardiothorac Imaging* 2020; **2**: e200117 [PMID: 33778567 DOI: 10.1148/ryct.2020200117]

23 **Foust AM**, Phillips GS, Chun WC, Daltro P, Das KM, Garcia-Peña P, Kilborn T, Winant AJ, Lee EY. International Expert Consensus Statement on Chest Imaging in Pediatric COVID-19 Patient Management: Imaging Findings, Imaging Study Reporting and Im-aging Study Recommendations. *Radiol Cardiothorac Imaging* 2020; **2:** e200214. [PMID: 33778577 DOI: 10.1148/ryct.2020200214]

24 **Jones BP**, Tay ET, Elikashvili I, Sanders JE, Paul AZ, Nelson BP, Spina LA, Tsung JW. Feasibility and Safety of Substituting Lung Ultrasonography for Chest Radiography When Diagnosing Pneumonia in Children: A Randomized Controlled Trial. *Chest* 2016; **150**: 131-138 [PMID: 26923626 DOI: 10.1016/j.chest.2016.02.643]

25 **Vazquez Martínez JL**, Pérez-Caballero Macarrón C, Coca Pérez A, Tapia Moreno R, Otheo de Tejada E. Short report - Usefulness of point-of-care ultrasound in pediatric SARS-CoV-2 infection. *Eur Rev Med Pharmacol Sci* 2020; **24**: 7801-7803 [PMID: 32744707 DOI: 10.26355/eurrev_202007_22284]

26 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for International Standardization of the Use of Lung Ultrasound for Patients With COVID-19: A Simple, Quantitative, Reproducible Method. *J Ultrasound Med* 2020; **39**: 1413-1419 [PMID: 32227492 DOI: 10.1002/jum.15285]

27 **Musolino AM**, Supino MC, Buonsenso D, Ferro V, Valentini P, Magistrelli A, Lombardi MH, Romani L, D'Argenio P, Campana A; Roman Lung Ultrasound Study Team for Pediatric COVID-19 (ROMULUS COVID Team). Lung Ultrasound in Children with COVID-19: Preliminary Findings. *Ultrasound Med Biol* 2020; **46**: 2094-2098 [PMID: 32409232 DOI: 10.1016/j.ultrasmedbio.2020.04.026]

28 **Hizal M**, Aykac K, Yayla BCC, Yilmaz A, Altun D, Akkaya HE, Bayhan GI, Kurt ANC, Karakaya J, Ozsurekci Y, Ceyhan M. Diagnostic value of lung ultrasonography in children with COVID-19.

Pediatr Pulmonol 2020 [PMID: 33085218 DOI: 10.1002/ppul.25127]

29 **Guitart C**, Suárez R, Girona M, Bobillo-Perez S, Hernández L, Balaguer M, Cambra FJ, Jordan I; KIDS-Corona study group, Kids Corona Platform. Lung ultrasound findings in pediatric patients with COVID-19. *Eur J Pediatr* 2021; **180**: 1117-1123 [PMID: 33089388 DOI: 10.1007/s00431-020-03839-6]

30 **Poissy J**, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S; Lille ICU Haemostasis COVID-19 Group. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation* 2020; **142**: 184-186 [PMID: 32330083 DOI: 10.1161/CIRCULATIONAHA.120.047430]

31 **Girona-Alarcon M**, Bobillo-Perez S, Sole-Ribalta A, Hernandez L, Guitart C, Suarez R, Balaguer M, Cambra FJ, Jordan I; KIDS-Corona study group; Kids Corona Platform. The different manifestations of COVID-19 in adults and children: a cohort study in an intensive care unit. *BMC Infect Dis* 2021; **21**: 87 [PMID: 33472588 DOI: 10.1186/s12879-021-05786-5]

32 **Wang T**, Du Z, Zhu F, Cao Z, An Y, Gao Y, Jiang B. Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet* 2020; **395**: e52 [PMID: 32171074 DOI: 10.1016/S0140-6736(20)30558-4]

33 **Inciardi RM**, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 819-824 [PMID: 32219357 DOI: 10.1001/jamacardio.2020.1096]

34 **Gnecchi M**, Moretti F, Bassi EM, Leonardi S, Totaro R, Perotti L, Zuccaro V, Perlini S, Preda L, Baldanti F, Bruno R, Visconti LO. Myocarditis in a 16-year-old boy positive for SARS-CoV-2. *Lancet* 2020; **395**: e116 [PMID: 32593338 DOI: 10.1016/S0140-6736(20)31307-6]

35 **Nie SF**, Yu M, Xie T, Yang F, Wang HB, Wang ZH, Li M, Gao XL, Lv BJ, Wang SJ, Zhang XB, He SL, Qiu ZH, Liao YH, Zhou ZH, Cheng X. Cardiac Troponin I Is an Independent Predictor for Mortality in Hospitalized Patients With COVID-19. *Circulation* 2020; **142**: 608-610 [PMID: 32539541 DOI: 10.1161/CIRCULATIONAHA.120.048789]

36 **Wacker J**, Malaspinas I, Aggoun Y, Bordessoule A, Vallée JP, Beghetti M. Coronary artery dilatation in a child with hyperinflammatory syndrome with SARS-CoV-2-positive serology. *Eur Heart J* 2020; **41**: 3103 [PMID: 32620946 DOI: 10.1093/eurheartj/ehaa536]

37 **Hameed S**, Elbaaly H, Reid CEL, Santos RMF, Shivamurthy V, Wong J, Jogeesvaran KH. Spectrum of Imaging Findings at Chest Radiography, US, CT, and MRI in Multisystem Inflammatory Syndrome in Children Associated with COVID-19. *Radiology* 2021; **298**: E1-E10 [PMID: 32584166 DOI: 10.1148/radiol.2020202543]

38 **Revzin MV**, Raza S, Warshawsky R, D'Agostino C, Srivastava NC, Bader AS, Malhotra A, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 1: Viral Pathogenesis and Pulmonary and Vascular System Complications. *Radiographics* 2020; **40**: 1574-1599 [PMID: 33001783 DOI: 10.1148/rg.2020200149]

39 **Revzin MV**, Raza S, Srivastava NC, Warshawsky R, D'Agostino C, Malhotra A, Bader AS, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 2: From Cardiac Complications to Pediatric Manifestations. *Radiographics* 2020; **40**: 1866-1892 [PMID: 33136488 DOI: 10.1148/rg.2020200195]

40 **Rodriguez-Gonzalez M**, Rodríguez-Campoy P, Sánchez-Códez M, Gutiérrez-Rosa I, Castellano-Martinez A, Rodríguez-Benítez A. New onset severe right ventricular failure associated with COVID-19 in a young infant without previous heart disease. *Cardiol Young* 2020; **30**: 1346-1349 [PMID: 32600496 DOI: 10.1017/S1047951120001857]

41 **Valverde I**, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, Kuciñska B, Mannarino S, Tamariz-Martel A, Gutierrez-Larraya F, Soda G, Vandekerckhove K, Gonzalez-Barlatay F, McMahon CJ, Marcora S, Napoleone CP, Duong P, Tuo G, Deri A, Nepali G, Ilina M, Ciliberti P, Miller O; AEPC COVID-19 Rapid Response Team*. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. *Circulation* 2021; **143**: 21-32 [PMID: 33166189 DOI: 10.1161/CIRCULATIONAHA.120.050065]

42 **Alsaied T**, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, Newburger JW, de Ferranti S, Friedman KG. Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children. *Circulation* 2021; **143**: 78-88 [PMID: 33166178 DOI: 10.1161/CIRCULATIONAHA.120.049836]

43 **Prieto LM**, Toral B, LLorente A, Coca D, Blázquez-Gamero D. Cardiovascular magnetic resonance imaging in children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 and heart dysfunction. *Clin Microbiol Infect* 2020 [PMID: 33049415 DOI: 10.1016/j.cmi.2020.10.005]

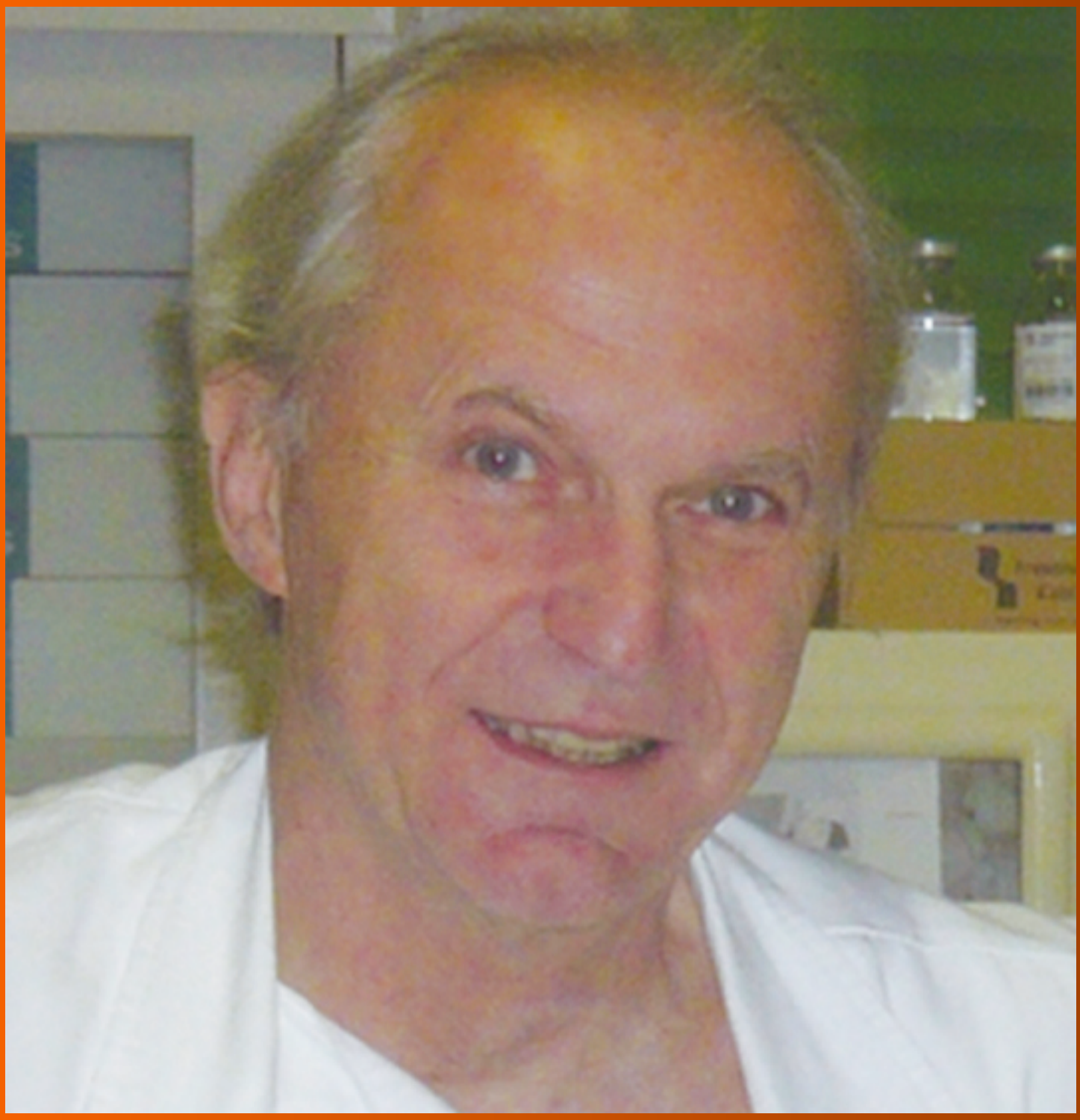
Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 May 28; 13(5): 102-148



Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 5 May 28, 2021

REVIEW

ORIGINAL ARTICLE

Prospective Study

World Journal of Radiology

Monthly Volume 13 Number 5 May 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Sergio Sartori, MD, Professor, Chief, Section of Interventional Ultrasound, Department of Internal Medicine, Azienda Ospedaliera Universitaria S. Anna, Ferrara 44100, Italy. srs@unife.it

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
May 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 May 28; 13(5): 102-121

DOI: 10.4329/wjr.v13.i5.102

ISSN 1949-8470 (online)

REVIEW

Challenges and optimization strategies in medical imaging service delivery during COVID-19

Yi Xiang Tay, Suchart Kothan, Sundaran Kada, Sihui Cai, Christopher Wai Keung Lai

ORCID number: Yi Xiang Tay 0000-0001-8322-1500; Suchart Kothan 0000-0001-7390-8878; Sundaran Kada 0000-0001-9241-6705; Sihui Cai 0000-0001-9104-9114; Christopher Wai Keung Lai 0000-0002-8010-7232.

Author contributions: Lai CWK contributed to the design of this review; Tay YX contributed to the first draft of this manuscript; all authors contributed to the review of the draft and final version of this manuscript.

Conflict-of-interest statement: No conflict of interest for this work.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear

Yi Xiang Tay, Sihui Cai, Radiography Department, Singapore General Hospital, Singapore 169608, Singapore

Suchart Kothan, Center of Radiation Research and Medical Imaging, Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai 50000, Thailand

Sundaran Kada, Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen Postbox 7030, 5020 Bergen, Norway

Christopher Wai Keung Lai, Department of Health and Social Sciences, Singapore Institute of Technology, Singapore 138683, Singapore

Corresponding author: Christopher Wai Keung Lai, PhD, Associate Professor, Department of Health and Social Sciences, Singapore Institute of Technology, 10 Dover Drive, Singapore 138683, Singapore. chris.lai@singaporetech.edu.sg

Abstract

In coronavirus disease 2019 (COVID-19), medical imaging plays an essential role in the diagnosis, management and disease progression surveillance. Chest radiography and computed tomography are commonly used imaging techniques globally during this pandemic. As the pandemic continues to unfold, many healthcare systems worldwide struggle to balance the heavy strain due to overwhelming demand for healthcare resources. Changes are required across the entire healthcare system and medical imaging departments are no exception. The COVID-19 pandemic had a devastating impact on medical imaging practices. It is now time to pay further attention to the profound challenges of COVID-19 on medical imaging services and develop effective strategies to get ahead of the crisis. Additionally, preparation for operations and survival in the post-pandemic future are necessary considerations. This review aims to comprehensively examine the challenges and optimization of delivering medical imaging services in relation to the current COVID-19 global pandemic, including the role of medical imaging during these challenging times and potential future directions post-COVID-19.

Key Words: COVID-19; Medical imaging service; Pandemic; Optimization strategies; Radiology department; Radiography

medicine and medical imaging

Country/Territory of origin: Singapore

Peer-review report's scientific quality classification

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

Received: January 10, 2021
Peer-review started: January 10, 2021
First decision: April 6, 2021
Revised: April 10, 2021
Accepted: May 10, 2021
Article in press: May 10, 2021
Published online: May 28, 2021

P-Reviewer: Maurea S
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Wang LL

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In coronavirus disease 2019 (COVID-19) testing, there is a need for quick and accurate diagnosis of the disease. This has affirmed the significance of medical imaging (chest radiography and computed tomography) in the battle against COVID-19. The pandemic and the consequent mitigation measures have had a significant impact on the practices in medical imaging. Despite the large and dynamic challenge presented, patient safety and care are paramount. Necessary precautions must be instituted to ensure the safety of medical imaging professionals, patients and the public. As the pandemic continues to ravage our globe, medical imaging service providers need to exercise flexibility without compromising on patient safety.

Citation: Tay YX, Kothan S, Kada S, Cai S, Lai CWK. Challenges and optimization strategies in medical imaging service delivery during COVID-19. *World J Radiol* 2021; 13(5): 102-121
URL: https://www.wjgnet.com/1949-8470/full/v13/i5/102.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i5.102

INTRODUCTION

A cluster of unknown pneumonia cases was reported in Wuhan, Hubei Province, China on December 31, 2019. There were both similarities and differences in various aspects of this pathogen with the severe acute respiratory syndrome (SARS) that originated in China's Guangdong Province on November 27, 2002[1]. Despite the difference in epidemiology, like SARS, it presented as a respiratory disease which was officially named and announced by the World Health Organization (WHO) as "COVID-19" (coronavirus disease 2019), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2]. Most patients infected with COVID-19 had pneumonia and hence medical imaging became vital in the early diagnosis and assessment of disease course[3]. Moreover, the medical imaging role in an infectious disease outbreak had been well described and was epitomized by the SARS epidemic[4]. While the use of medical imaging techniques—chest radiography and computed tomography (CT) differed across countries, there was no doubt about the significance and importance of medical imaging in this COVID-19 pandemic[3,4]. The aim of this review is to highlight the challenges and optimization strategies in medical imaging service delivery in Singapore and around the world during this COVID-19 pandemic.

ESSENTIAL ROLES IN THE DIAGNOSIS OF COVID-19: CHEST RADIOGRAPHY AND CT

Chest radiography played an important role in the diagnosis of SARS during the 2003 outbreak in Hong Kong[5,6]. Despite poor sensitivity, patients with clinical and epidemiologic suspicion of SARS were evaluated by serial chest radiography[7]. A similar practice of serial chest radiography was also adopted in Singapore (together with Hong Kong, one of the 10 countries with the most cumulated numbers of cases)[8,9]. This practice included chest radiography for patients with contact history who had developed respiratory symptoms, even if afebrile, when person-to-person transmission was evident globally[5]. In fact, this was in line with the Centres for Disease Control and Prevention (CDC) recommendation at that time[5].

With the global resurgence of person-to-person transmission in the form of COVID-19, the sense of Déjà vu was vivid. During this pandemic, despite the trajectory use of CT scan in China as a screening tool[10], most radiology societies still do not endorse routine screening CT for COVID-19 pneumonia[11,12]. Although the WHO rapid advice guide for the use of chest imaging in COVID-19[13] highlighted considerations for choice of imaging modalities, it stopped short of recommending specific imaging modalities for different categories of patients. This could be attributed to the different community norms and public health directives[14].

Chest radiography was of greater value in patients with advanced symptoms as compared to those in the early course of their disease[14,15]. For patients who were encouraged to present once symptomatic, as was the case in Wuhan, China, chest radiography had little value as it was insensitive in mild or early COVID-19 infection[14-16]. In a similar vein, Singapore also had the public health directive for citizens to consult a doctor even when they had mild respiratory symptoms[17]. However, in Singapore, chest radiography remains the primary imaging modality of choice in COVID-19 screening, with a CT scan used only as a problem-solving tool[4,18]. On the other hand, some countries such as South Korea uses reverse transcription polymerase chain reaction (RT-PCR) for initial screening instead of relying on diagnostic imaging studies[19]. Nevertheless, chest radiography is a fundamental tool in the diagnosis, management and monitoring of disease[20-22]. Moreover, chest radiography is widely available (less resource intensive), coupled with features of rapid execution, low cost and function of bedside radiography. This enables chest radiography to be an important complement to clinical and epidemiological features in the battle against COVID-19[13,22].

On the other hand, although a CT scan has relatively low specificity, it has a relatively higher sensitivity as compared to chest radiography and RT-PCR[10,13]. This is useful in patients with some pre-existing pulmonary diseases and when results of RT-PCR tests are negative[10,13,14]. While there were differing views on the first assessment medical imaging technique for COVID-19 infection, there was no doubt of the importance of medical imaging services in the battle against COVID-19. Considerations on the choice of medical imaging technique were usually dependent on local practice patterns and resource availability[14].

Nevertheless, as mentioned in the multinational consensus statement from the Fleischner Society[14] — the choice of medical imaging techniques should be based on the clinical judgement of the clinical teams while considering the attributes of the techniques, local resources and expertise. In addition, the involvement of all stakeholders — referring clinician, radiologist and patient, in the decision-making on the choice of medical imaging of COVID-19 was encouraged[13]. Similarly, whenever possible, the patient should be provided with information on the chosen medical imaging techniques and the potential of the multiple imaging requirement highlighted[13].

CHALLENGES IN THE PROVISION OF MEDICAL IMAGING SERVICE DURING COVID-19

Limited manpower

Maintaining a healthy and adequate workforce is crucial in any infectious disease epidemic. Moreover, with screening, monitoring and evaluation roles undertaken by radiology in this COVID-19 pandemic, managing manpower was even more important. Given that more COVID-19 patients were being admitted and enough manpower would be required to meet the demands of increased workload, ensuring functional staff for continued service should not be undermined[23].

Within a month (January 30, 2020) after the first reported confirmed case of SARS-CoV-2, there were 82 confirmed cases outside of China with the majority of cases reported in Asia[24]. The WHO subsequently released its strategic objectives for the pandemic which included early identification, isolation and care of patients, including providing optimized care for infected patients[25]. Clearly, a substantial number of staff was required in response to this new infectious disease, especially when there was unprecedented numbers of people diagnosed with COVID-19 and seeking treatment.

At the early onset of the battle against COVID-19, Singapore faced the possibility of the healthcare system being overwhelmed. The Singapore Ministry of Health responded to the threat by initiating an island-wide call for former healthcare professionals (HCPs) to support the country's fight against the coronavirus, including doctors and allied health professionals[26]. A similar picture was seen globally, where retired doctors, nurses and medical students were mobilized to join the fight[26-30].

As the pandemic unfolded, many radiology departments experienced an increase in manpower demand due to many factors which included the increase in workload, and procedure time and the impact of team segregation[4,31,32]. A similar experience was also reported in low resource settings such as Ghana and Iran, although some regions reported a decline in general workload, in line with reports from North America and Europe, which could be attributed to low COVID-19 case intensities in these

regions[33,34]. Nonetheless, it was well established that the healthcare workforce was facing high adversity and workload as more countries were impacted by the spread of COVID-19[35].

To respond to the sudden surge and new waves of COVID-19, the radiology workforce had to be redeployed or re-assigned to other imaging modalities[33,36-38]. In tandem with the call for former HCPs, there was a need to reskill and/or upskill the returning workforce to support the current workforce. Clearly, a substantial amount of time had to be invested in creating training opportunities for staff to be prepared to face the pandemic. However, that would result in hours away from the clinical environment. Indeed, it was suggested that tens of thousands of radiographer hours would be invested to develop information to help radiographers worldwide to manage the imaging of COVID-19 patients using mobile chest radiography with appropriate infection control measures[39]. Notwithstanding, there was also the potential of the massive amount of replication of information globally while attempting to address this information deficiency[39]. Moreover, departments had to grapple with understaffing at the peak of the outbreak due to HCPs infections, self-isolation due to contact with positive cases and statutory paid sick leave in many countries globally[40].

Enhancement of infection control measures

In a radiology department, radiographers may be exposed to SARS-CoV-2 during mobile radiography and chest CT procedures. As these procedures were more often performed as part of routine diagnosis, assessment and monitoring of the disease, there was an increased risk of radiographers contracting COVID-19[41]. In addition, procedures with prolonged patient contact such as ultrasound and interventional radiology expose radiology staff to an even higher risk of infection[41-44]. At the same time, radiology services are a crossroad of heterogeneous subjects within hospitals; measures had to be taken to mitigate the risk of the radiology workforce being infected to protect other HCPs, patients and the general public[41,45].

It is well established that the shortage of personal protective equipment (PPE), lack of training in infection control measures, and poor PPE usage increase the risk of patient-HCP transmission of infection[46,47]. Indeed, the provision of adequate PPE is of paramount importance and is a critical component of infection control and prevention during this pandemic. However, globally, many departments were facing a shortage of PPE[48]. In fact, multiple reports of shortages of PPE, medical supplies and COVID-19 test kits had surfaced in various countries ranging from developing countries in Southeast Asia to developed countries like the United States[49,50]. This was worrying as previous lessons from other infectious disease outbreaks had identified PPE as a crucial element in reducing infections and deaths of HCPs[47]. During this pandemic, SARS-CoV-2 infection among HCPs was not unheard-of. China and Italy both reported infections and deaths of HCPs[50,51], while United States[52], Spain[46] and Qatar[53] all reported COVID-19 infection among its HCPs. This could lead to a decline in the healthcare workforce, resulting in unstable healthcare infrastructure, thus reducing the quality and quantity of care available while increasing the workload on remaining staff[47,54].

Although ensuring that HCPs are well protected is crucial in reducing viral transmission and sustaining health system capacity[47], equipment used in the radiology department is also a potential vector for transmission of the virus. Identified equipment include ultrasound units, non-portable modalities, such as CT or magnetic resonance imaging (MRI) and mobile radiography units[31,41,43,55,56]. The immerse challenge for infection control in the CT suite was epitomized in China where CT was often the first-line investigation for COVID-19[15]. The equipment had to be disinfected after exposure according to recommended guidelines by the vendors or institutions. Similarly, accessories such as keyboards, mice, viewing stations and blood pressure cuffs had to be disinfected accurately with appropriate and safe disinfectant[57,58]. Clearly, all potentially contaminated surfaces had to be disinfected to reduce the risk of virus transmission.

Limited resources

Provision of medical imaging services to many patients suspected of having or confirmed to have COVID-19 during the pandemic was a herculean task. The procedure duration was lengthened and complicated by strict infection control measures to mitigate infection risk in the radiology department[14,41,59]. This was highlighted by the American College of Radiology (ACR)[60] where it noted that CT decontamination after scanning COVID-19 patients might disrupt radiologic service availability. Studies sharing recommendations for infection control in the CT suite

were widely available. However, it also demonstrated the substantial time and resources needed during, pre- and post-CT scans, which was highlighted by the ACR[57,61,62]. While hospitals with more than one scanner could dedicate one scanner for scanning COVID-19 patients, it could not be instituted in all hospitals[63,64]. Therefore, in this pandemic, in some countries, CT cannot be superseded by chest radiography due to limited scanners[15].

To mitigate the limitation, coupled with long turnaround times for RT-PCR, countries such as Italy and United Kingdom had adopted chest radiography as a first-line triage tool[15]. This could also be attributed to the favourable feature of a mobile unit — portability, where chest radiography could be performed at the bedside instead of transporting the patient to the scanner[14]. This effectively reduced patient transfer and minimized the risk of cross-infection to others[13,55]. Given the obvious benefit of mobile chest radiography, the uptake and demand of chest radiography as a first-line assessment tool would increase over time. This posed a challenge to even a large hospital — where Singapore's largest acute tertiary referral medical centre had to acquire additional mobile units to meet the increasing clinical demands[55]. A similar challenge was also noted in South-East Queensland, Australia where purchase, rapid acquisition and deployment of additional mobile units were initiated[65].

However, with the urgent delivery and growing orders for mobile units, some vendors could not meet the urgent delivery timeframe[66]. Against this backdrop, many hospitals in England were struggling with equipment shortage and backlog[67]. Many were in urgent need of more staff and imaging equipment — CT, MRI, ultrasound and mobile units, to deal with backlog cases. It was particularly vivid in the United Kingdom where it was reported to have the lowest number of scanners when compared with other Organization for Economic Co-operation and Development countries[67]. This resulted in a significant block capacity gap within the United Kingdom, prompting The Royal College of Radiologists (RCR) to describe the situation as a perfect storm in terms of delivering capacity[67].

Faced with the challenge of limited delivering capacity and mounting wait lists, patient access to medical imaging services was profoundly affected. This was evident in Canada where waiting time for medical imaging is now twice as long when compared with pre-COVID times — significantly beyond the acceptable standards[68]. A similar picture was painted in the UK where statistics had highlighted the knock-on impact of pausing non-emergency imaging during the peak of COVID-19 infection — a substantial increase in waiting time for CT or MRI scans[69]. In particular, the RCR[69] warned of a continuum of such figures if without more sustained investment.

Well-being

In the battle against COVID-19, the most important and valuable assets were HCPs[70]. However, a recent systematic review[71] highlighted that many HCPs faced aggravated psychological pressure and even mental illness. The intensive work drained the HCPs physically and emotionally[72]. This was especially vivid for the HCPs who had neither infectious disease expertise nor experienced the SARS outbreak[72,73]. They had to adjust to a new working environment in this extraordinarily stressful situation. Low resource countries such as Nepal, had considerable mental health symptoms among HCPs[74]. In fact, Iraqi communities who are already afflicted by the ongoing conflict, political instability and social upheavals now face an even more challenging task to secure the mental well-being of their HCPs[75].

It was reported that frontline HCPs like radiographers, who often had to take on the role of caring directly for patients with COVID-19 were at a higher-level risk of having severe mental health symptoms than those in secondary roles[76]. They had to work with the constant changing protocols with some reported to have inadvertent exposure to COVID-19 positive patients without suitable PPE — a result of poor communication[77]. Moreover, some radiographers experienced burnout as they were subjected to 12-hour shifts in order to meet the service needs and for team segregation[78]. This was in line with the systematic review which identified long working hours as a factor for increased risk of various psychological and mental illness as well as physical and emotional distress[71].

Similarly, radiologists were vulnerable to experiencing burnout with the increased emphasis on reporting speed and studies per day, long working hours, and limited personal interaction[79]. Coupled with the pre-COVID reasons for increased rates of burnout in radiology, all these stressors were being magnified exponentially during this COVID-19 pandemic[80]. As mentioned by Wolfman *et al*[80], the medical imaging profession is now facing an untenable situation where "COVID had turned a smouldering ember into a blazing fire".

Undeniably, both radiographers and radiologists were at risk of burnout. In addition, they were also at risk of fatigue[81]. This had concerning implications as it resulted in a negative outcome in terms of patient safety in medical imaging. This could not be emphasized further with burnout and fatigue being highlighted in the joint paper[82] released by the European Society of Radiology and the European Federation of Radiographer Societies on patient safety in medical imaging. Indeed, ensuring the physical and psychological well-being of the professionals is crucial for safe delivery of medical imaging. A summary of the challenges in the provision of medical imaging service during COVID-19 is shown in Table 1.

STRATEGIES TO OPTIMIZE MEDICAL IMAGING SERVICE DELIVERY DURING COVID-19

During this pandemic, timely decisions need to be made and strategies promptly executed to mitigate the risk of widespread transmission. As the pandemic unfolds, the continuity of an effective medical imaging service for both COVID-19 and non-COVID-19 patients is essential. Notably, radiology departments must now adhere to the strictest infection control practices, different countries' varying healthcare and lock down policies and continue to value add to patient care amidst this unprecedented challenge.

Leadership

During this period of COVID-19, strong clinical and compassionate leadership is paramount in improving the provision of quality care[83]. Similarly, Shingler-Nace[84] identified: Staying calm, communication, collaboration, coordination and providing support, as the five elements to successful leadership during this pandemic. Undeniably, this pandemic has caused a global turmoil in many aspects in our way of life and continues to challenge established leadership models[85].

Fortunately, there was a substantial amount of materials to guide radiology leaders as the profession navigates through unchartered waters[86,87]. Moreover, leadership lessons from prior pandemics were invaluable and augmented the available resources in this COVID-19 pandemic[88]. Radiology leaders demonstrated good leadership qualities in the face of adversity[89-91]. Comparably, radiographers had also shown their ability to contribute as highly effective COVID-19 leaders in safely and sustainably reorganizing radiography services[55].

There was no doubt that adaptability, flexibility, teamwork, clear communication, patient and staff safety as well as staff well-being were key principles for managing leadership teams in this pandemic[89-93]. While many would agree upon the key principles emphasized, Dr Gerada[94] highlighted in her presentation delivered at the prestigious Sir Godfrey Hounsfield Lecture, that a successful leader in the COVID-19 is one who offers hope yet bounded by realism. Clearly, one should not forget about instilling hope in times of crisis.

Use of technology

With chest radiography preferred in many countries to screen and monitor the progression of COVID-19, mobile units were in high demand. By using mobile digital radiography (DR) units instead of conventional radiography (CR) units, mobile DR solutions were a key element in turning the tide in COVID-19 management. Mobile DR units had the advantages of delivering high quality DR images in real time and had the feature of wireless data transmission which enabled early reporting and access by clinicians[55,95]. Moreover, some DR mobile units had added features to help reduce contamination, mitigating the risk of cross-infection[96]. The use of the DR mobile unit was supported and endorsed by the ACR task force on COVID-19 where it was highlighted that the surfaces of the unit could be cleaned with ease and therefore well suited for use in ambulatory care facilities[97]. In fact, recognizing the mobile DR units' advantages, hospitals in Brazil and Namibia have since adopted a retrofit solution to their mobile CR units to meet the increasing demands[98,99].

Reducing contamination was not only a key feature in mobile DR units. CT systems were also embracing such a norm. In China where CT scans were in high demand, artificial intelligence (AI) was empowering automated patient positioning and scanning from the control console room[100]. Such an approach reduces cross infection between the radiographers and patients. Other uses of technology can be appreciated in the form of leveraging medical imaging data — remote diagnosis, data-driven

Table 1 Summary of the challenges in the provision of medical imaging service during coronavirus disease 2019

Challenge	Experiences of medical imaging departments
Coping with limited manpower	Team segregation; Increased workload; Increased responsibility; Increased procedure time due to infection control measures and terminal cleaning of equipment; Self-isolation due to contact with positive cases; Statutory paid sick leave
Coping with strict infection control measures	Shortage of PPE; Increased risk of exposure from prolonged patient contact; Resource and labour intensive due to terminal cleaning of equipment
Coping with limited resources	Equipment segregation; Inadequate mobile radiography units; Delay in delivery of equipment due to increased orders; overseas shipment of equipment delayed; Poor imaging service delivery due to a lack of imaging equipment
Safeguarding of medical imaging professionals' well-being	Aggravated psychological pressure and mental illness; Physical and emotional distress among medical imaging professionals; Burnout; Fatigue

PPE: Personal protective equipment.

management of COVID-19 operations, mounting imaging backlog and a foundation for ongoing monitoring and research on COVID-19[100,101]. Lastly, the use of AI to provide COVID-19 specific education, screening, triage and home monitoring can also help to reduce unnecessary demand on medical imaging services by supporting and providing guidance to all patients[102].

Communication

As the pandemic continues to spread globally, clear communication with radiographers is necessary to ensure infection control[103]. If radiographers are communicated promptly regarding the health of the patient to be scanned, appropriate PPE can be worn in advance — avoiding repetition of miscommunication incidents that led to radiographers in Ireland[77] being exposed to COVID-19 positive patients without donning appropriate PPE. Moreover, such clear communication is crucial in ensuring that radiographers comply and perform self-monitoring for symptoms when exposed to positive cases[101]. This can be in the form of daily routine instructions, newsletters, open forums and one-on-one communications[103,104]. Similarly, other forms of communique such as websites, virtual telecommuting and team-based communication can be utilized to ensure timely updates of current guidance and policies[105].

Clear and frequent communication amongst all members of the healthcare team has been of utmost importance throughout the pandemic[105]. This was especially crucial in the communication of imaging examination findings. In addition, rapid and prompt communication of results is also essential for staff safety and management of the patient[103]. This was highlighted by the radiology experts from Norway and Germany[106] who accentuated the role of structured reporting in communicating clear results to the rest of the team. In fact, the importance of structured reporting could not be emphasized enough with structured reporting templates that were endorsed by the Society of Thoracic Radiology, the ACR and The Radiological Society of North America being made available[107]. Such reporting language and a template for chest radiography have also since surfaced[108,109].

Review of processes, protocol and policies

To prepare for any sudden patient surge and to minimize potential staff or patient exposure, many elective/non-urgent imaging procedures were postponed[110]. This was implemented with the consideration of prioritizing urgent and emergency visits while preserving PPE as the COVID-19 pandemic escalated[111]. Both the ACR[111] and RCR[112] released an advisory in the support of postponing non-urgent outpatients' visits such as elective radiology-related procedures, cancer screenings and mammography. The postponement of breast imaging related screening was also supported by various societies[113,114]. Likewise, many non-high priority nuclear medicine procedures were also rescheduled[115]. In tandem, radiologists were tasked to review and prioritize all scheduled outpatients on the necessity of imaging at that juncture[111]. It was clear that such a decision was made deliberately with the safety of patients and staff as the utmost priority.

Patients who were scheduled for imaging procedures during this period had to be triaged before they could enter the radiology department. In Sichuan, China, a three-level triage was introduced to categorize patients according to the different risk levels[116]. Other triaging approaches were also reported such as an external triage

unit in Switzerland[117] and a pre-access telephone triage in Italy[118]. These were supported by evidence from China[119,120] which suggested that the procedure of triaging patients effectively screened patients and identified any high-risk populations. The importance of establishing a triage area was well established with the WHO regional office for Africa releasing a document[121] to provide guidance on how to rapidly establish a triage area at a healthcare facility.

As part of safe/physical distancing, radiology departments in Singapore adopted temporal and physical segregation policies to reduce the risk of cross-infection to staff and other patients and to maintain staff capabilities to meet the demand of medical imaging services[31]. For similar purposes, radiographers were segregated to different teams based on clinical location with the roster pattern fixed and synchronized with the nurses' and radiologists' rosters to facilitate contact tracing[55]. A similar approach was also adopted in China with success as institutions in Singapore and China reported no COVID-19 positive cases in their radiographers[55,122].

Like many hospitals globally, at the initial phase of the outbreak, many medical and radiography students were immediately withdrawn from the clinical setting or had their clinical rotations suspended for their protection[122-124]. Other work processes such as isolation mobile radiography workflow[55] and dedicated workflow management processes for modalities that required high staff numbers[125] were modified to adapt and optimize imaging services to meet the current clinical needs. Similarly, technical operations such as the undertaking of mobile radiography through side room windows[126], and the radiologist's responsibility were also included in the review with the primary aim of optimizing the radiology protocol during the pandemic[116].

Places and equipment

The safety of HCP is paramount during a pandemic. Strict cleaning and disinfection procedures were in place to mitigate the risk of infection. Practical alternatives are needed to augment current practices especially when new waves of outbreak surface globally. This includes introduction of an imaging booth (SG SAFE.R) for chest radiography where the patient can have a chest X-ray done without contact with the radiographer—reducing the need for additional manpower while improving safety[127]. A similar booth set up (Radiology Annex) was also reported by Penn State Health which commented that such an X-ray booth offered quick scans to COVID-19 patients while eliminating the time needed to wipe down the equipment and exchange the air[128].

Radiological equipment used for scanning of COVID-19 patients should be reorganized as part of the segregation of patients to reduce the risk of cross-infection and continuum of routine radiology services[122]. Many hospitals in Singapore and China assigned dedicated equipment exclusively for suspected and confirmed cases of COVID-19[4,122]. This practice was advocated by many authors and societies [58,129-131]. In addition, a dedicated transport team, low traffic access routes, lift lobbies, dedicated waiting area and scanners with negative-pressure capability were established and used[4,122,129,132]. Hospitals constrained by the availability of equipment can navigate this challenge by assigning dedicated time for COVID-19 cases[122]. Moreover, such scanning can be scheduled only towards the end of the work-day[4]. This not only reduces the risk of cross-contamination but also increases work efficiency and room utilization considering the substantial time required for cleaning the scan room[4,116]. Most importantly, terminal cleaning needs to be performed by a specialized team[4,132].

With mobile radiography and CT scans in high demand during the COVID-19 pandemic, the radiology department risks being a site of potential spread[132]. Therefore, it is paramount to ensure utmost safety of radiology staff and to reduce staff and patient transmission. Mobile units require to be disinfected according to a fixed cleaning regime which might include the subsequent process of exposing the unit to ultraviolet light for more than 30 min before being used on the next patient[132,133]. Other examples of protocol included having the mobile units and X-ray cassettes covered with layers of polythene sheet sealed with adhesive tapes or leucoplast[134] and wrapping of mobile DR flat detectors with disposable sheets[135]. Such protocols have since been established beyond mobile radiography and CT to include ultrasound, MRI and interventional radiology[132,136-139]. A summary of the strategies to optimize medical imaging service delivery during COVID-19 is shown in Table 2.

Table 2 Summary of the strategies to optimize medical imaging service delivery during coronavirus disease 2019

Theme	Strategies
The need for strong and compassionate leadership	Staying calm, communication, collaboration, coordination and providing support; Practising adaptability, flexibility, and teamwork; Ensuring the safety of patients and staff; Safeguarding the well-being of staff; Instilling hope in times of crisis
Embracing technological usage	Adopting mobile DR units in the department; Adopting AI to reduce contamination of equipment; Harnessing capability of AI in: (1) Remote diagnosis; (2) Data-driven management of COVID-19 operations; (3) Mounting imaging backlog; (4) Ongoing monitoring and research on COVID-19; and (5) Supporting and provision of guidance to patients
Clear communication	Communication among staff through: (1) Routine instructions; (2) Newsletters; (3) Open forum; and (4) One-to-one communications. Timely updates and dissemination of current guidance and policies through: (1) Websites; (2) Virtual telecommuting; and (3) Team-based communication. Structured reporting in communicating imaging results
Enhancing processes, protocol, and policies	Postponement of elective/non-urgent imaging procedures; Review and prioritisation of outpatient schedules by radiologists; Triaging of patients prior to entering the radiology department; Temporal and physical segregation; Suspension of students' placement; Dedicated workflow management process; Development of isolation mobile radiography workflow; Involvement of medical imaging professionals in technical operations; Reorganisation of radiological equipment and assigning of dedicated equipment for suspect and confirmed cases; Implementation of dedicated transport team, routes, lift lobbies and waiting area for COVID-19 patients; End of day schedules for COVID-19 patients
Innovation	Developing new solutions to minimise patient contact

COVID-19: Coronavirus disease 2019; AI: Artificial intelligence; DR: Digital radiography.

FUTURE DIRECTION

In this pandemic, there is no doubt regarding the critical role played by HCPs in the national and local responses. It is crucial to ensure that HCPs are "pandemic ready" as most of the actions required to prepare for the COVID-19 pandemic can be applied or adapted to the management of other emergencies or crises[140]. Such pandemic guidance which included recommendations were released by WHO and various public health agencies globally for more than 15 years[141]. They were likely prompted by 2 major healthcare events—H5N1 avian influenza outbreak in 2002-2005 and SARS in 2003[141]. According to WHO[140], preparedness tasks for HCPs include the development and implementation of training programmes that are based on the staff roles in an emergency, and to develop protocols to provide staff with training in an emergency and provide staff with social and psychological support. Clearly, mechanisms and systems must be in place before the pandemic to ensure that radiology staff are pandemic prepared.

To prepare HCPs for and respond to such events, it is advocated by the WHO to ensure appropriate and quality training and education are in place for all staff. Various authors have responded with remarkable vigour in sharing the approaches to prepare radiology staff for a pandemic. They included curated on-boarding programmes[142], film discussion sessions[143], use of a skill-set inventory[144], and introducing hospital arranged tutorials and video awareness campaigns[145]. It is essential to ensure that radiology staff who were battling the pandemic had the knowledge and skills needed to provide the best care for the patients while maintaining safety. In tandem, resources should be readily available to safeguard the mental health and wellbeing of radiology staff during the pandemic[144,146].

The COVID-19 pandemic had also highlighted the importance of academic institutions in raising the pandemic readiness of students. Rainford *et al*[147] identified that radiography students might not be fully confident in using PPE and suggested that practical training sessions be conducted before their placement—an approach that a Singapore academic institution adopted[123]. New norms of teaching HCPs have also been suggested by many authors ranging from virtual teaching[148,149], adoption of technology-based platforms[150,151], simulation and virtual reality[152,153]. Similar to qualified HCPs, medical students who are recruited to assist in a pandemic need to undergo specific training programmes. Such student disaster training programmes improve the students' readiness, knowledge and skills which can play a valuable role in pandemic management[154].

Compared to SARS, COVID-19 has had a significant impact on the way education is being delivered. Lessons from SARS have resulted in academic institutions establishing and increasing their online presence through effective learning management systems, video conference facilities and facilitators' experience in e-learning[155]. During this COVID-19 pandemic, many academic institutions successfully switched to online learning with just a few days of preparation[155,156].

Clearly, post-SARS, there was an increased digital trajectory in the provision of education. However, this pandemic has demonstrated that online education is still not universally embraced in countries such as Argentina, Zimbabwe and Malaysia[155]. It is now incumbent upon all educators to explore online learning technology's full potential as this pandemic can be an inflection point for further acceleration. Likewise, educators should also ensure that there is adequate training, bandwidth, and preparation for online education where it is believed to have become an integral component of school education[156].

In parallel, the preparation and practices of many radiology departments during this pandemic have been heavily influenced by the SARS experience. This has included formulation of rigorous protocols and reconfiguration of facilities to prevent in-hospital transmission, improvement of diagnostic capabilities, resourcing, communication and coordinated outbreak response[4,91,157,158]. It is undeniable that the SARS lessons have provided valuable experience for the healthcare community and was crucial in our battle against COVID-19.

Clear differences between SARS and COVID-19 have emerged. A paper published in The Lancet[159] shared the differences between both situations and the outbreak measures. Unlike SARS which was effectively eradicated by implementing top-down measures to stop all human-to human transmission, but due to the nature and extent of spread, mitigation measures must be implemented instead of containment in view of the current situation of COVID-19[159].

It was noted in a paper in Clinical Radiology[160] that the use of infection control advocated procedures might have contributed to the low staff sickness levels during COVID-19—which could be maintained after COVID-19. In addition, the need to embrace information technology was also required to develop a more robust digital platform for patients while minimizing waiting room utilization—a negative outcome of waiting room distancing and increased time for cleaning of rooms in this pandemic. Likewise, remote working and physical distancing have their pros and cons. A thorough reflection after the pandemic is required to facilitate the thought processes on practices to keep, and which to revert to pre-COVID[160]. In tandem, special attention should be paid towards building trust in the radiologist-to-clinician relationship amid the "distance" between these professionals[161]. Indeed, despite the valuable lessons from previous experiences, adaptations to practices and responses will be necessary to prepare the department for the next pandemic.

There is no doubt that effective, safe and high-quality medical imaging is paramount in healthcare. The number of global imaging procedures is increasing considerably. The role of medical imaging in medical decision-making and minimization of unnecessary interventions cannot be emphasized enough[82,162]. As highlighted by the European Society of Radiology and the European Federation of Radiographer Societies in a joint paper[82], radiographers and radiologists are essential in the provision of medical imaging services to patients, while continuously safeguarding patient care and safety. The joint paper distinctly reflects the concern of the medical imaging field where patient safety is key.

To date, a substantial amount of money and resources have been invested in AI for medical imaging[163]. There were profound concerns about medical imaging professionals being replaced or obsolete. Fortunately, they were not destined to become dodos. The American Medical Association (AMA) deliberately adopted the term augmented intelligence in place of the more common term AI and highlighted why AI could not replace medicine's human component where it was believed that medicine could harness AI in ways that safely and effectively improved patient care[164].

As advocated by the AMA, AI is designed to enhance human intelligence and the patient-physician relationship but not to replace it[165]. Moreover, AI can help improve human effectiveness and efficiency in the form of a decision aid for clinical reasoning and decision making[166]. Similarly, for radiographers, AI can be used as a decision support tool to ensure that the examination performed is correct for a patient with dose optimization to answer the clinical question[167]. Importantly, AI will enable physicians to spend more precious time with their patients, improving the humanistic touch. Indeed, with the adoption of AI, radiologists can be freed up to perform more value-added tasks, while playing a more vital role in integrated clinical teams to improve patient care[168].

Undeniably, COVID-19 has become a catalyst for change in the development of telemedicine and AI in medical imaging services. With the global positive cases skyrocketing and many countries grappling with the sudden surge in waves of coronavirus, telemedicine must be considered and optimized. This is in line with the current guidance from the CDC for healthcare facilities[169]. Of which, the need for physical distancing has acted as a springboard for the rapid adoption of telemedicine

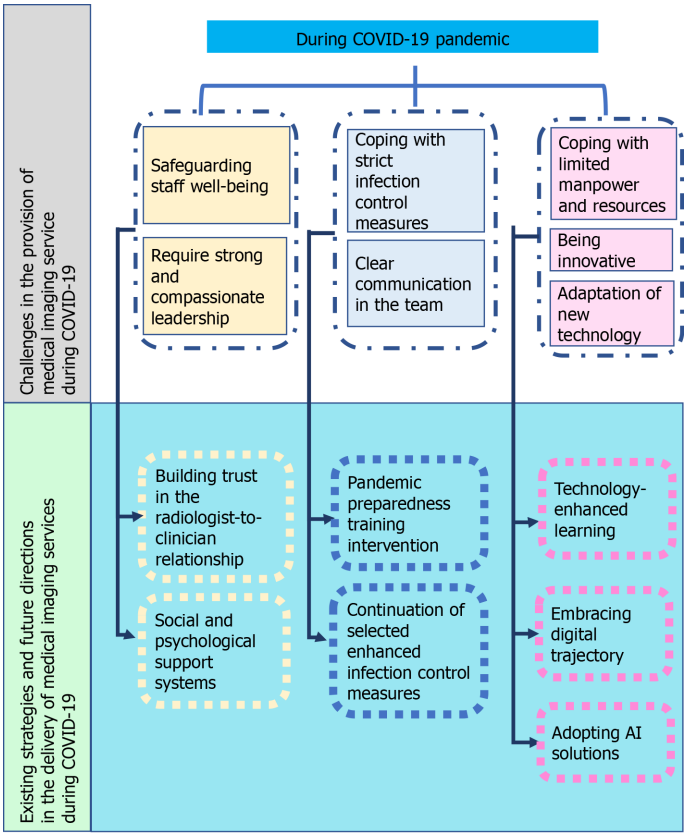


Figure 1 Delivery of medical imaging services: current challenges, strategies, and the path for future directions. COVID-19: Coronavirus disease 2019; AI: Artificial intelligence.

solutions globally[170]. Through telemedicine, critical medical care can be provided to patients while reducing transmission of COVID-19 and preserving scarce resources amid the pandemic[171]. According to results of a nationally representative survey published by the AMA in 2018, radiology had the highest use of telemedicine for patient interactions although its scope has been limited[172,173]. While there is variability in the adoption of telemedicine across the world, the evidence is suggesting a positive role in this technology for developed countries in improving health systems' performance and outcomes[174]. Indeed, COVID-19 has served as a reminder about the need and future potential of telemedicine.

During this pandemic, AI has been harnessed in medical imaging to fight COVID-19. A collaborative network led by the National Institute of Biomedical Imaging and Bioengineering[175] has been formed to develop new tools for physicians in the early detection and optimization of treatment for COVID-19 patients. In addition, the integration of AI with medical imaging has the capability of advancing predictive medicine, preventive medicine and personalized medicine[176]. Other forms of digital transformation in medical imaging services include the use of AI in precision diagnosis, optimization of workflow and productivity[177-179]. Looking ahead, AI will be critical in empowering radiologists and radiographers across the world to address the challenges brought about by COVID-19. It is now time for medical imaging to embrace AI and the opportunities it may present in the post-COVID-19 world to enhance our patient care and patient outcome. The current challenges, strategies, and a path for future directions is described in Figure 1.

CONCLUSION

In an unprecedented pandemic, there are significant challenges globally in delivering medical imaging services and this crisis has further highlighted how complicated these challenges can be. Amid the crisis, health care is still being delivered and with the integral role of medical imaging services in the ongoing battle against COVID-19, the quality and safety of care become more important. There are dramatic implications associated with sub-optimal radiology practices and service delivery. Implementing

strategies to optimize medical imaging service delivery will ensure quality healthcare in the era of COVID-19 and beyond where patient care processes continue to change rapidly. Ultimately, through the collaborative efforts of all radiology staff, we can assure provision of high-quality and safe medical imaging services while safeguarding the health of the public, patients and HCPs.

REFERENCES

1 **Caldaria A**, Conforti C, Di Meo N, Dianzani C, Jafferany M, Lotti T, Zalaudek I, Giuffrida R. COVID-19 and SARS: Differences and similarities. *Dermatol Ther* 2020; **33**: e13395 [PMID: 32277530 DOI: 10.1111/dth.13395]

2 **World Health Organization**. Naming the coronavirus disease (COVID-19) and the virus that cause. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

3 **Zu ZY**, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology* 2020; **296**: E15-E25 [PMID: 32083985 DOI: 10.1148/radiol.2020200490]

4 **Tan BP**, Lim KC, Goh YG, Kok SSX, Teo SY, Poh ACC, Kaw GJL, Quek ST, Wong SBS, Chan LP, Tan BS. Radiology Preparedness in the Ongoing Battle against COVID-19: Experiences from Large to Small Public Hospitals in Singapore. *Radiol Cardiothorac Imaging* 2020; **2**: e200140 [PMID: 33778570 DOI: 10.1148/ryct.2020200140]

5 **Chan SS**, Mak PS, Shing KK, Chan PN, Ng WH, Rainer TH. Chest radiograph screening for severe acute respiratory syndrome in the ED. *Am J Emerg Med* 2005; **23**: 525-530 [PMID: 16032625 DOI: 10.1016/j.ajem.2004.10.014]

6 **Antonio GE**, Wong KT, Chu WC, Hui DS, Cheng FW, Yuen EH, Chung SS, Fok TF, Sung JJ, Ahuja AT. Imaging in severe acute respiratory syndrome (SARS). *Clin Radiol* 2003; **58**: 825-832 [PMID: 14581005 DOI: 10.1016/s0009-9260(03)00308-8]

7 **Hsu LY**, Lee CC, Green JA, Ang B, Paton NI, Lee L, Villacian JS, Lim PL, Earnest A, Leo YS. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* 2003; **9**: 713-717 [PMID: 12781012 DOI: 10.3201/eid0906.030264]

8 **Lam WK**, Zhong NS, Tan WC. Overview on SARS in Asia and the world. *Respirology* 2003; **8** Suppl: S2-S5 [PMID: 15018125 DOI: 10.1046/j.1440-1843.2003.00516.x]

9 **Kaw GJ**, Tan DY, Leo YS, Tsou IY, Wansaicheong G, Chee TS. Chest radiographic findings of a case of severe acute respiratory syndrome (SARS) in Singapore. *Singapore Med J* 2003; **44**: 201-204 [PMID: 12952033]

10 **Fang Y**, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296**: E115-E117 [PMID: 32073353 DOI: 10.1148/radiol.2020200432]

11 **American College of Radiology**. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. [cited 26 December 2020]. In: American College of Radiology [Internet]. Available from: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection

12 **Society of Thoracic Radiology**. Society of Thoracic Radiology/American Society of Emergency Radiology COVID-19 Position Statement. [cited 26 December 2020]. In: Society of Thoracic Radiology [Internet]. Available from: https://thoracicrad.org

13 **World Health Organization**. Use of chest imaging in COVID-19. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications-detail-redirect/use-of-chest-imaging-in-covid-19

14 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin O, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. *Radiology* 2020; **296**: 172-180 [PMID: 32255413 DOI: 10.1148/radiol.2020201365]

15 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

16 **Cleverley J**, Piper J, Jones MM. The role of chest radiography in confirming covid-19 pneumonia. *BMJ* 2020; **370**: m2426 [PMID: 32675083 DOI: 10.1136/bmj.m2426]

17 **Government of Singapore**. Steps to take when you're unwell. [cited 26 December 2020]. In: Government of Singapore [Internet]. Available from: https://www.gov.sg/article/steps-to-take-when-youre-unwell

18 **Pung R**, Chiew CJ, Young BE, Chin S, Chen MI, Clapham HE, Cook AR, Maurer-Stroh S, Toh

MPHS, Poh C, Low M, Lum J, Koh VTJ, Mak TM, Cui L, Lin RVTP, Heng D, Leo YS, Lye DC, Lee VJM; Singapore 2019 Novel Coronavirus Outbreak Research Team. Investigation of three clusters of COVID-19 in Singapore: implications for surveillance and response measures. *Lancet* 2020; **395**: 1039-1046 [PMID: 32192580 DOI: 10.1016/S0140-6736(20)30528-6]

19 **Jung JI**. Radiologists' Solutions for COVID-19 in Korea. *Korean J Radiol* 2020; **21**: 1196-1197 [PMID: 32767869 DOI: 10.3348/kjr.2020.0848]

20 **Yasin R**, Gouda W. Chest X-ray findings monitoring COVID-19 disease course and severity. *Egypt J Radiol Nucl Med* 2020; **51**: 193 [DOI: 10.1186/s43055-020-00296-x]

21 **Oterino Serrano C**, Alonso E, Andrés M, Buitrago NM, Pérez Vigara A, Parrón Pajares M, Cuesta López E, Garzón Moll G, Martin Espin I, Bueno Barriocanal M, De Ceano-Vivas la Calle M, Calvo Rey C, Bret-Zurita M. Pediatric chest x-ray in covid-19 infection. *Eur J Radiol* 2020; **131**: 109236 [PMID: 32932176 DOI: 10.1016/j.ejrad.2020.109236]

22 **Cellina M**, Orsi M, Toluian T, Valenti Pittino C, Oliva G. False negative chest X-Rays in patients affected by COVID-19 pneumonia and corresponding chest CT findings. *Radiography (Lond)* 2020; **26**: e189-e194 [PMID: 32423842 DOI: 10.1016/j.radi.2020.04.017]

23 **Hwang J**, Yong E, Cheong K, Ling ZJ, Goh LH, Lim FS, Loh V, Bagdasarian N, Somani J, Archuleta S, Sng J, Lim SM. Responding to the COVID-19 pandemic: The role of occupational health services in a tertiary hospital in Singapore. *J Occup Health* 2020; **62**: e12172 [PMID: 33058404 DOI: 10.1002/1348-9585.12172]

24 **World Health Organization**. Novel Coronavirus (2019-nCoV)- Situation Report 10. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200130-sitrep-10-ncov.pdf?sfvrsn=d0b2e480_2

25 **World Health Organization**. Coronavirus disease 2019 (COVID-19)- Situation Report 31. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200220-sitrep-31-covid-19.pdf

26 **Singapore Healthcare Corps**. Join the SG Healthcare Corps. [cited 26 December 2020]. In: Singapore Healthcare Corps [Internet]. Available from: https://healthcarecorps.gov.sg/

27 **Center for Strategic and International Studies**. Strengths and vulnerabilities in Southeast Asia's response to the Covid-19 pandemic. [cited 26 December 2020]. In: Center for Strategic and International Studies [Internet]. Available from: https://www.csis.org/analysis/strengths-and-vulnerabilities-southeast-asias-response-covid-19-pandemic

28 **Reuters**. Ireland's call for retired medics to return to work gets huge response. [cited 26 December 2020]. In: Reuters [Internet]. Available from: https://www.reuters.com/article/us-health-coronavirus-ireland/irelands-call-for-retired-medics-to-return-to-work-gets-huge-response-idUSKBN2153JX

29 **National Health Service**. Clinicians considering a return to the NHS. [cited 26 December 2020]. In: National Health Service [Internet]. Available from: https://www.england.nhs.uk/coronavirus/returning-clinicians/

30 **De Avila J**, Chen T. To fight coronavirus, states call on retired medical staff and new graduates. The Wall Street Journal. 31 March 2020. Available from: https://www.wsj.com/articles/to-fight-coronavirus-states-call-on-retired-medical-staff-and-new-graduates-11585647003 Cited 26 December 2020.

31 **Goh Y**, Chua W, Lee JKT, Ang BWL, Liang CR, Tan CA, Choong DAW, Hoon HX, Ong MKL, Quek ST. Operational Strategies to Prevent Coronavirus Disease 2019 (COVID-19) Spread in Radiology: Experience From a Singapore Radiology Department After Severe Acute Respiratory Syndrome. *J Am Coll Radiol* 2020; **17**: 717-723 [PMID: 32298643 DOI: 10.1016/j.jacr.2020.03.027]

32 **Elshami W**, Akudjedu TN, Abuzaid M, David LR, Tekin HO, Cavli B, Issa B. The radiology workforce's response to the COVID-19 pandemic in the Middle East, North Africa and India. *Radiography (Lond)* 2021; **27**: 360-368 [PMID: 33032889 DOI: 10.1016/j.radi.2020.09.016]

33 **Akudjedu TN**, Botwe BO, Wuni AR, Mishio NA. Impact of the COVID-19 pandemic on clinical radiography practice in low resource settings: The Ghanaian radiographers' perspective. *Radiography (Lond)* 2021; **27**: 443-452 [PMID: 33168371 DOI: 10.1016/j.radi.2020.10.013]

34 **Shoja E**, Aghamohammadi V, Bazyar H, Moghaddam HR, Nasiri K, Dashti M, Choupani A, Garaee M, Aliasgharzadeh S, Asgari A. Covid-19 effects on the workload of Iranian healthcare workers. *BMC Public Health* 2020; **20**: 1636 [PMID: 33138798 DOI: 10.1186/s12889-020-09743-w]

35 **Morgantini LA**, Naha U, Wang H, Francavilla S, Acar Ö, Flores JM, Crivellaro S, Moreira D, Abern M, Eklund M, Vigneswaran HT, Weine SM. Factors contributing to healthcare professional burnout during the COVID-19 pandemic: A rapid turnaround global survey. *PLoS One* 2020; **15**: e0238217 [PMID: 32881887 DOI: 10.1371/journal.pone.0238217]

36 **Akudjedu TN**, Lawal O, Sharma M, Elliott J, Stewart S, Gilleece T, McFadden S, Franklin JM. Impact of the COVID-19 pandemic on radiography practice: findings from a UK radiography workforce survey. *BJR Open* 2020; **2**: 20200023 [PMID: 33178980 DOI: 10.1259/bjro.20200023]

37 **Shi J**, Giess CS, Martin T, Lemaire KA, Curley PJ, Bay C, Mayo-Smith WW, Boland GW, Khorasani R. Radiology Workload Changes During the COVID-19 Pandemic: Implications for Staff Redeployment. *Acad Radiol* 2021; **28**: 1-7 [PMID: 33036897 DOI: 10.1016/j.acra.2020.09.008]

38 **Albano D**, Bruno A, Bruno F, Calandri M, Caruso D, Clemente A, Coppolino P, Cozzi D, De Robertis R, Gentili F, Grazzini I, Jannone ML, Liguori C, Natella R, Pace G, Posa A, Scalise P,

Accarino B, Bibbolino C, Barile A, Grassi R, Messina C; Young SIRM Working Group. Impact of coronavirus disease 2019 (COVID-19) emergency on Italian radiologists: a national survey. *Eur Radiol* 2020; **30**: 6635-6644 [PMID: 32661585 DOI: 10.1007/s00330-020-07046-7]

39 **Hogg P**, Holmes K, McNulty J, Newman D, Keene D, Beardmore C. Covid-19: Free resources to support radiographers. *Radiography (Lond)* 2020; **26**: 189-191 [PMID: 32419768 DOI: 10.1016/j.radi.2020.05.002]

40 **Vox**. The critical role of paid sick leave in the COVID-19 health and labour market crisis. [cited 26 December 2020]. In: Vox [Internet]. Available from: https://voxeu.org/article/paid-sick-leave-during-covid-19-health-and-labour-market-crisis

41 **Heng AL**, Ooi CC, Wen Eu BJ, San Kiew Y, Wong ASK, Da Zhuang K. The bug stops with me: Prevention of COVID-19 nosocomial transmission during radiographic procedures. *J Med Imaging Radiat Sci* 2020; **51**: 540-545 [PMID: 32907790 DOI: 10.1016/j.jmir.2020.07.054]

42 **Peh WM**, Ting Chan SK, Lee YL, Gare PS, Ho VK. Lung ultrasound in a Singapore COVID-19 intensive care unit patient and a review of its potential clinical utility in pandemic. *J Ultrason* 2020; **20**: e154-e158 [PMID: 32609971 DOI: 10.15557/JoU.2020.0025]

43 **World Federation for Ultrasound in Medicine and Biology Safety Committee (Jacques S**. , Abramowicz JS, Basseal JM. World Federation for Ultrasound in Medicine and Biology Position Statement: How to Perform a Safe Ultrasound Examination and Clean Equipment in the Context of COVID-19. *Ultrasound Med Biol* 2020; **46**: 1821-1826 [PMID: 32327199 DOI: 10.1016/j.ultrasmedbio.2020.03.033]

44 **Gogna A**, Punamiya S, Gopinathan A, Irani F, Toh LHW, Wen Cheong LH, Babu S, Wee B, Goh P, Tan BP, Damodharan K, Venkatanarasimha N, Chan SJM, Chandramohan S, Too CW, Chung R, Ong SJ, Tan A, Tan BS, Tay KH. Preparing IR for COVID-19: The Singapore Experience. *J Vasc Interv Radiol* 2020; **31**: 869-875 [PMID: 32331919 DOI: 10.1016/j.jvir.2020.03.021]

45 **Mossa-Basha M**, Meltzer CC, Kim DC, Tuite MJ, Kolli KP, Tan BS. Radiology Department Preparedness for COVID-19: *Radiology* Scientific Expert Review Panel. *Radiology* 2020; **296**: E106-E112 [PMID: 32175814 DOI: 10.1148/radiol.2020200988]

46 **Suárez-García I**, Martínez de Aramayona López MJ, Sáez Vicente A, Lobo Abascal P. SARS-CoV-2 infection among healthcare workers in a hospital in Madrid, Spain. *J Hosp Infect* 2020; **106**: 357-363 [PMID: 32702465 DOI: 10.1016/j.jhin.2020.07.020]

47 **Cohen J**, Rodgers YVM. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. *Prev Med* 2020; **141**: 106263 [PMID: 33017601 DOI: 10.1016/j.ypmed.2020.106263]

48 **Burki T**. Global shortage of personal protective equipment. *Lancet Infect Dis* 2020; **20**: 785-786 [PMID: 32592673 DOI: 10.1016/S1473-3099(20)30501-6]

49 **Nortajuddin A**. Medical supplies shortage in ASEAN. The ASEAN Post. 25 March 2020. Available from: https://theaseanpost.com/article/medical-supplies-shortage-asean Cited 26 December 2020.

50 **Ranney ML**, Griffeth V, Jha AK. Critical Supply Shortages - The Need for Ventilators and Personal Protective Equipment during the Covid-19 Pandemic. *N Engl J Med* 2020; **382**: e41 [PMID: 32212516 DOI: 10.1056/NEJMp2006141]

51 **Zhan M**, Qin Y, Xue X, Zhu S. Death from Covid-19 of 23 Health Care Workers in China. *N Engl J Med* 2020; **382**: 2267-2268 [PMID: 32294342 DOI: 10.1056/NEJMc2005696]

52 **Jeremias A**, Nguyen J, Levine J, Pollack S, Engellenner W, Thakore A, Lucore C. Prevalence of SARS-CoV-2 Infection Among Health Care Workers in a Tertiary Community Hospital. *JAMA Intern Med* 2020; **180**: 1707-1709 [PMID: 32780100 DOI: 10.1001/jamainternmed.2020.4214]

53 **Alajmi J**, Jeremijenko AM, Abraham JC, Alishaq M, Concepcion EG, Butt AA, Abou-Samra AB. COVID-19 infection among healthcare workers in a national healthcare system: The Qatar experience. *Int J Infect Dis* 2020; **100**: 386-389 [PMID: 32949777 DOI: 10.1016/j.ijid.2020.09.027]

54 **Lewis S**, Mulla F. Diagnostic radiographers' experience of COVID-19, Gauteng South Africa. *Radiography (Lond)* 2021; **27**: 346-351 [PMID: 33004276 DOI: 10.1016/j.radi.2020.09.009]

55 **Sim WY**, Chen RC, Aw LP, Abu Bakar R, Tan CC, Heng AL, Ooi CC. How to safely and sustainably reorganise a large general radiography service facing the COVID-19 pandemic. *Radiography (Lond)* 2020; **26**: e303-e311 [PMID: 32419769 DOI: 10.1016/j.radi.2020.05.001]

56 **Christopher WK**. Contamination of X-Ray Cassettes with MRSA During Portable X-Ray Examination. *J Microbiol Pathol* 2014; **1**: 007

57 **Stogiannos N**, Fotopoulos D, Woznitza N, Malamateniou C. COVID-19 in the radiology department: What radiographers need to know. *Radiography (Lond)* 2020; **26**: 254-263 [PMID: 32532596 DOI: 10.1016/j.radi.2020.05.012]

58 **Kooraki S**, Hosseiny M, Myers L, Gholamrezanezhad A. Coronavirus (COVID-19) Outbreak: What the Department of Radiology Should Know. *J Am Coll Radiol* 2020; **17**: 447-451 [PMID: 32092296 DOI: 10.1016/j.jacr.2020.02.008]

59 **Yu J**, Ding N, Chen H, Liu XJ, He WJ, Dai WC, Zhou ZG, Lin F, Pu ZH, Li DF, Xu HJ, Wang YL, Zhang HW, Lei Y. Infection Control against COVID-19 in Departments of Radiology. *Acad Radiol* 2020; **27**: 614-617 [PMID: 32276755 DOI: 10.1016/j.acra.2020.03.025]

60 **American College of Radiology**. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. [cited 26 December 2020]. In: American College of Radiology [Internet]. Available from: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-

Suspected-COVID19-Infection

61 **Yan C**, Lin J, Xu Y. Recommendations for coronavirus disease 2019 (COVID-19) prevention and infection control in the radiology department: Chinese experience. *Clin Imaging* 2021; **69**: 33-36 [PMID: 32652455 DOI: 10.1016/j.clinimag.2020.06.044]

62 **Qu J**, Yang W, Yang Y, Qin L, Yan F. Infection Control for CT Equipment and Radiographers' Personal Protection During the Coronavirus Disease (COVID-19) Outbreak in China. *AJR Am J Roentgenol* 2020; **215**: 940-944 [PMID: 32352309 DOI: 10.2214/AJR.20.23112]

63 **The BMJ**. Lessons from the frontline of the covid-19 outbreak. [cited 26 December 2020]. In: The BMJ [Internet]. Available from: https://blogs.bmj.com/bmj/2020/03/20/Lessons-from-the-frontline-of-the-covid-19-outbreak/?utm_campaign=shareaholic&utm_medium=twitter&utm_source=socialnetwork

64 **Huang Z**, Zhao S, Li Z, Chen W, Zhao L, Deng L, Song B. The Battle Against Coronavirus Disease 2019 (COVID-19): Emergency Management and Infection Control in a Radiology Department. *J Am Coll Radiol* 2020; **17**: 710-716 [PMID: 32208140 DOI: 10.1016/j.jacr.2020.03.011]

65 **Eastgate P**, Neep MJ, Steffens T, Westerink A. COVID-19 Pandemic - considerations and challenges for the management of medical imaging departments in Queensland. *J Med Radiat Sci* 2020; **67**: 345-351 [PMID: 32827241 DOI: 10.1002/jmrs.423]

66 **Small Caps**. Coronavirus prompts more orders for Micro-X's mobile x-ray units. [cited 26 December 2020]. In: Small Caps [Internet]. Available from: https://smallcaps.com.au/coronavirus-prompts-more-orders-micro-x-mobile-x-ray-units/

67 **Marsh S**, Asthana, A, Barr C. English hospitals in urgent need of more scanners and staff to deal with backlog. [cited 26 December 2020]. In: The Guardian [Internet]. Available from: https://www.theguardian.com/society/2020/jul/14/english-nhs-hospitals-in-urgent-need-of-more-scanners-and-staff-to-deal-with-backlog

68 **Applied Radiology**. Canadian Association of Radiologists Works to Restore Timely Imaging During COVID. [cited 26 December 2020]. In: Applied Radiology [Internet]. Available from: https://www.appliedradiology.com/articles/canadian-association-of-radiologists-works-to-restore-timely-imaging-during-covid

69 **The Royal College of Radiologists**. RCR responds to NHSE diagnostic waiting times figures for June. [cited 26 December 2020]. In: The Royal College of Radiologists [Internet]. Available from: https://www.appliedradiology.com/articles/canadian-association-of-radiologists-works-to-restore-timely-imaging-during-covid

70 **McKay D**, Heisler M, Mishori R, Catton H, Kloiber O. Attacks against health-care personnel must stop, especially as the world fights COVID-19. *Lancet* 2020; **395**: 1743-1745 [PMID: 32445692 DOI: 10.1016/S0140-6736(20)31191-0]

71 **Vizheh M**, Qorbani M, Arzaghi SM, Muhidin S, Javanmard Z, Esmaeili M. The mental health of healthcare workers in the COVID-19 pandemic: A systematic review. *J Diabetes Metab Disord* 2020; 1-12 [PMID: 33134211 DOI: 10.1007/s40200-020-00643-9]

72 **Liu Q**, Luo D, Haase JE, Guo Q, Wang XQ, Liu S, Xia L, Liu Z, Yang J, Yang BX. The experiences of health-care providers during the COVID-19 crisis in China: a qualitative study. *Lancet Glob Health* 2020; **8**: e790-e798 [PMID: 32573443 DOI: 10.1016/S2214-109X(20)30204-7]

73 **Tay YX**, Cai S, Chow HC, Lai C. The needs and concerns of clinical educators in radiography education in the face of COVID-19 pandemic. *J Med Imaging Radiat Sci* 2021; **52**: 3-8 [PMID: 33139232 DOI: 10.1016/j.jmir.2020.10.004]

74 **Khanal P**, Devkota N, Dahal M, Paudel K, Joshi D. Mental health impacts among health workers during COVID-19 in a low resource setting: a cross-sectional survey from Nepal. *Global Health* 2020; **16**: 89 [PMID: 32977818 DOI: 10.1186/s12992-020-00621-z]

75 **Seidi PAM**, Ardebil MD, Jaff D. COVID-19 pandemic: New challenge to securing mental well-being in conflict settings. *Asian J Psychiatr* 2020; **51**: 102151 [PMID: 32408247 DOI: 10.1016/j.ajp.2020.102151]

76 **Ayanian JZ**. Mental Health Needs of Health Care Workers Providing Frontline COVID-19 Care. *JAMA Health Forum* 2020; **1**: e200397 [DOI: 10.1001/jamahealthforum.2020.0397]

77 **Foley SJ**, O'Loughlin A, Creedon J. Early experiences of radiographers in Ireland during the COVID-19 crisis. *Insights Imaging* 2020; **11**: 104 [PMID: 32986225 DOI: 10.1186/s13244-020-00910-6]

78 **Ooi JWL**, Er ATW, Lee WC, Chee HC. The 12-hour shift: radiographers' perspectives and its applicability during a pandemic. *Radiography (Lond)* 2021; **27**: 512-518 [PMID: 33243565 DOI: 10.1016/j.radi.2020.11.007]

79 **Diagnostic Imaging**. Radiologist wellness and burnout in the COVID-19 era. [cited 26 December 2020]. In: Diagnostic Imaging [Internet]. Available from: https://www.diagnosticimaging.com/view/radiologist-wellness-and-burnout-in-the-covid-19-era

80 **Wolfman DJ**, Porter KK, Johnson DL, Parikh JR. Unsustainable: COVID-19 Demands Increased Support for Radiologists. *Clin Imaging* 2021; **73**: 18-19 [PMID: 33254029 DOI: 10.1016/j.clinimag.2020.11.038]

81 **Waite S**, Kolla S, Jeudy J, Legasto A, Macknik SL, Martinez-Conde S, Krupinski EA, Reede DL. Tired in the Reading Room: The Influence of Fatigue in Radiology. *J Am Coll Radiol* 2017; **14**: 191-197 [PMID: 27956140 DOI: 10.1016/j.jacr.2016.10.009]

82 **European Society of Radiology (ESR)**; European Federation of Radiographer Societies (EFRS). Patient Safety in Medical Imaging: a joint paper of the European Society of Radiology (ESR) and

the European Federation of Radiographer Societies (EFRS). *Insights Imaging* 2019; **10**: 45 [PMID: 30949870 DOI: 10.1186/s13244-019-0721-y]

83 **Graham RNJ**, Woodhead T. Leadership for continuous improvement in healthcare during the time of COVID-19. *Clin Radiol* 2021; **76**: 67-72 [PMID: 32943234 DOI: 10.1016/j.crad.2020.08.008]

84 **Shingler-Nace A**. COVID-19: When Leadership Calls. *Nurse Lead* 2020; **18**: 202-203 [PMID: 32346358 DOI: 10.1016/j.mnl.2020.03.017]

85 **NEJM Catalyst**. What health care leaders and clinicians say about the covid-19 pandemic. [cited 26 December 2020]. In: NEJM Catalyst [Internet]. Available from: https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0177

86 **American College of Radiology**. ACR COVID-19 radiology leadership resources. [cited 26 December 2020]. In: American College of Radiology [Internet]. Available from: https://www.acr.org/Practice-Management-Quality-Informatics/Radiology-Leadership-Institute/COVID-19-Leadership-Resources

87 **Radiological Society of North America**. RSNA Webinar – crisis leadership during COVID-19. [cited 26 December 2020]. In: Radiological Society of North America [Internet]. Available from: https://www2.rsna.org/shared_society_pages/standard_meeting_reg/webinar_home.cfm

88 **Georgiades C**. Leadership Lessons From Prior Pandemics: Turning the Coronavirus Disease 2019 (COVID-19) Pandemic Into an Opportunity. *J Am Coll Radiol* 2020; **17**: 906-908 [PMID: 32387088 DOI: 10.1016/j.jacr.2020.04.027]

89 **Seghers VJ**, Desai NK, Masand PM, Nasir S, Foster TL, Indiero DA, Johnson TD, Huisman TAGM. After the initial COVID-19 surge: a phased radiology departmental re-opening plan. *Pediatr Radiol* 2020; **50**: 1551-1559 [PMID: 32827259 DOI: 10.1007/s00247-020-04792-0]

90 **Mahoney MC**. Radiology Leadership in a Time of Crisis: A Chair's Perspective. *Acad Radiol* 2020; **27**: 1214-1216 [PMID: 32660753 DOI: 10.1016/j.acra.2020.05.042]

91 **Tay KH**, Ooi CC, Mahmood MIB, Aw LP, Chan LP, Ng DCE, Tan BS. Reconfiguring the radiology leadership team for crisis management during the COVID-19 pandemic in a large tertiary hospital in Singapore. *Eur Radiol* 2021; **31**: 468-474 [PMID: 32780206 DOI: 10.1007/s00330-020-07116-w]

92 **Diagnostic Imaging**. 10 traits of highly effective COVID-19 Leaders. [cited 26 December 2020]. In: Diagnostic Imaging [Internet]. Available from: https://www.diagnosticimaging.com/view/10-traits-of-highly-effective-covid-19-leaders

93 **Garver KA**, Young AM, Fessell D, Dombrowski JC. How to Be a Positive Radiology Leader in Times of Crisis. *Acad Radiol* 2020; **27**: 1116-1118 [PMID: 32553828 DOI: 10.1016/j.acra.2020.05.022]

94 **Healthcare-in-europe**. How the Covid-19 crisis defines good leadership. [cited 26 December 2020]. In: Healthcare-in-europe [Internet]. Available from: https://healthcare-in-europe.com/en/news/how-the-covid-19-crisis-defines-good-leadership.html

95 **Express Healthcare**. Mobile DR solutions turning the tide in COVID. [cited 26 December 2020]. In: Express Healthcare [Internet]. Available from: https://www.expresshealthcare.in/blogs/guest-blogs-healthcare/mobile-dr-solutions-turning-the-tide-in-covid-management/426038/

96 **Imaging Technology News**. Carestream increasing production of mobile imaging systems during pandemic. [cited 26 December 2020]. In: Imaging Technology News [Internet]. Available from: https://www.itnonline.com/content/carestream-increasing-production-mobile-imaging-systems-during-pandemic

97 **Informa Tech**. Combatting COVID-19 via X-ray powered imaging. [cited 26 December 2020]. In: Informa Tech [Internet]. Available from: https://omdia.tech.informa.com/OM006079/Combatting-COVID-19-via-X-ray-powered-imaging

98 **Agfa-Gevaert Group**. #CountOnUs: Brazil hospital turns analog mobile systems into DR with Agfa's Retrofit in their fight against COVID-19. [cited 26 December 2020]. In: Agfa-Gevaert Group [Internet]. Available from: https://medimg.agfa.com/main/countonus-brazil-hospital-turns-analog-mobile-systems-into-dr-with-agfas-retrofit-in-their-fight-against-covid-19/

99 **Agfa-Gevaert Group**. #CountOnUs: Namibia hospital selects Agfa mobile unit combined with retrofit solution to handle COVID-19 workload. [cited 26 December 2020]. In: Agfa-Gevaert Group [Internet]. Available from: https://medimg.agfa.com/main/countonus-namibia-hospital-selects-agfa-mobile-unit-combined-with-retrofit-solution-to-handle-covid-19-workload

100 **Imaging Technology News**. United imaging sends out more than 100 CT scanners and X-ray machines to aid diagnosis of the coronavirus. [cited 26 December 2020]. In: Imaging Technology News [Internet]. Available from: https://www.itnonline.com/content/united-imaging-sends-out-more-100-ct-scanners-and-x-ray-machines-aid-diagnosis-coronavirus

101 **Imaging Technology News**. 3 strategies to leverage medical imaging data during the pandemic. [cited 26 December 2020]. In: Imaging Technology News [Internet]. Available from: https://www.itnonline.com/article/3-strategies-leverage-medical-imaging-data-during-pandemic

102 **Gartner**. Healthcare technology innovations for identifying and managing COVID-19 patients. [cited 26 December 2020]. In: Gartner [Internet]. Available from: https://www.gartner.com/en/documents/3983039/healthcare-technology-innovations-for-identifying-and-ma

103 **Mamlouk MD**, McCormick CM, Jun P, MD; Tang JC, Kim BS, Shen PY, Baker BL. Fighting COVID-19: One Radiology Department's Experience. *Appl Radiol* 2020; 49: 16-18

104 **Cheng LT**, Chan LP, Tan BH, Chen RC, Tay KH, Ling ML, Tan BS. Déjà Vu or Jamais Vu? *AJR*

Am J Roentgenol 2020; **214**: 1206-1210 [PMID: 32130047 DOI: 10.2214/AJR.20.22927]

105 **Vagal A**, Reeder SB, Sodickson DK, Goh V, Bhujwalla ZM, Krupinski EA. The Impact of the COVID-19 Pandemic on the Radiology Research Enterprise: Radiology Scientific Expert Panel. *Radiology* 2020; **296**: E134-E140 [PMID: 32293224 DOI: 10.1148/radiol.2020201393]

106 **Healthcare-in-europe**. Radiology and COVID-19: How to establish safe workflows. [cited 26 December 2020]. In: Healthcare-in-europe [Internet]. Available from: https://healthcare-in-europe.com/en/news/radiology-covid-19-how-to-establish-safe-workflows.html

107 **Radiological Society of North America**. RSNA Structured Reporting. [cited 26 December 2020]. In: Radiological Society of North America [Internet]. Available from: https://www.rsna.org/en/covid-19/RSNA-Structured-Reporting

108 **Litmanovich DE**, Chung M, R Kirkbride R, Kicska G, P Kanne J. Review of Chest Radiograph Findings of COVID-19 Pneumonia and Suggested Reporting Language. *J Thorac Imaging* 2020 [PMID: 32520846 DOI: 10.1097/RTI.0000000000000541]

109 **Yates A**, Dempsey PJ, Vencken S, MacMahon PJ, Hutchinson BD. Structured reporting in portable chest radiographs: An essential tool in the diagnosis of COVID-19. *Eur J Radiol* 2021; **134**: 109414 [PMID: 33246271 DOI: 10.1016/j.ejrad.2020.109414]

110 **British Columbia Centre for Disease Control**. Provincial guidance for medical imaging services within British Columbia during the COVID-19 pandemic phases. [cited 26 December 2020]. In: British Columbia Centre for Disease Control [Internet]. Available from: http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID19_MedicalImagingGuidePractitioners.pdf

111 **Vagal A**, Mahoney M, Allen B, Kapur S, Udstuen G, Wang L, Braley S, Makramalla A, Chadalavada S, Choe KA, Scheler J, Brown A, England E, Hudepohl J, Rybicki FJ. Rescheduling Nonurgent Care in Radiology: Implementation During the Coronavirus Disease 2019 (COVID-19) Pandemic. *J Am Coll Radiol* 2020; **17**: 882-889 [PMID: 32473108 DOI: 10.1016/j.jacr.2020.05.010]

112 **The Royal College of Radiologists**. RCR advice on non-urgent and cancer imaging during the coronavirus pandemic. [cited 26 December 2020]. In: The Royal College of Radiologists [Internet]. Available from: https://www.rcr.ac.uk/college/coronavirus-covid-19-what-rcr-doing/clinical-information/rcr-advice-non-urgent-and-cancer

113 **The American Society of Breast Surgeons**. ASBrS and ACR Joint Statement on Breast Screening Exams During the COVID-19 Pandemic. [cited 26 December 2020]. In: The American Society of Breast Surgeons [Internet]. Available from: https://www.breastsurgeons.org/news/?id=45

114 **Society of Breast Imaging**. Society of Breast Imaging Statement on Breast Imaging during the COVID-19 Pandemic. [cited 26 December 2020]. In: Society of Breast Imaging [Internet]. Available from: https://www.sbi-online.org/Portals/0/Position%20Statements/2020/society-of-breast-imaging-statement-on-breast-imaging-during-COVID19-pandemic.pdf

115 **Czernin J**, Fanti S, Meyer PT, Allen-Auerbach M, Hacker M, Sathekge M, Hicks R, Scott AM, Hatazawa J, Yun M, Schöder H, Bartenstein P, Herrmann K. Nuclear Medicine Operations in the Times of COVID-19: Strategies, Precautions, and Experiences. *J Nucl Med* 2020; **61**: 626-629 [PMID: 32238430 DOI: 10.2967/jnumed.120.245738]

116 **Pan L**, Zeng J, Pu H, Peng S. How to optimize the Radiology protocol during the global COVID-19 epidemic: Keypoints from Sichuan Provincial People's Hospital. *Clin Imaging* 2021; **69**: 324-327 [PMID: 33045477 DOI: 10.1016/j.clinimag.2020.07.008]

117 **Peros G**, Gronki F, Molitor N, Streit M, Sugimoto K, Karrer U, Lunger F, Adamina M, Breitenstein S, Lamdark T. Organizing a COVID-19 triage unit: a Swiss perspective. *Emerg Microbes Infect* 2020; **9**: 1506-1513 [PMID: 32579076 DOI: 10.1080/22221751.2020.1787107]

118 **Rossi A**, Prochowski Iamurri A, Cerchione C, Gentili N, Danesi V, Altini M, Paganelli G, Barone D. Radiology imaging management in an Italian cancer center (IRST IRCCS) during the COVID-19 pandemic. *Insights Imaging* 2020; **11**: 129 [PMID: 33270166 DOI: 10.1186/s13244-020-00935-x]

119 **Wang Q**, Wang X, Lin H. The role of triage in the prevention and control of COVID-19. *Infect Control Hosp Epidemiol* 2020; **41**: 772-776 [PMID: 32362296 DOI: 10.1017/ice.2020.185]

120 **Huang T**, Guo Y, Li S, Zheng Y, Lei L, Zeng X, Zhong Q, Liu Y, Liu L. Application and effects of fever screening system in the prevention of nosocomial infection in the only designated hospital of coronavirus disease 2019 (COVID-19) in Shenzhen, China. *Infect Control Hosp Epidemiol* 2020; **41**: 978-981 [PMID: 32279675 DOI: 10.1017/ice.2020.119]

121 **World Health Organization**. Establishing COVID-19 triage stations at healthcare facilities: Key instructions and tips. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://www.afro.who.int/sites/default/files/Covid-19/Techinical%20documents/Establishing%20COVID-19%20triage%20stations%20at%20healthcare%20facilities%20-%20Key%20instructions%20and%20tips.pdf

122 **Chen Q**, Zu ZY, Jiang MD, Lu L, Lu GM, Zhang LJ. Infection Control and Management Strategy for COVID-19 in the Radiology Department: Focusing on Experiences from China. *Korean J Radiol* 2020; **21**: 851-858 [PMID: 32524785 DOI: 10.3348/kjr.2020.0342]

123 **Tay YX**, Sng LH, Chow HC, Zainuldin MR. Clinical placements for undergraduate diagnostic radiography students amidst the COVID-19 pandemic in Singapore: Preparation, challenges and strategies for safe resumption. *J Med Imaging Radiat Sci* 2020; **51**: 560-566 [PMID: 32868260 DOI: 10.1016/j.jmir.2020.08.012]

124 **Garg T**, Shrigiriwar A, Patel K. Trainee education during COVID-19. *Neuroradiology* 2020; **62**:

1057-1058 [PMID: 32556422 DOI: 10.1007/s00234-020-02478-w]

125 **Health Management**. New Ways of Optimising Imaging Services. [cited 26 December 2020]. In: Health Management [Internet]. Available from: https://healthmanagement.org/c/imaging/issuearticle/new-ways-of-optimising-imaging-services

126 **Sng LH**, Arlany L, Toh LC, Loo TY, Ilzam NS, Wong BSS, Lanca L. Initial data from an experiment to implement a safe procedure to perform PA erect chest radiographs for COVID-19 patients with a mobile radiographic system in a "clean" zone of the hospital ward. *Radiography (Lond)* 2021; **27**: 48-53 [PMID: 32517970 DOI: 10.1016/j.radi.2020.05.011]

127 **Singapore General Hospital**. Ideas bloom amid COVID-19 pressure. [cited 26 December 2020]. In: Singapore General Hospital [Internet]. Available from: https://www.sgh.com.sg/news/singapore-health/ideas-bloom-amid-COVID-19-pressure

128 **Diagnostic Imaging**. Walk-Up X-ray Booth Offers Quick Scans to COVID-19 Patients. [cited 26 December 2020]. In: Diagnostic Imaging [Internet]. Available from: https://www.diagnosticimaging.com/view/walk-x-ray-booth-offers-quick-scans-covid-19-patients

129 **Myers L**, Balakrishnan S, Reddy S, Gholamrezanezhad A. Coronavirus Outbreak: Is Radiology Ready? *J Am Coll Radiol* 2020; **17**: 724-729 [PMID: 32304643 DOI: 10.1016/j.jacr.2020.03.025]

130 **European Society of Cardiology**. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. [cited 26 December 2020]. In: European Society of Cardiology [Internet]. Available from: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

131 **SCMR's COVID-19 Preparedness Toolkit**. Society for Cardiovascular Magnetic Resonance. [cited 26 December 2020]. In: SCMR's COVID-19 Preparedness Toolkit [Internet]. Available from: https://scmr.org/page/COVID19

132 **Chia AQX**, Cheng LT, Wijaya L, Png MA, Sim WY, Hong WL, Chen RC. Chest Radiographs and CTs in the Era of COVID-19: Indications, Operational Safety Considerations and Alternative Imaging Practices. *Acad Radiol* 2020; **27**: 1193-1203 [PMID: 32703648 DOI: 10.1016/j.acra.2020.06.022]

133 **Niu Y**, Xian J, Lei Z, Liu X, Sun Q. Management of infection control and radiological protection in diagnostic radiology examination of COVID-19 cases. *Radiat Med Prot* 2020; **1**: 75-80 [PMID: 32835346 DOI: 10.1016/j.radmp.2020.05.005]

134 **Mohakud S**, Ranjan A, Naik S, Deep N. COVID-19 preparedness for portable x-rays in an Indian hospital - Safety of the radiographers, the frontline warriors. *Radiography (Lond)* 2020; **26**: 270-271 [PMID: 32327384 DOI: 10.1016/j.radi.2020.04.008]

135 **Zhao Y**, Xiang C, Wang S, Peng C, Zou Q, Hu J. Radiology department strategies to protect radiologic technologists against COVID19: Experience from Wuhan. *Eur J Radiol* 2020; **127**: 108996 [PMID: 32344294 DOI: 10.1016/j.ejrad.2020.108996]

136 **Gogna A**, Yogendra P, Lee SHE, Aziz A, Cheong E, Chan LP, Venkatanarasimha N. Diagnostic Ultrasound Services During the Coronavirus Disease (COVID-19) Pandemic. *AJR Am J Roentgenol* 2020; **215**: 1130-1135 [PMID: 32520580 DOI: 10.2214/AJR.20.23167]

137 **Kooraki S**, Hosseiny M, Raman SS, Myers L, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19) Precautions: What the MRI Suite Should Know. *J Am Coll Radiol* 2020; **17**: 830 [PMID: 32473107 DOI: 10.1016/j.jacr.2020.05.018]

138 **Too CW**, Wen DW, Patel A, Abdul Syafiq AR, Liu J, Leong S, Gogna A, Lo RHG, Tashi S, Lee KA, Kumar P, Lie SA, Tay YC, Lee LC, Ling ML, Tan BS, Tay KH. Interventional Radiology Procedures for COVID-19 Patients: How we Do it. *Cardiovasc Intervent Radiol* 2020; **43**: 827-836 [PMID: 32342154 DOI: 10.1007/s00270-020-02483-9]

139 **Ierardi AM**, Wood BJ, Gaudino C, Angileri SA, Jones EC, Hausegger K, Carrafiello G. How to Handle a COVID-19 Patient in the Angiographic Suite. *Cardiovasc Intervent Radiol* 2020; **43**: 820-826 [PMID: 32277272 DOI: 10.1007/s00270-020-02476-8]

140 **World Health Organization**. Hospital Preparedness for Epidemics. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://apps.who.int/iris/bitstream/handle/10665/151281/9789241548939_eng.pdf

141 **Springer Nature**. Research in the time of a pandemic: Healthcare preparedness and response. [cited 26 December 2020]. In: Springer Nature [Internet]. Available from: https://www.springernature.com/gp/researchers/the-source/blog/blogposts-communicating-research/research-in-the-time-of-a-pandemic--healthcare-preparedness/18099038

142 **Tay YX**, Wei YM, Aw LP, Lai C. The strategy to develop newly joined radiographers in a COVID-19 world: a curated orientation programme. *J Med Imaging Radiat Sci* 2020 [PMID: 33189638 DOI: 10.1016/j.jmir.2020.10.006]

143 **Chow C**, Shahdadpuri R, Kai-Qian K, Hwee CY. The Next Pandemic: Supporting COVID-19 Frontline Doctors Through Film Discussion. *J Med Humanit* 2020; **41**: 585-595 [PMID: 32889676 DOI: 10.1007/s10912-020-09662-2]

144 **Ertl-Wagner BB**, Lee W, Manson DE, Amaral JG, Bojic Z, Cote MS, Fernandes JM, Murray D, Shammas A, Therrien-Miller N, Shroff MM. Preparedness for the COVID-19 pandemic in a tertiary pediatric radiology department. *Pediatr Radiol* 2020; **50**: 1059-1068 [PMID: 32495178 DOI: 10.1007/s00247-020-04704-2]

145 **Mohammad SA**, Osman AM, Abd-Elhameed AM, Ahmed KA, Taha NM, Saleh A, Omar A, El-Meteini M, Mohamed MA. The battle against Covid-19: the experience of an Egyptian radiology department in a university setting. *Egypt J Radiol Nucl Med* 2020; **51**: 216 [DOI:

10.1186/s43055-020-00335-7]
146 **Greenberg N**. Mental health of health-care workers in the COVID-19 era. *Nat Rev Nephrol* 2020; **16**: 425-426 [PMID: 32561871 DOI: 10.1038/s41581-020-0314-5]
147 **Rainford LA**, Zanardo M, Buissink C, Decoster R, Hennessy W, Knapp K, Kraus B, Lanca L, Lewis S, Mahlaola TB, McEntee M, O'Leary D, Precht H, Starc T, McNulty JP. The impact of COVID-19 upon student radiographers and clinical training. *Radiography (Lond)* 2021; **27**: 464-474 [PMID: 33223416 DOI: 10.1016/j.radi.2020.10.015]
148 **Wilcha RJ**. Effectiveness of Virtual Medical Teaching During the COVID-19 Crisis: Systematic Review. *JMIR Med Educ* 2020; **6**: e20963 [PMID: 33106227 DOI: 10.2196/20963]
149 **Darras KE**, Spouge RJ, de Bruin ABH, Sedlic A, Hague C, Forster BB. Undergraduate Radiology Education During the COVID-19 Pandemic: A Review of Teaching and Learning Strategies [Formula: see text]. *Can Assoc Radiol J* 2021; **72**: 194-200 [PMID: 32749165 DOI: 10.1177/0846537120944821]
150 **Tay YX**, Chow HC, Ooi CC. Impact on clinical learning during coronavirus disease 2019 pandemic: from disruption to recovery and the new norms. *Korean J Med Educ* 2020; **32**: 297-305 [PMID: 33296573 DOI: 10.3946/kjme.2020.176]
151 **McRoy C**, Patel L, Gaddam DS, Rothenberg S, Herring A, Hamm J, Chelala L, Weinstein J, Smith E, Awan O. Radiology Education in the Time of COVID-19: A Novel Distance Learning Workstation Experience for Residents. *Acad Radiol* 2020; **27**: 1467-1474 [PMID: 32800692 DOI: 10.1016/j.acra.2020.08.001]
152 **Radiological Society of North America**. Simulation, Virtual Reality are the Future of Radiology Education. [cited 26 December 2020]. In: Radiological Society of North America [Internet]. Available from: https://www.rsna.org/en/news/2019/September/Future-Of-Radiology-Education
153 **Health Imaging**. Simulated daily readout program mimics pre-COVID workflow, earning praise from radiology residents and faculty. [cited 26 December 2020]. In: Health Imaging [Internet]. Available from: https://www.healthimaging.com/topics/practice-management/simulated-readout-pre-covid-earning-praise-radiology-residents
154 **Ashcroft J**, Byrne MHV, Brennan PA, Davies RJ. Preparing medical students for a pandemic: a systematic review of student disaster training programmes. *Postgrad Med J* 2020 [PMID: 32518075 DOI: 10.1136/postgradmedj-2020-137906]
155 **University World News**. Putting fairness at the heart of higher education. [cited 26 December 2020]. In: University World News [Internet]. Available from: https://www.universityworldnews.com/post.php?story=20200417094523729
156 **World Economic Forum**. The COVID-19 pandemic has changed education forever. This is how. [cited 26 December 2020]. In: World Economic Forum [Internet]. Available from: https://www.weforum.org/agenda/2020/04/coronavirus-education-global-covid19-online-digital-learning/
157 **Wong ASK**, Ooi CC, Leow MQH, Kiew YS, Yeo KCW, Tan SG, Tay KH. Adapting Lessons From SARS for the COVID-19 Pandemic-Perspectives From Radiology Nursing in Singapore. *J Radiol Nurs* 2020; **39**: 164-167 [PMID: 32837391 DOI: 10.1016/j.jradnu.2020.06.008]
158 **Pua U**, Wong D. What Is Needed to Make Interventional Radiology Ready for COVID-19? *Korean J Radiol* 2020; **21**: 629-631 [PMID: 32174055 DOI: 10.3348/kjr.2020.0163]
159 **Wilder-Smith A**, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? *Lancet Infect Dis* 2020; **20**: e102-e107 [PMID: 32145768 DOI: 10.1016/S1473-3099(20)30129-8]
160 **Hudson BJ**, Loughborough WW, Oliver HC, Callow ME, Pressdee DJ, Bond SJ, Freeman RJ, Wood RJ, Laugharne MJ, Hughes-Roberts Y, Colliver RJ, Robinson G, Rodrigues JCL, Phillips AJ. Lasting lessons learnt in the radiology department from the battle with COVID-19. *Clin Radiol* 2020; **75**: 586-591 [PMID: 32553357 DOI: 10.1016/j.crad.2020.06.001]
161 **Norbash AM**, Moore AV Jr, Recht MP, Brink JA, Hess CP, Won JJ, Jain S, Sun X, Brown M, Enzmann D. Early-Stage Radiology Volume Effects and Considerations with the Coronavirus Disease 2019 (COVID-19) Pandemic: Adaptations, Risks, and Lessons Learned. *J Am Coll Radiol* 2020; **17**: 1086-1095 [PMID: 32717183 DOI: 10.1016/j.jacr.2020.07.001]
162 **World Health Organization**. Diagnostic imaging. [cited 26 December 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/diagnostic_imaging/en/
163 **Alexander A**, Jiang A, Ferreira C, Zurkiya D. An Intelligent Future for Medical Imaging: A Market Outlook on Artificial Intelligence for Medical Imaging. *J Am Coll Radiol* 2020; **17**: 165-170 [PMID: 31918875 DOI: 10.1016/j.jacr.2019.07.019]
164 **American Medical Association**. Why health care AI can't replace medicine's human component. [cited 26 December 2020]. In: American Medical Association [Internet]. Available from: https://www.ama-assn.org/practice-management/digital/why-health-care-ai-can-t-replace-medicine-s-human-component
165 **American Medical Association**. Augmented intelligence in health care - Policy. [cited 26 December 2020]. In: American Medical Association [Internet]. Available from: https://www.ama-assn.org/system/files/2019-08/ai-2018-board-policy-summary.pdf
166 **Harvard Business Review**. How Hospitals Are Using AI to Battle Covid-19. [cited 26 December 2020]. In: Harvard Business Review [Internet]. Available from: https://hbr.org/2020/04/how-hospitals-are-using-ai-to-battle-covid-19
167 **European Society of Radiology**. What the increasing presence of AI means for radiographers.

[cited 26 December 2020]. In: European Society of Radiology [Internet]. Available from: https://ai.myesr.org/healthcare/what-the-increasing-presence-of-ai-means-for-radiographers/

168 **Ahuja AS**. The impact of artificial intelligence in medicine on the future role of the physician. *PeerJ* 2019; **7**: e7702 [PMID: 31592346 DOI: 10.7717/peerj.7702]

169 **Centers for Disease Control and Prevention**. Healthcare Facilities: Managing Operations During the COVID-19 Pandemic. [cited 26 December 2020]. In: Centers for Disease Control and Prevention [Internet]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-hcf.html

170 **Blandford A**, Wesson J, Amalberti R, AlHazme R, Allwihan R. Opportunities and challenges for telehealth within, and beyond, a pandemic. *Lancet Glob Health* 2020; **8**: e1364-e1365 [PMID: 32791119 DOI: 10.1016/S2214-109X(20)30362-4]

171 **Calton B**, Abedini N, Fratkin M. Telemedicine in the Time of Coronavirus. *J Pain Symptom Manage* 2020; **60**: e12-e14 [PMID: 32240756 DOI: 10.1016/j.jpainsymman.2020.03.019]

172 **Health Imaging**. Radiology uses telemedicine more than any other specialty, AMA survey finds. [cited 26 December 2020]. In: Health Imaging [Internet]. Available from: https://www.healthimaging.com/topics/imaging-informatics/radiology-uses-telemedicine-most-ama-finds

173 **Radiological Society of North America**. Teleradiology Soars During COVID-19 Pandemic. [cited 26 December 2020]. In: Radiological Society of North America [Internet]. Available from: https://www.rsna.org/en/news/2020/April/Telehealth-Surge

174 **Bhaskar S**, Bradley S, Chattu VK, Adisesh A, Nurtazina A, Kyrykbayeva S, Sakhamuri S, Yaya S, Sunil T, Thomas P, Mucci V, Moguilner S, Israel-Korn S, Alacapa J, Mishra A, Pandya S, Schroeder S, Atreja A, Banach M, Ray D. Telemedicine Across the Globe-Position Paper From the COVID-19 Pandemic Health System Resilience PROGRAM (REPROGRAM) International Consortium (Part 1). *Front Public Health* 2020; **8**: 556720 [PMID: 33178656 DOI: 10.3389/fpubh.2020.556720]

175 **National Institutes of Health**. NIH harnesses AI for COVID-19 diagnosis, treatment, and monitoring. [cited 26 December 2020]. In: National Institutes of Health [Internet]. Available from: https://www.nih.gov/news-events/news-releases/nih-harnesses-ai-covid-19-diagnosis-treatment-monitoring

176 **Becker's Healthcare**. AI is transforming diagnostic imaging. [cited 26 December 2020]. In: Becker's Healthcare [Internet]. Available from: https://www.beckershospitalreview.com/healthcare-information-technology/ai-is-transforming-diagnostic-imaging.html

177 **Philips**. Seven ways COVID-19 is accelerating digital transformation in healthcare. [cited 26 December 2020]. In: Philips [Internet]. Available from: https://www.philips.com/a-w/about/news/archive/blogs/innovation-matters/2020/20200608-seven-ways-covid-19-is-accelerating-digital-transformation-in-healthcare.html

178 **General Electric Company**. 5 Ways to Improve Workflow and Productivity in Radiology Departments. [cited 26 December 2020]. In: General Electric Company [Internet]. Available from: https://www.gehealthcare.com/Long-article/5-ways-to-improve-workflow-and-productivity-in-radiology-departments

179 **Healthcare IT News**. Tech optimization: Peak performance for imaging technology. [cited 26 December 2020]. In: Healthcare IT News [Internet]. Available from: https://www.healthcareitnews.com/news/tech-optimization-peak-performance-imaging-technology

World Journal of Radiology

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

World J Radiol 2021 May 28; 13(5): 122-136

DOI: 10.4329/wjr.v13.i5.122

ISSN 1949-8470 (online)

REVIEW

Highlighting COVID-19: What the imaging exams show about the disease

Lorena Sousa de Carvalho, Ronaldo Teixeira da Silva Júnior, Bruna Vieira Silva Oliveira, Yasmin Silva de Miranda, Nara Lúcia Fonseca Rebouças, Matheus Sande Loureiro, Samuel Luca Rocha Pinheiro, Regiane Santos da Silva, Paulo Victor Silva Lima Medrado Correia, Maria José Souza Silva, Sabrina Neves Ribeiro, Filipe Antônio França da Silva, Breno Bittencourt de Brito, Maria Luísa Cordeiro Santos, Rafael Augusto Oliveira Sodré Leal, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo

ORCID number: Lorena Sousa de Carvalho 0000-0003-1876-9240; Ronaldo Teixeira da Silva Júnior 0000-0003-0835-4092; Bruna Vieira Silva Oliveira 0000-0002-1861-4233; Yasmin Silva de Miranda 0000-0002-3243-3527; Nara Lúcia Fonseca Rebouças 0000-0003-3262-0143; Matheus Sande Loureiro 0000-0002-5140-2996; Samuel Luca Rocha Pinheiro 0000-0002-8877-892X; Regiane Santos da Silva 0000-0003-3431-5780; Paulo Victor Silva Lima Medrado Correia 0000-0001-7494-7414; Maria José Souza Silva 0000-0002-2329-5978; Sabrina Neves Ribeiro 0000-0003-3530-0575; Filipe Antônio França da Silva 0000-0002-0550-1109; Breno Bittencourt de Brito 0000-0002-1831-7909; Maria Luísa Cordeiro Santos 0000-0001-7078-9789; Rafael Augusto Oliveira Sodré Leal 0000-0001-9122-0081; Márcio Vasconcelos Oliveira 0000-0002-8959-0478; Fabrício Freire de Melo 0000-0002-5680-2753.

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting, critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No

Lorena Sousa de Carvalho, Ronaldo Teixeira da Silva Júnior, Bruna Vieira Silva Oliveira, Yasmin Silva de Miranda, Nara Lúcia Fonseca Rebouças, Matheus Sande Loureiro, Samuel Luca Rocha Pinheiro, Regiane Santos da Silva, Paulo Victor Silva Lima Medrado Correia, Maria José Souza Silva, Sabrina Neves Ribeiro, Filipe Antônio França da Silva, Breno Bittencourt de Brito, Maria Luísa Cordeiro Santos, Rafael Augusto Oliveira Sodré Leal, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo, Department of Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45029-094, Bahia, Brazil

Corresponding author: Fabrício Freire de Melo, MSc, PhD, Postdoc, Professor, Department of Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Rua Hormindo Barros, 58, Quadra 17, Lote 58-Candeias, Vitória da Conquista 45029-094, Bahia, Brazil.
freiremelo@yahoo.com.br

Abstract

Coronavirus disease 2019 (COVID-19), a global emergency, is caused by severe acute respiratory syndrome coronavirus 2. The gold standard for its diagnosis is the reverse transcription polymerase chain reaction, but considering the high number of infected people, the low availability of this diagnostic tool in some contexts, and the limitations of the test, other tools that aid in the identification of the disease are necessary. In this scenario, imaging exams such as chest X-ray (CXR) and computed tomography (CT) have played important roles. CXR is useful for assessing disease progression because it allows the detection of extensive consolidations, besides being a fast and cheap method. On the other hand, CT is more sensitive for detecting lung changes in the early stages of the disease and is also useful for assessing disease progression. Of note, ground-glass opacities are the main COVID-19-related CT findings. Positron emission tomography combined with CT can be used to evaluate chronic and substantial damage to the lungs and other organs; however, it is an expensive test. Lung ultrasound (LUS) has been shown to be a promising technique in that context as well, being useful in the screening and monitoring of patients, disease classification, and management related to mechanical ventilation. Moreover, LUS is an inexpensive alternative available at the bedside. Finally, magnetic resonance imaging, although not usually requested, allows the detection of pulmonary,

financial support.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

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

Received: January 27, 2021
Peer-review started: January 27, 2021
First decision: March 1, 2021
Revised: March 16, 2021
Accepted: May 7, 2021
Article in press: May 7, 2021
Published online: May 28, 2021

P-Reviewer: Zhu CW
S-Editor: Fan JR
L-Editor: Webster JR
P-Editor: Wang LL

cardiovascular, and neurological abnormalities associated with COVID-19. Furthermore, it is important to consider the challenges faced in the radiology field in the adoption of control measures to prevent infection and in the follow-up of post-COVID-19 patients.

Key Words: SARS-CoV-2; COVID-19; Pneumonia; Pandemic; Radiology; Tomography

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Imaging exams have played an important role in the current coronavirus disease 2019 pandemic. Thus, even though reverse transcription polymerase chain reaction is the gold standard method for the diagnosis, the use of computed tomography (CT) in the management of severe acute respiratory syndrome coronavirus 2-infected individuals has been highlighted. On the other hand, X-Ray, positron emission tomography combined with CT, and magnetic resonance imaging, along with ultrasound, can also assist in this process. We herein discuss the main evidence on the use of such exams and the challenges to the radiology field in that context as well.

Citation: de Carvalho LS, da Silva Júnior RT, Oliveira BVS, de Miranda YS, Rebouças NLF, Loureiro MS, Pinheiro SLR, da Silva RS, Correia PVSLM, Silva MJS, Ribeiro SN, da Silva FAF, de Brito BB, Santos MLC, Leal RAOS, Oliveira MV, de Melo FF. Highlighting COVID-19: What the imaging exams show about the disease. *World J Radiol* 2021; 13(5): 122-136
URL: https://www.wjgnet.com/1949-8470/full/v13/i5/122.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i5.122

INTRODUCTION

In December 2019, several cases of a pneumonia of unknown cause with a clinical presentation compatible with conditions of viral etiology were reported in the city of Wuhan, Hubei province, China[1-4]. Later, it was found to be caused by a new type of coronavirus that was subsequently called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease came to be called coronavirus disease 2019 (COVID-19)[5,6]. Since then, the number of cases has increased, becoming a major outbreak and a global emergency[7,8]. By 19 January 2021, more than 93956883 cases and 2029084 deaths have been confirmed by the World Health Organization[9].

The SARS-CoV-2 is a β-coronavirus with spherical RNA and spike proteins that protrude on its surface[10]. It primarily infects the respiratory system but other organs such as the kidneys, heart, ileum, and spleen can also be infected[11]. The pathophysiological mechanisms involved in this process are complex, and includes virus attachment, recognition between specific cell receptors, and transmembrane Spike glycoprotein (S-protein) receptor-binding domain, along with protease cleaving by host cellular transmembrane serine protease (TMPRSS)[12]. Angiotensin-converting enzyme type 2 (ACE2) receptors are expressed in various human cells, including epithelial cells in the lungs, cardiomyocytes, neuronal and glial cells in the brain[13], glandular cells of the gastric, duodenal, and rectal epithelia, and enterocytes of the small intestine[14,15]. The main pathway by which SARS-CoV-2 enters cells is through the binding of S-protein to ACE2[14,15], and protein cleavage by enzymes, such as TMPRSS2[16].

The SARS-CoV-2 infection has variable clinical presentations, from asymptomatic to severe cases, which can lead to death[1,5]. The main symptoms involve fever, dry cough, dyspnea, and fatigue[17-20]. The gold standard diagnostic test for COVID-19 is the reverse transcription polymerase chain reaction (RT-PCR)[21,22]. However, due to the low availability of this diagnostic tool in some contexts, failures in sample collections, and the possibility of false-negative results, it has become necessary to use other methods to increase the accuracy of infection identification[23].

In this context, some imaging exams such as lung ultrasound (LUS), chest X-Ray (CXR), magnetic resonance imaging (MRI), and especially chest computed tomography (CT) have been very useful in the diagnosis of COVID-19[24]. It is noteworthy that in places of low prevalence of the disease or in asymptomatic

individuals, imaging tests may have problems with false positive or missed detection. Thus, factors such as epidemiological data, clinical condition, laboratory tests and imaging exams can contribute to the screening of COVID-19, but for the final diagnosis the identification of viral RNA using RT-PCR is necessary[25,26].

CT is able to show important findings for early detection of the infection even when negative results are obtained in the RT-PCR, such as ground-glass opacities (GGO)[27]. It is worth mentioning that CXR is more often used in the evaluation of disease progression than in the detection of the infection itself due to its lower value in the early identification of GGO compared to CT[28]. LUS is a faster and safer method than the aforementioned methods and, even though it provides images with an inferior quality than those obtained with a CT scan, it has become very useful due to its practicality, as it is possible to perform this technique at the patient's bedside, whereas the other procedures involve displacement and longer periods of time[29]. Of course, all available resources for patient care should always be taken into consideration, but when dealing with a pandemic, it is of unequal importance to thoroughly evaluate aspects related to the speed and efficiency of diagnostic methods[30].

In the initial phase of the COVID-19 outbreak, when RT-PCR tests had limited availability, countries presented divergent opinions regarding the use of imaging exams in the diagnosis of the infection worldwide. With the increase in the availability of RT-PCR kits throughout the pandemic, the criteria for the use of imaging tests began to gain consensus. But, it is worth mentioning that the national guidelines vary according to factors such CT scanner availability, personal protective equipment availability, and *in vitro* testing infrastructure[31]. Therefore, this review aims to describe the use of imaging exams for the detection of COVID-19, providing a broad overview on the main methods used in this context and discussing the challenges in the radiology field during the pandemic.

WHAT DO THE IMAGING EXAMS SHOW ABOUT THE DISEASE?

Although the detection of SARS-CoV-2 RNA using the RT-PCR remains the gold standard diagnostic method, the unspecific or asymptomatic initial stage of COVID-19 highlights the important role of imaging exams in assisting the early diagnosis, as well as in monitoring and identifying complications[32,29]. Figure 1 summarizes the main points regarding the imaging modalities used in COVID-19.

CXR

The reduced capacity of CXR to reveal GGO, an early finding in the disease, limits its use in COVID-19 diagnosis. However, extensive consolidations, which are visible in the CXR, are common as the disease progresses[33].

Despite the sparse data in the literature on radiography in the COVID-19 context[34], the consolidation is the most common finding in the radiographs of infected patients, being predominantly observed in peripheral areas of the lower zones[35], with a peak of severity 10-12 d after the onset of symptoms[36]. Among 9 patients in Korea, the CXR detected parenchymal abnormalities in three of them, most with peripheral consolidation that was later confirmed by CT[37]. Moreover, a severity score can be used to quantify the extent of infection, with a score assigned to each lung that ranges from 0 to 4 according to the extent of lung involvement: 0 = no involvement; 1 corresponding to less than 25%; 2 = 25%-50%; 3 = 50%-75% and 4 to more than 75%. The scores obtained for each lung are then added together to provide the final gravity points[36].

A study published in October 2020 showed that chest radiographs may be reliable in predicting results from definitive COVID-19 diagnostic methods, particularly in places with limited resources and a high number of cases[38]. Radiography is the fastest and cheapest method to evaluate COVID-19 patients and it is broadly available in clinics, emergency rooms, and hospitals worldwide[39,40]. Moreover, this method is associated with a low exposure to ionizing radiation in users. In addition, the portable X-Ray units, whose mobility and cleaning are easy, have been considered as facilitating resources in emergencies[41].

However, the CXR abnormalities observed in COVID-19 are nonspecific and may overlap with findings from other infectious diseases such as influenza[42,43]. Thus, the analysis of imaging patterns on chest radiography in SARS-CoV-2 infection is complex, time-consuming, and prone to error. This evaluation is a challenge that must be considered, mainly due to the lack of specialized radiologists[39,41]. Therefore, an artificial intelligence (AI) algorithm could be used and programmed to distinguish

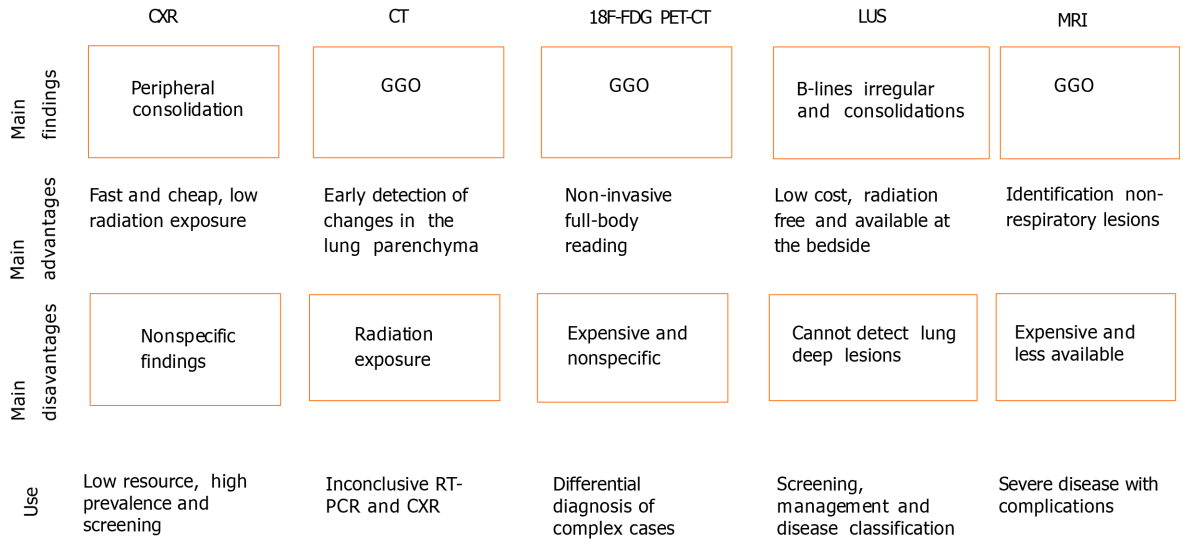


Figure 1 Highlights of imaging modalities in coronavirus disease 2019. CXR: Chest X-ray; CT: Computed tomography; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/CT; LUS: Lung ultrasound; MRI: Magnetic resonance imaging; GGO: Ground-glass opacities; RT-PCR: Real-time reverse transcription polymerase chain reaction.

COVID-19 pneumonia from non-COVID-19 pneumonia through CXR images[44]. The main goal of AI, when gathering imaging data and clinical information is to read image studies accurately, preferably as a screening tool[34].

A study observed sensibility and specificity of 95% and 71%, respectively, for the association between COVID-19 pneumonia with the involvement of 4 or more zones and clinical deterioration, in both critical and non-critical patients[45]. An analysis performed to determine the CXR diagnostic precision in comparison to RT-PCR in 569 patients with suspected SARS-CoV-2 infection showed, in the initial CXR, 61% sensibility and 76% specificity in the hospital environment[46]. In November 2020, an evaluation of the CXR associated with AI support for COVID-19 detection reported an increase in the diagnostic sensibility from 47% to 61%, even though the specificity reduced from 79% to 75%. This is a promising result for the possible use of AI to enhance the accuracy of this exam[39]. In conclusion, the CXR may be indicated in situations of low resources and high prevalence of the disease.

CT

There is a vast amount of information regarding CT findings in COVID-19 reported in different studies around the world[47]. It is known that the characteristics of the lung fields at CT scan change over time, with different presentations according to the stage and severity of the pulmonary infection[48].

The main feature found on a CT scan as a consequence of COVID-19 is the presence of GGO, with a predominantly bilateral and peripheral distribution[49]. Vascular enlargement is seen in GGO, representing interstitial peribronchovascular edema/inflammation and possible increased cardiac diameter[50].

In the initial stage of COVID-19, chest CT is characterized by single or multiple scattered patchy or agglomerated GGOs[51]. Subsequently, there may be an increase in the number and extent of lesions[52]. As far as the disease progresses, images show diffuse consolidation of the lungs, air bronchograms, and bronchial dilation. The resolution of the GGO and pulmonary consolidation occurs gradually, with some residual opacities remaining characteristic of fibrosis[53].

Chest CT may be useful for early diagnosis in cases of clinical suspicion, indefinite pulmonary abnormalities on CXR, and unavailable or negative RT-PCR test, and in the follow-up of severe cases[54].

A study used a chest CT severity score (CT-SS) that is based on the sum of scores from 20 regions of the lung. Each region receives a score from 0 to 2 according to the intensity of parenchymal opacification. A CT-SS threshold value of 19.5 was identified as a reliable cut-off to detect severe COVID-19, suggesting that this method may be useful in identifying people who need hospitalization[55]. Another method that aims to facilitate and standardize the assessment of patients with moderate-to-severe symptoms of COVID-19 on CT images is the COVID-19 reporting and data system (CO-RADS), which is determined according to the level of suspicion of pulmonary

involvement, varying from CO-RADS 1 (very low) to CO-RADS 5 (very high). Moreover, there are some extra classifications: CO-RADS 0 for technically insufficient tests and CO-RADS 6 for cases confirmed by RT-PCR[56]. Figure 2 summarizes the aforementioned scores.

Compared with the CXR, CT is more sensitive for detecting changes in the lung parenchyma in the early stages of the disease, besides enabling the monitoring of disease progression and possible differential diagnoses[57]. However, special attention is needed for non-infectious etiologies and other infectious causes, such as non-COVID-19 viral pneumonia, *Mycoplasma pneumoniae, Pneumocystis jiroveci*, and pulmonary granulomatous infections that may be similar to CT findings in COVID-19. In these cases, clinical manifestations, laboratory tests, and immunological status should also be considered to assist in the differential diagnosis[58].

Furthermore, evidence shows that some patients with a CT pattern suggestive of COVID-19 pneumonia initially have a negative RT-PCR test result, suggesting the need to repeat the diagnostic tests if there is high clinical suspicion[59]. In this sense, it is even considered that chest CT should be performed in symptomatic patients who will undergo surgery in a context that requires a quick diagnosis and RT-PCR is not available. This is important considering the high perioperative mortality of patients infected with SARS-CoV-2[60].

Despite the potential advantages of CT, factors such as the period needed to clean the imaging exam rooms, the risk of viral transmission for healthcare professionals, and radiation exposure to the patient must also be considered[61]. There is no standard for the radiation dose in cases of COVID-19, but some studies suggest single-phase, non-contrast, low-dose chest CT, which varies depending on factors such as the patient's body habitus, in those of small and medium size, for example, volume CT dose index < 3 mGy can be sufficient[62].

Regarding diagnostic accuracy, a meta-analysis that included studies with high-risk patients for COVID-19 reported a relatively high sensitivity of chest CT ranging from 92.9% to 97%, whereas specificity was poor, varying from 25% to 71.9%[63]. It is important to emphasize that these studies are influenced by several factors such as patient selection, disease prevalence, and medical interpretation, influencing the generalization of these results[64]. A French study[65], for example, suggested that chest CT has an important role in early diagnosis in areas with a high prevalence of COVID-19. However, Kim *et al*[66] indicated that in low-prevalence settings, many false positives can occur with the use of chest CT. Table 1 summarizes diagnostic accuracy values of CXR and CT for COVID-19.

Positron emission tomography combined with CT

Although positron emission tomography combined with CT (PET/CT) and the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) tracer in PET/CT are more complex than a simple chest CT, these imaging exams can provide morphological and functional information on infectious and inflammatory diseases[67]. The cells of the inflammatory process pick up ^{18}F-FDG, which showed potential in the differential diagnosis of complex cases, as well as lung lesions caused by SARS-CoV-2[68].

^{18}F-FDG PET/CT plays an important role in the evaluation of infectious and inflammatory lung diseases, including the detection of involved pulmonary segments, estimating the extent of the lesion, monitoring progression and responses to treatment[69]. In COVID-19, PET/CT could be used as a non-invasive full-body reading to assess chronic and substantial damage to the lungs and other organs[68]. In a previous study, 38.46% of patients submitted to ^{18}F-FDG PET/CT were diagnosed with COVID-19 before undergoing RT-PCR. Therefore, the authors concluded that the test can possibly identify SARS-CoV-2 infection when the findings, clinical history, and epidemiological context are related[70]. Moreover, this exam should also be done to evaluate the impact of possible damage, especially in patients from groups at increased risk for severe disease who present with respiratory symptoms[71]. Previous studies have reported that the main COVID-19 imaging findings were accidentally detected in cancer patients submitted to the exam[72,73]. When these findings were correlated with clinical and epidemiological data, they strongly suggested the SARS-CoV-2 infection[70], facilitating the patient's management.

The main imaging findings reported using ^{18}F-FDG PET/CT in COVID-19 are the presence of GGOs with areas of focal consolidation, mainly in the peripheral regions, as well as an interlobular septal thickening in one or both lungs[74,75]. Furthermore, positive ^{18}F-FDG lymph nodes in the mediastinal, hilar, and subclavian regions can also be observed[74]. In the early stages, COVID-19 pneumonia presents with segmental GGO and nodal involvement in the peripheral and posterior regions of the lungs, while disease progression is accompanied by an increase in the number of

Table 1 Sensibility and specificity of chest X-Ray and computed tomography for diagnosing COVID-19

	Chest X-Ray	Computed tomography
Sensibility	61%[46]	90%[65]
	55%[1][108]	93%[109]
	79%[2][108]	97%[110]
Specificity	76%[46]	91%[65]
	83%[1][108]	53%[109]
	70%[2][108]	25%[110]

[1]At ≤ 2 d after symptom onset.
[2]At > 11 d after symptom onset.

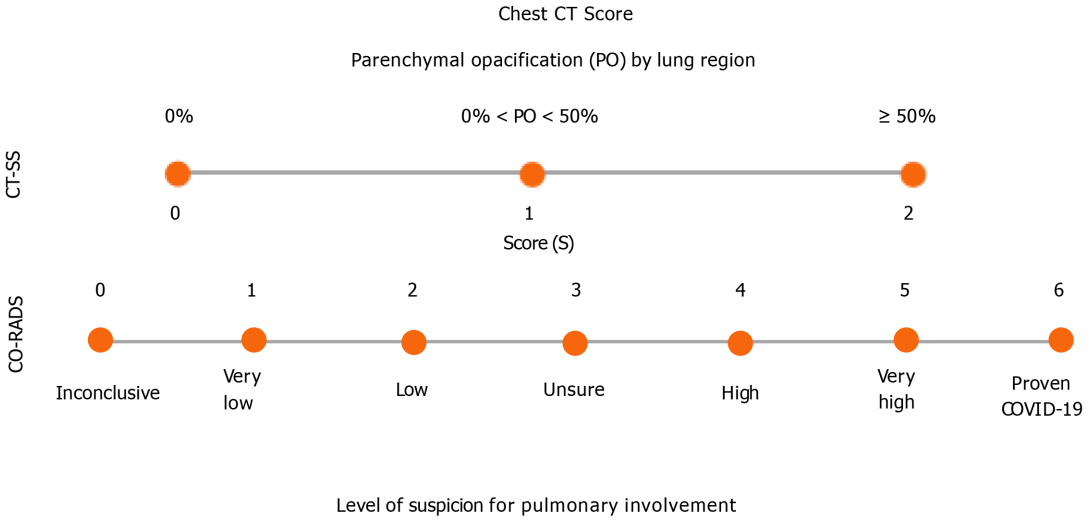


Figure 2 Summary of chest computed tomography scores to assess coronavirus disease 2019. CT-SS: Computed tomography severity score; COVID-19: Coronavirus disease 2019; CO-RADS: COVID-19 Reporting and Data System; PO: Parenchymal opacification.

lesions as well as in their extension and density. In addition, a mosaic paving pattern and air bronchogram sign have also been identified[76].

The ^{18}F-FDG PET/CT exam has important disadvantages. The test is still expensive and inaccessible for some people, especially those living in poor countries[77]. In addition, the low physical half-life, approximately 110 min, of ^{18}F-FDG is a problem, because this limitation prevents the examination from being carried out in places distant from the producers of this tracer[78]. Another important difficulty associated with the use of this substance is that it is unable to differentiate distinct populations of immune cells and it is not specific for viral infections[72]. Thus, these limitations are very relevant when considering performing this exam.

The level of accuracy of this imaging exam in the diagnosis of COVID-19 is still uncertain. Therefore, further studies using larger cohorts are needed to understand the usefulness of this exam in COVID-19[68]. Of note, the long-term follow-up of patients is very important to identify possible chronic damage caused by COVID-19 and the role of ^{18}F-FDG PET/CT in detecting such damage[71].

LUS

LUS has evolved over the years in the diagnosis of lung diseases, becoming in the current COVID-19 pandemic an alternative mode of first-line imaging because it is a viable and highly accurate imaging exam when used at the bedside[79]. It has the advantage of being an economical alternative, more accessible to low and middle-income countries, available at the bedside, in real time, and free of radiation risks[30,80]. LUS can also assist in the screening of symptomatic patients, classification of disease severity, monitoring of patients with pulmonary findings, management related to mechanical ventilation, and treatment allocation and evaluation[81].

The challenges of using ultrasound include prolonged operator exposure and the need for scanner plates and transducers that need to be completely disinfected, in addition, another limitation of this exam is that it cannot detect deep lesions in the lung[81,82]. Although a limited number of studies have evaluated this method in COVID-19, this procedure has high sensitivity and a high level of accuracy as a diagnostic tool for pneumonia, with a sensitivity of 93% and a specificity of 95% in the evaluation of patients with the disease. Some studies have also shown high sensitivity (93%-98%) for acute respiratory distress syndrome[82]. Thus, LUS is comparable to CT, but CT shows intra-pulmonary and apical lesions more clearly and comprehensively than LUS[29]. LUS is considered advantageous for detecting smaller lesions and peripulmonary effusions as well as pleural injuries, and is a dynamic and easily accessible method[34].

The evaluation of patients with COVID-19 using LUS often shows signs that include various forms of B-lines (often separated and coalescing), an irregular or fragmented pleural line, subpleural consolidations, pleural effusions, and absence of pulmonary slippage. These findings are variable and non-pathognomonic for SARS-CoV-2 infection[34]. The specificity for this disease occurs when irregular bilateral vertical artifacts and multifocal white lung signs are present, suggesting interstitial-alveolar damage[83]. The demonstration of B-lines are described as laser-like hyperechoic artifacts that resemble a "comet tail" or "light beam" and have been commonly observed in cases of COVID-19 pneumonia; these B-lines may be associated with an interstitial syndrome and decreased aeration and when the confluents may appear as a "white lung" equivalent to the frosted glass opacities of CT. These characteristics suggest a more severe loss of lung aeration[84,29].

LUS has been a promising alternative, which can be performed very quickly, is non-invasive, can be used to identify probable COVID-19 patients in association with RT-PCR and to identify pulmonary involvement and possible complications, differentiating acute signs of respiratory failure from normal function[80,85]. These characteristics aid in the management of the patient, whether in defining the need for hospitalization, ventilation or another specific therapy, and of great importance in the current pandemic[85].

MRI

MRI is not often performed in COVID-19, unlike CT[86]. However, when requested, a thoracic MRI is obtained with the respiratory navigator during the expiratory phase, thus providing valuable information for clinical evaluation[87]. MRI allows the detection of minute and fine aspects of the pulmonary parenchyma. Moreover, it detects pleural effusion and lymphadenopathy, and is a promising diagnostic tool in the detection of pulmonary nodules[88].

The most common finding in the thoracic MRI scan is GGO, which comes up due to slight interstitial thickening, edema, and hyaline membranes in the lung and may come together to form interlobular septum consolidation. This consolidation in COVID-19 occurs when there is increased density in the alveoli, and is multifocal, segmental, irregular, subpleural or peribroncovascular[88,89].

Due to the presence of the ACE2 receptor in other systems, the affinity between SARS-CoV-2 and ACE2, as well as other systemic consequences of this infection, can lead to cardiotoxicity and cardiovascular injury or thromboembolic event[90]. For this reason, greater attention should be paid to the possibility of some myocardial involvement even in recovered patients who had cardiac symptoms[91]. Within this framework, MRI has been of great value in patients with cardiovascular conditions, such as arrhythmias, fulminant myocarditis, and acute coronary syndromes[92].

In this context, cardiovascular MRI (CMR) allows the visualization of several myocarditis characteristics, such as contractile dysfunction, inflammatory edema, pulmonary artery filling defects, and necrosis[92,93]. The main methods are conventional cine images, T2-weighted sequences, parametric T1 and T2 maps, and late gadolinium enhanced images. Thus, CMR allows an anatomical and functional evaluation, revealing the different patterns of cardiac tissue damage, whether inflammatory or ischemic[93].

Moreover, MRI has become a very efficient tool in the investigation of a possible relationship between SARS-CoV-2 and nervous system abnormalities. Some studies have already suggested a neurotropism of the virus in infected patients who present with persistent severe anosmia and dysgeusia[94]. In this context, significant differences are observed in the signal intensity emitted at MRI of the olfactory bulb in patients with anosmia, presenting a T2/FLAIR hyperintensity[95].

The olfactory bulb MRI is very enlightening as it provides visualization of anatomical details and allows monitoring of the volume reduction of the bulb and respiratory tract that is directly linked to the clinical picture and presentation of anosmia[96]. This finding may be related to an initial inflammatory reaction of the nasal mucosa by the virus, as well as in the neuroepithelium of the olfactory fissure, in patients with a total loss of smell, affecting neural smell as was noted on MRI of anosmic patients[95].

It is important to note that, despite its importance, MRI is less available and more expensive than CT. However, its use is essential in the screening and monitoring of some serious neurological complications resulting from COVID-19 such as stroke, encephalitis, encephalopathy, and Guillain Barré syndrome[97].

The main indications for MRI are cases with worsening of the disease such as in the occurrence of acute necrotizing encephalopathy, with medial portion hypersignal of the thalamus on T2-weighted MRI and FLAIR sequences as well as in the subinsular region and medial portion of the temporal lobes from gadolinium ring uptake on T1-weighted sequences[89]. Furthermore, the aforementioned radiological signals are often detected in patients seeking MRI for other reasons. Thus, the radiologist's ability to recognize those characteristic findings is crucial to detect them even in patients without a prior COVID-19 diagnosis[86].

CHALLENGES FOR THE RADIOLOGY DEPARTMENT

Infection control protocols

Radiologists, as they are among the health professionals exposed to COVID-19, must be aware of the infection control protocols, in order to prevent viral spreading among patients or between patients and healthcare professionals[31,98].

Firstly, an infection control team should be established for the radiology department[99]. It is important to use personal protection equipment (PPE), which is divided into categories according to the radiologists' contact with patients[99]. In this sense, disposable protective caps, surgical masks, and goggles must be worn by everyone, as well as good hand hygiene[100]. For health professionals whose protection is level one, that is, people who manage registration and screening for review, disposable latex gloves and, if possible, N95 masks are recommended[100]. In levels two and three, which include those who perform diagnostic examinations such as X-Ray and CT in confirmed or suspected patients, should use the aforementioned PPE, plus a face shield as well as a disposable apron and shoe protectors[101,102]. Moreover, the people who are responsible for cleaning equipment and places, and those involved in the safe disposal of infectious medical waste, must use level two PPE[103]. Figure 3 illustrates the PPE indicated to prevent infection in the radiology room.

The removal of clothing should be carried out after contact with suspected or confirmed individuals, and new PPE is required to proceed with a new service. The patients must always wear surgical masks[101,103]. The equipment and the environment that the patient had contact with must undergo a decontamination process[82], using soap and water or a disinfectant such as alcohol and, after cleaning, it is recommended that the room be left unused for 1 h for air circulation[43,99].

Follow-up post-COVID-19

Another challenge that emerges for the radiologists during the pandemic is the post-infection follow-up, *i.e.*, to control complications and assist patients during recovery. Given the lack of concrete evidence on the long-term effects of COVID-19, the British Thoracic Society guidelines determined two follow-up algorithms[104]: (1) In patients who had the most severe COVID-19 pneumonia, it is suggested that a clinical review should be conducted between 4 to 6 wk after discharge and, if CXR still shows abnormalities, new radiography must be performed within 6-8 wk; (2) In patients who had mild or moderate COVID-19 pneumonia, it is suggested that CXR be performed 12 wk after discharge[105].

However, a study of 110 patients followed for 8 to 12 wk after admission, pointed out that CXRs are not necessary in those who did not need oxygen during infection, because they are unlikely to present any abnormalities[106].

Another study noted that point-of-care ultrasound findings, performed after hospital discharge, assist in monitoring the progress of severe COVID-19 pneumonia. During follow-up, besides LUS, chest CT was used for patients with suspected residual lung injury as well as CT pulmonary angiography and echocardiography for

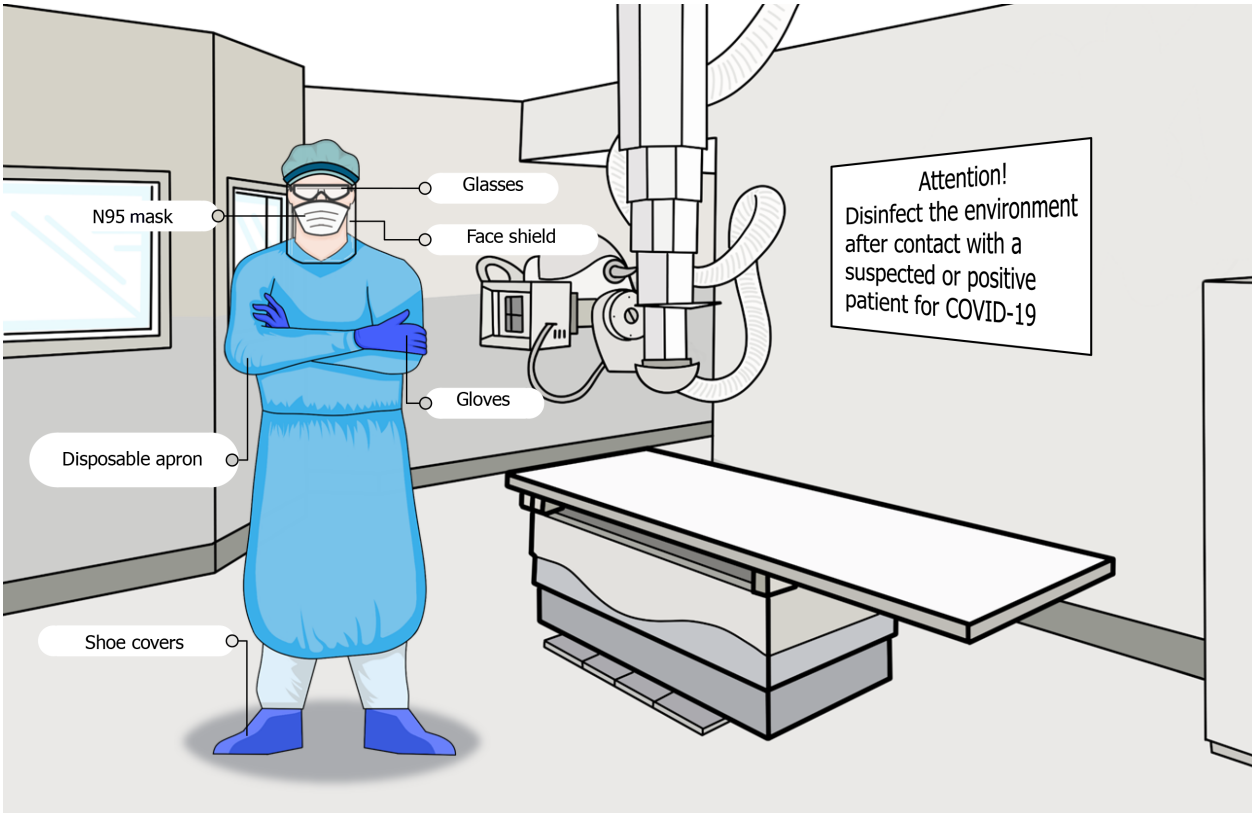


Figure 3 Safety measures to prevent infection in the radiology department. COVID-19: Coronavirus disease 2019.

patients with residual thromboembolic disease[107].

CONCLUSION

The COVID-19 pandemic has brought several challenges to health care systems. Due to the high rate of viral transmission, early diagnosis is essential to monitor and isolate the patient, reducing the risk of further contamination. In the initial phase of the pandemic, with the limited availability of RT-PCR tests, imaging techniques were important tools to assist in the diagnosis of COVID-19. Even with the improved availability of RT-PCR tests, over time, imaging remains useful not only for diagnosis but also for assessing disease progression and severity. Even in countries with financial and technical difficulties, imaging exams, if well managed, can assist in the diagnosis and monitoring of patients, enabling better results and reducing health costs. As the pandemic advances, some challenges are perpetuated, such as the need to maintain control to prevent and reduce risks of contamination in the radiology department, and others arise, such as the monitoring of post-COVID-19 patients. However, different to the initial phase of the pandemic, accumulated knowledge has enabled a better understanding of the main imaging findings associated with COVID-19 and the regional guidelines provide guidance on the proper use of imaging modalities considering the reality of each location. In addition, the use of AI has contributed to a more accurate diagnosis in the radiology field.

REFERENCES

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

2 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*

2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
3 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]
4 **Lu H**, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020; **92**: 401-402 [PMID: 31950516 DOI: 10.1002/jmv.25678]
5 **Coronaviridae Study Group of the International Committee on Taxonomy of Viruses**. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020; **5**: 536-544 [PMID: 32123347 DOI: 10.1038/s41564-020-0695-z]
6 **Lai CC**, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents* 2020; **55**: 105924 [PMID: 32081636 DOI: 10.1016/j.ijantimicag.2020.105924]
7 **Sohrabi C**, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 2020; **76**: 71-76 [PMID: 32112977 DOI: 10.1016/j.ijsu.2020.02.034]
8 **Phelan AL**, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. *JAMA* 2020; **323**: 709-710 [PMID: 31999307 DOI: 10.1001/jama.2020.1097]
9 **World Health Organization**. Geneva: 2020. Weekly operational update on COVID-19. [cited 19 January 2021]. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---19-january-2021
10 **Ashour HM**, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. *Pathogens* 2020; **9** [PMID: 32143502 DOI: 10.3390/pathogens9030186]
11 **Kabir MT**, Uddin MS, Hossain MF, Abdulhakim JA, Alam MA, Ashraf GM, Bungau SG, Bin-Jumah MN, Abdel-Daim MM, Aleya L. nCOVID-19 Pandemic: From Molecular Pathogenesis to Potential Investigational Therapeutics. *Front Cell Dev Biol* 2020; **8**: 616 [PMID: 32754599 DOI: 10.3389/fcell.2020.00616]
12 **Gu J**, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. *Gastroenterology* 2020; **158**: 1518-1519 [PMID: 32142785 DOI: 10.1053/j.gastro.2020.02.054]
13 **Villapol S**. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. *Transl Res* 2020; **226**: 57-69 [PMID: 32827705 DOI: 10.1016/j.trsl.2020.08.004]
14 **Wong SH**, Lui RN, Sung JJ. Covid-19 and the digestive system. *J Gastroenterol Hepatol* 2020; **35**: 744-748 [PMID: 32215956 DOI: 10.1111/jgh.15047]
15 **Lai CC**, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. *Int J Antimicrob Agents* 2020; **56**: 106024 [PMID: 32450197 DOI: 10.1016/j.ijantimicag.2020.106024]
16 **Stopsack KH**, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. *TMPRSS2* and COVID-19: Serendipity or Opportunity for Intervention? *Cancer Discov* 2020; **10**: 779-782 [PMID: 32276929 DOI: 10.1158/2159-8290.CD-20-0451]
17 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]
18 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
19 **Zhang G**, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res* 2020; **21**: 74 [PMID: 32216803 DOI: 10.1186/s12931-020-01338-8]
20 **Yan Y**, Shin WI, Pang YX, Meng Y, Lai J, You C, Zhao H, Lester E, Wu T, Pang CH. The First 75 Days of Novel Coronavirus (SARS-CoV-2) Outbreak: Recent Advances, Prevention, and Treatment. *Int J Environ Res Public Health* 2020; **17** [PMID: 32235575 DOI: 10.3390/ijerph17072323]
21 **Tahamtan A**, Ardebili A. Real-time RT-PCR in COVID-19 detection: issues affecting the results. *Expert Rev Mol Diagn* 2020; **20**: 453-454 [PMID: 32297805 DOI: 10.1080/14737159.2020.1757437]
22 **Carvalho ARVS**, Cezarotti Filho ML, Azevedo PCP, Silveira Filho RN, Barbosa FT, Rocha TJM, Sousa-Rodrigues CF, Ramos FWDS. Epidemiology, diagnosis, treatment, and future perspectives concerning SARS-COV-2: a review article. *Rev Assoc Med Bras (1992)* 2020; **66**: 370-374 [PMID: 32520160 DOI: 10.1590/1806-9282.66.3.370]
23 **Aljondi R**, Alghamdi S. Diagnostic Value of Imaging Modalities for COVID-19: Scoping Review. *J Med Internet Res* 2020; **22**: e19673 [PMID: 32716893 DOI: 10.2196/19673]
24 **Güneyli S**, Atçeken Z, Doğan H, Altınmakas E, Atasoy KÇ. Radiological approach to COVID-19 pneumonia with an emphasis on chest CT. *Diagn Interv Radiol* 2020; **26**: 323-332 [PMID: 32352917

DOI: 10.5152/dir.2020.20260]
25 **Meng X**, Liu Y. Chest Imaging Tests versus RT-PCR Testing for COVID-19 Pneumonia: There Is No Best, Only a Better Fit. *Radiology* 2020; **297**: E345 [PMID: 33079001 DOI: 10.1148/radiol.2020203792]
26 **Akl EA**, Blažić I, Yaacoub S, Frija G, Chou R, Appiah JA, Fatehi M, Flor N, Hitti E, Jafri H, Jin ZY, Kauczor HU, Kawooya M, Kazerooni EA, Ko JP, Mahfouz R, Muglia V, Nyabanda R, Sanchez M, Shete PB, Ulla M, Zheng C, van Deventer E, Perez MDR. Use of Chest Imaging in the Diagnosis and Management of COVID-19: A WHO Rapid Advice Guide. *Radiology* 2021; **298**: E63-E69 [PMID: 32729811 DOI: 10.1148/radiol.2020203173]
27 **Xie X**, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* 2020; **296**: E41-E45 [PMID: 32049601 DOI: 10.1148/radiol.2020200343]
28 **Pascarella G**, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 2020; **288**: 192-206 [PMID: 32348588 DOI: 10.1111/joim.13091]
29 **Gandhi D**, Ahuja K, Grover H, Sharma P, Solanki S, Gupta N, Patel L. Review of X-ray and computed tomography scan findings with a promising role of point of care ultrasound in COVID-19 pandemic. *World J Radiol* 2020; **12**: 195-203 [PMID: 33033574 DOI: 10.4329/wjr.v12.i9.195]
30 **Aquino EML**, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Rocha AS, Ferreira A, Victor A, Teixeira C, Machado DB, Paixão E, Alves FJO, Pilecco F, Menezes G, Gabrielli L, Leite L, Almeida MCC, Ortelan N, Fernandes QHRF, Ortiz RJF, Palmeira RN, Junior EPP, Aragão E, Souza LEPF, Netto MB, Teixeira MG, Barreto ML, Ichihara MY, Lima RTRS. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. *Cien Saude Colet* 2020; **25**: 2423-2446 [PMID: 32520287 DOI: 10.1590/1413-81232020256.1.10502020]
31 **Tan BS**, Dunnick NR, Gangi A, Goergen S, Jin ZY, Neri E, Nomura CH, Pitcher RD, Yee J, Mahmood U. RSNA International Trends: A Global Perspective on the COVID-19 Pandemic and Radiology in Late 2020. *Radiology* 2021; **299**: E193-E203 [PMID: 33289616 DOI: 10.1148/radiol.2020204267]
32 **Bhat R**, Hamid A, Kunin JR, Saboo SS, Batra K, Baruah D, Bhat AP. Chest Imaging in Patients Hospitalized With COVID-19 Infection - A Case Series. *Curr Probl Diagn Radiol* 2020; **49**: 294-301 [PMID: 32305134 DOI: 10.1067/j.cpradiol.2020.04.001]
33 **Zu ZY**, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology* 2020; **296**: E15-E25 [PMID: 32083985 DOI: 10.1148/radiol.2020200490]
34 **Kaufman AE**, Naidu S, Ramachandran S, Kaufman DS, Fayad ZA, Mani V. Review of radiographic findings in COVID-19. *World J Radiol* 2020; **12**: 142-155 [PMID: 32913561 DOI: 10.4329/wjr.v12.i8.142]
35 **Ng MY**, Lee EYP, Yang J, Yang F, Li X, Wang H, Lui MM, Lo CS, Leung B, Khong PL, Hui CK, Yuen KY, Kuo MD. Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review. *Radiol Cardiothorac Imaging* 2020; **2**: e200034 [PMID: 33778547 DOI: 10.1148/ryct.2020200034]
36 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]
37 **Yoon SH**, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, Park CM, Kim YH. Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea. *Korean J Radiol* 2020; **21**: 494-500 [PMID: 32100485 DOI: 10.3348/kjr.2020.0132]
38 **Cellina M**, Panzeri M, Oliva G. Chest Radiography Features Help to Predict a Favorable Outcome in Patients with Coronavirus Disease 2019. *Radiology* 2020; **297**: E238 [PMID: 32484419 DOI: 10.1148/radiol.2020202326]
39 **Dorr F**, Chaves H, Serra MM, Ramirez A, Costa ME, Seia J, Cejas C, Castro M, Eyheremendy E, Fernández Slezak D, Farez MF; Study Collaborators. COVID-19 pneumonia accurately detected on chest radiographs with artificial intelligence. *Intell Based Med* 2020; **3**: 100014 [PMID: 33230503 DOI: 10.1016/j.ibmed.2020.100014]
40 **Zhang R**, Tie X, Qi Z, Bevins NB, Zhang C, Griner D, Song TK, Nadig JD, Schiebler ML, Garrett JW, Li K, Reeder SB, Chen GH. Diagnosis of Coronavirus Disease 2019 Pneumonia by Using Chest Radiography: Value of Artificial Intelligence. *Radiology* 2021; **298**: E88-E97 [PMID: 32969761 DOI: 10.1148/radiol.2020202944]
41 **Gianchandani N**, Jaiswal A, Singh D, Kumar V, Kaur M. Rapid COVID-19 diagnosis using ensemble deep transfer learning models from chest radiographic images. *J Ambient Intell Humaniz Comput* 2020; 1-13 [PMID: 33224307 DOI: 10.1007/s12652-020-02669-6]
42 **Holshue ML**, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK; Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020; **382**: 929-936 [PMID: 32004427 DOI: 10.1056/NEJMoa2001191]
43 **Kooraki S**, Hosseiny M, Myers L, Gholamrezanezhad A. Coronavirus (COVID-19) Outbreak: What the Department of Radiology Should Know. *J Am Coll Radiol* 2020; **17**: 447-451 [PMID: 32092296

DOI: 10.1016/j.jacr.2020.02.008]
44 **Kerpel A**, Apter S, Nissan N, Houri-Levi E, Klug M, Amit S, Konen E, Marom EM. Diagnostic and Prognostic Value of Chest Radiographs for COVID-19 at Presentation. *West J Emerg Med* 2020; **21**: 1067-1075 [PMID: 32970556 DOI: 10.5811/westjem.2020.7.48842]
45 **Al-Smadi AS**, Bhatnagar A, Ali R, Lewis N, Johnson S. Correlation of chest radiography findings with the severity and progression of COVID-19 pneumonia. *Clin Imaging* 2021; **71**: 17-23 [PMID: 33166898 DOI: 10.1016/j.clinimag.2020.11.004]
46 **Tsakok M**, Shaw R, Murchison A, Ather S, Xie C, Watson R, Brent A, Andersson M, Benamore R, MacLeod F, Gleeson F. Diagnostic accuracy of initial chest radiograph compared to SARS-CoV-2 PCR in patients with suspected COVID-19. *BJR Open* 2020; **2**: 20200034 [PMID: 33178988 DOI: 10.1259/bjro.20200034]
47 **Salehi S**, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *AJR Am J Roentgenol* 2020; **215**: 87-93 [PMID: 32174129 DOI: 10.2214/AJR.20.23034]
48 **Hani C**, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, Revel MP. COVID-19 pneumonia: A review of typical CT findings and differential diagnosis. *Diagn Interv Imaging* 2020; **101**: 263-268 [PMID: 32291197 DOI: 10.1016/j.diii.2020.03.014]
49 **Parekh M**, Donuru A, Balasubramanya R, Kapur S. Review of the Chest CT Differential Diagnosis of Ground-Glass Opacities in the COVID Era. *Radiology* 2020; **297**: E289-E302 [PMID: 32633678 DOI: 10.1148/radiol.2020202504]
50 **Plesner LL**, Dyrberg E, Hansen IV, Abild A, Andersen MB. [Diagnostic imaging findings in COVID-19]. *Ugeskr Laeger* 2020; **182** [PMID: 32286216]
51 **Jin YH**, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang XH; , for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020; **7**: 4 [PMID: 32029004 DOI: 10.1186/s40779-020-0233-6]
52 **Carotti M**, Salaffi F, Sarzi-Puttini P, Agostini A, Borgheresi A, Minorati D, Galli M, Marotto D, Giovagnoni A. Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med* 2020; **125**: 636-646 [PMID: 32500509 DOI: 10.1007/s11547-020-01237-4]
53 **Yang W**, Sirajuddin A, Zhang X, Liu G, Teng Z, Zhao S, Lu M. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). *Eur Radiol* 2020; **30**: 4874-4882 [PMID: 32296940 DOI: 10.1007/s00330-020-06827-4]
54 **Floridi C**, Fogante M, Agostini A, Borgheresi A, Cellina M, Natella R, Bruno F, Cozzi D, Maggialetti N, Palumbo P, Miele V, Carotti M, Giovagnoni A. Radiological diagnosis of Coronavirus Disease 2019 (COVID-19): a Practical Guide. *Acta Biomed* 2020; **91**: 51-59 [PMID: 32945279 DOI: 10.23750/abm.v91i8-S.9973]
55 **Yang R**, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. *Radiol Cardiothorac Imaging* 2020; **2**: e200047 [PMID: 33778560 DOI: 10.1148/ryct.2020200047]
56 **Prokop M**, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**: E97-E104 [PMID: 32339082 DOI: 10.1148/radiol.2020201473]
57 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin O, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. *Radiology* 2020; **296**: 172-180 [PMID: 32255413 DOI: 10.1148/radiol.2020201365]
58 **Hochhegger B**, Zanon M, Altmayer S, Mandelli NS, Stüker G, Mohammed TL, Verma N, Meirelles GSP, Marchiori E. COVID-19 mimics on chest CT: a pictorial review and radiologic guide. *Br J Radiol* 2021; **94**: 20200703 [PMID: 33296607 DOI: 10.1259/bjr.20200703]
59 **Cartocci G**, Colaiacomo MC, Lanciotti S, Andreoli C, De Cicco ML, Brachetti G, Pugliese S, Capoccia L, Tortora A, Scala A, Valentini C, Almberger M, D'Aprile MR, Avventurieri G, Giura R, Kharrub Z, Leonardi A, Boccia M, Catalano C, Ricci P. Correction to: Chest CT for early detection and management of coronavirus disease (COVID-19): a report of 314 patients admitted to Emergency Department with suspected pneumonia. *Radiol Med* 2021; **126**: 642 [PMID: 33277677 DOI: 10.1007/s11547-020-01292-x]
60 **Shao JM**, Ayuso SA, Deerenberg EB, Elhage SA, Augenstein VA, Heniford BT. A systematic review of CT chest in COVID-19 diagnosis and its potential application in a surgical setting.

Colorectal Dis 2020; **22**: 993-1001 [PMID: 32644268 DOI: 10.1111/codi.15252]

61 **Koo HJ**, Choi SH, Sung H, Choe J, Do KH. *RadioGraphics* Update: Radiographic and CT Features of Viral Pneumonia. *Radiographics* 2020; **40**: E8-E15 [PMID: 32501740 DOI: 10.1148/rg.2020200097]

62 **Kalra MK**, Homayounieh F, Arru C, Holmberg O, Vassileva J. Chest CT practice and protocols for COVID-19 from radiation dose management perspective. *Eur Radiol* 2020; **30**: 6554-6560 [PMID: 32621238 DOI: 10.1007/s00330-020-07034-x]

63 **Adams HJA**, Kwee TC, Yakar D, Hope MD, Kwee RM. Systematic Review and Meta-Analysis on the Value of Chest CT in the Diagnosis of Coronavirus Disease (COVID-19): *Sol Scientiae, Illustra Nos*. *AJR Am J Roentgenol* 2020; **215**: 1342-1350 [PMID: 32478562 DOI: 10.2214/AJR.20.23391]

64 **Suchá D**, van Hamersvelt RW, van den Hoven AF, de Jong PA, Verkooijen HM. Suboptimal Quality and High Risk of Bias in Diagnostic Test Accuracy Studies on Chest Radiography and Computed Tomography in the Acute Setting of the COVID-19 Pandemic: A Systematic Review. *Radiol Cardiothorac Imaging* 2020; **2**: e200342 [PMID: 33778613 DOI: 10.1148/ryct.2020200342]

65 **Herpe G**, Lederlin M, Naudin M, Ohana M, Chaumoitre K, Gregory J, Vilgrain V, Freitag CA, De Margerie-Mellon C, Flory V, Ludwig M, Mondot L, Fitton I, Jacquier ARR, Ardilouze P, Petit I, Gervaise A, Bayle O, Crombe A, Mekuko Sokeng M, Thomas C, Henry G, Bliah V, Le Tat T, Guillot MS, Gendrin P, Garetier M, Bertolle E, Montagne C, Langlet B, Kalaaji A, Kayayan H, Desmots F, Dhaene B, Saulnier PJ, Guillevin R, Bartoli JM, Beregi JP, Tasu JP. Efficacy of Chest CT for COVID-19 Pneumonia Diagnosis in France. *Radiology* 2021; **298**: E81-E87 [PMID: 32870139 DOI: 10.1148/radiol.2020202568]

66 **Kim H**, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse Transcriptase Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. *Radiology* 2020; **296**: E145-E155 [PMID: 32301646 DOI: 10.1148/radiol.2020201343]

67 **Treglia G**. Diagnostic Performance of ^{18}F-FDG PET/CT in Infectious and Inflammatory Diseases according to Published Meta-Analyses. *Contrast Media Mol Imaging* 2019; **2019**: 3018349 [PMID: 31427907 DOI: 10.1155/2019/3018349]

68 **Lütje S**, Marinova M, Kütting D, Attenberger U, Essler M, Bundschuh RA. Nuclear medicine in SARS-CoV-2 pandemia: 18F-FDG-PET/CT to visualize COVID-19. *Nuklearmedizin* 2020; **59**: 276-280 [PMID: 32259853 DOI: 10.1055/a-1152-2341]

69 **Capitanio S**, Nordin AJ, Noraini AR, Rossetti C. PET/CT in nononcological lung diseases: current applications and future perspectives. *Eur Respir Rev* 2016; **25**: 247-258 [PMID: 27581824 DOI: 10.1183/16000617.0051-2016]

70 **Setti L**, Kirienko M, Dalto SC, Bonacina M, Bombardieri E. FDG-PET/CT findings highly suspicious for COVID-19 in an Italian case series of asymptomatic patients. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1649-1656 [PMID: 32342191 DOI: 10.1007/s00259-020-04819-6]

71 **Deng Y**, Lei L, Chen Y, Zhang W. The potential added value of FDG PET/CT for COVID-19 pneumonia. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1634-1635 [PMID: 32198615 DOI: 10.1007/s00259-020-04767-1]

72 **Olivari L**, Riccardi N, Rodari P, Buonfrate D, Diodato S, Formenti F, Angheben A, Salgarello M. Accidental diagnosis of COVID-19 pneumonia after 18F FDG PET/CT: a case series. *Clin Transl Imaging* 2020; 1-8 [PMID: 32989417 DOI: 10.1007/s40336-020-00388-8]

73 **Habouzit V**, Sanchez A, Dehbi S, Prevot N, Bonnefoy PB. Incidental Finding of COVID-19 Lung Infection in 18F-FDG PET/CT: What Should We Do? *Clin Nucl Med* 2020; **45**: 649-651 [PMID: 32558722 DOI: 10.1097/RLU.0000000000003135]

74 **Qin C**, Liu F, Yen TC, Lan X. ^{18}F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1281-1286 [PMID: 32088847 DOI: 10.1007/s00259-020-04734-w]

75 **Jajodia A**, Ebner L, Heidinger B, Chaturvedi A, Prosch H. Imaging in corona virus disease 2019 (COVID-19)-A Scoping review. *Eur J Radiol Open* 2020; **7**: 100237 [PMID: 32395567 DOI: 10.1016/j.ejro.2020.100237]

76 **Han R**, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early Clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia. *AJR Am J Roentgenol* 2020; **215**: 338-343 [PMID: 32181672 DOI: 10.2214/AJR.20.22961]

77 **Caetano R**, Schluckebier L, Bastos C, Silva R, Carneiro M, Silva J, Biz AN. Análise dos custos do procedimento PET-TC com 18F-FDG na perspectiva do SUS provedor: estudo em uma unidade pú blica de saúde do Rio de Janeiro, Brasil. *Cad Saúde Pública* 2014; **30**: 379-392 [DOI: 10.1590/0102-311X00016413]

78 **Ducharme J**, Goertzen AL, Patterson J, Demeter S. Practical Aspects of 18F-FDG PET When Receiving 18F-FDG from a Distant Supplier. *J Nucl Med Technol* 2009; **37**: 164-169 [PMID: 19692456 DOI: 10.2967/jnmt.109.062950]

79 **Volpicelli G**, Lamorte A, Villén T. What's new in lung ultrasound during the COVID-19 pandemic. *Intensive Care Med* 2020; **46**: 1445-1448 [PMID: 32367169 DOI: 10.1007/s00134-020-06048-9]

80 **Kulkarni S**, Down B, Jha S. Point-of-care lung ultrasound in intensive care during the COVID-19 pandemic. *Clin Radiol* 2020; **75**: 710.e1-710. e4 [PMID: 32405081 DOI: 10.1016/j.crad.2020.05.001]

81 **Sultan LR**, Sehgal CM. A Review of Early Experience in Lung Ultrasound in the Diagnosis and Management of COVID-19. *Ultrasound Med Biol* 2020; **46**: 2530-2545 [PMID: 32591166 DOI: 10.1016/j.ultrasmedbio.2020.05.012]

82 **Stogiannos N**, Fotopoulos D, Woznitza N, Malamateniou C. COVID-19 in the radiology department: What radiographers need to know. *Radiography (Lond)* 2020; **26**: 254-263 [PMID: 32532596 DOI: 10.1016/j.radi.2020.05.012]

83 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? *J Ultrasound Med* 2020; **39**: 1459-1462 [PMID: 32198775 DOI: 10.1002/jum.15284]

84 **Vetrugno L**, Bove T, Orso D, Barbariol F, Bassi F, Boero E, Ferrari G, Kong R. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. *Echocardiography* 2020; **37**: 625-627 [PMID: 32239532 DOI: 10.1111/echo.14664]

85 **Sorlini C**, Femia M, Nattino G, Bellone P, Gesu E, Francione P, Paternò M, Grillo P, Ruffino A, Bertolini G, Cariati M, Cortellaro F; Fenice Network (Italian Group for Clinical Research in Emergency Medicine). The role of lung ultrasound as a frontline diagnostic tool in the era of COVID-19 outbreak. *Intern Emerg Med* 2021; **16**: 749-756 [PMID: 33090353 DOI: 10.1007/s11739-020-02524-8]

86 **Garcia JVR**, Fonseca EKUN, Chate RC, Strabelli DG, Farias LPG, Loureiro BMC, Ferreira LC, Sawamura MVY. COVID-19 on resonance magnetic: an incidental but important finding in times of pandemic. *Einstein (Sao Paulo)* 2020; **18**: eAI5891 [PMID: 33206814 DOI: 10.31744/einstein_journal/2020AI5891]

87 **Torkian P**, Rajebi H, Zamani T, Ramezani N, Kiani P, Akhlaghpoor S. Magnetic resonance imaging features of coronavirus disease 2019 (COVID-19) pneumonia: The first preliminary case series. *Clin Imaging* 2021; **69**: 261-265 [PMID: 33002753 DOI: 10.1016/j.clinimag.2020.09.002]

88 **Ates OF**, Taydas O, Dheir H. Thorax Magnetic Resonance Imaging Findings in Patients with Coronavirus Disease (COVID-19). *Acad Radiol* 2020; **27**: 1373-1378 [PMID: 32830031 DOI: 10.1016/j.acra.2020.08.009]

89 **Meirelles GSP**. COVID-19: a brief update for radiologists. *Radiol Bras* 2020; **53**: 320-328 [PMID: 33071376 DOI: 10.1590/0100-3984.2020.0074]

90 **Caballeros Lam M**, de la Fuente Villena A, Hernández Hernández A, García de Yébenes M, Bastarrika Alemañ G. Cardiac magnetic resonance characterization of COVID-19 myocarditis. *Rev Esp Cardiol (Engl Ed)* 2020; **73**: 863-864 [PMID: 32694081 DOI: 10.1016/j.rec.2020.06.018]

91 **Puntmann VO**, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265-1273 [PMID: 32730619 DOI: 10.1001/jamacardio.2020.3557]

92 **Huang L**, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020; **13**: 2330-2339 [PMID: 32763118 DOI: 10.1016/j.jcmg.2020.05.004]

93 **Galea N**, Catapano F, Marchitelli L, Cundari G, Maestrini V, Panebianco V, Mancone M, Fedele F, Catalano C, Francone M. How to perform a cardio-thoracic magnetic resonance imaging in COVID-19: comprehensive assessment of heart, pulmonary arteries, and lung parenchyma. *Eur Heart J Cardiovasc Imaging* 2020 [PMID: 33325495 DOI: 10.1093/ehjci/jeaa335]

94 **Politi LS**, Salsano E, Grimaldi M. Magnetic Resonance Imaging Alteration of the Brain in a Patient With Coronavirus Disease 2019 (COVID-19) and Anosmia. *JAMA Neurol* 2020; **77**: 1028-1029 [PMID: 32469400 DOI: 10.1001/jamaneurol.2020.2125]

95 **Chetrit A**, Lechien JR, Ammar A, Chekkoury-Idrissi Y, Distinguin L, Circiu M, Saussez S, Ballester MC, Vasse M, Berradja N, Hans S, Carlier R, Edjlali M. Magnetic resonance imaging of COVID-19 anosmic patients reveals abnormalities of the olfactory bulb: Preliminary prospective study. *J Infect* 2020; **81**: 816-846 [PMID: 32739489 DOI: 10.1016/j.jinf.2020.07.028]

96 **Galougahi MK**, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. Olfactory Bulb Magnetic Resonance Imaging in SARS-CoV-2-Induced Anosmia: The First Report. *Acad Radiol* 2020; **27**: 892-893 [PMID: 32295727 DOI: 10.1016/j.acra.2020.04.002]

97 **Garg RK**, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: A review. *J Med Virol* 2021; **93**: 206-222 [PMID: 32558956 DOI: 10.1002/jmv.26207]

98 **Nakajima K**, Kato H, Yamashiro T, Izumi T, Takeuchi I, Nakajima H, Utsunomiya D. COVID-19 pneumonia: infection control protocol inside computed tomography suites. *Jpn J Radiol* 2020; **38**: 391-393 [PMID: 32185669 DOI: 10.1007/s11604-020-00948-y]

99 **Chen Q**, Zu ZY, Jiang MD, Lu L, Lu GM, Zhang LJ. Infection Control and Management Strategy for COVID-19 in the Radiology Department: Focusing on Experiences from China. *Korean J Radiol* 2020; **21**: 851-858 [PMID: 32524785 DOI: 10.3348/kjr.2020.0342]

100 **Niu Y**, Xian J, Lei Z, Liu X, Sun Q. Management of infection control and radiological protection in diagnostic radiology examination of COVID-19 cases. *Radiat Med Prot* 2020; **1**: 75-80 [PMID: 32835346 DOI: 10.1016/j.radmp.2020.05.005]

101 **European Centre for Disease Prevention and Control**. Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19. Stockholm: ECDC; 2020. [cited 19 January 2021]. Available from: https://www. ecdc.europa.eu/sites/default/files/documents/COVID-19-guidance-wearingand-removing-personal-protective-equipment-healthcare-settings-updated. pdf

102 **Zhang HW**, Yu J, Xu HJ, Lei Y, Pu ZH, Dai WC, Lin F, Wang YL, Wu XL, Liu LH, Li M, Mo YQ, Zhang H, Luo SP, Chen H, Lyu GW, Zhou ZG, Liu WM, Liu XL, Song HY, Chen FZ, Zeng L, Zhong H, Guo TT, Hu YQ, Yang XX, Liu PN, Li DF. Corona Virus International Public Health Emergencies: Implications for Radiology Management. *Acad Radiol* 2020; **27**: 463-467 [PMID: 32113880 DOI: 10.1016/j.acra.2020.02.003]

103 **Ding J**, Fu H, Liu Y, Gao J, Li Z, Zhao X, Zheng J, Sun W, Ni H, Ma X, Feng J, Wu A, Liu J, Wang Y, Geng P, Chen Y. Prevention and control measures in radiology department for COVID-19. *Eur Radiol* 2020; **30**: 3603-3608 [PMID: 32300968 DOI: 10.1007/s00330-020-06850-5]

104 **George PM**, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, Gibbons MA, Hart N, Jenkins RG, McAuley DF, Patel BV, Thwaite E, Spencer LG. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax* 2020; **75**: 1009-1016 [PMID: 32839287 DOI: 10.1136/thoraxjnl-2020-215314]

105 **McStay R**, Johnstone A, Hare SS, Jacob J, Nair A, Rodrigues JCL, Edey A, Robinson G. COVID-19: looking beyond the peak. Challenges and tips for radiologists in follow-up of a novel patient cohort. *Clin Radiol* 2021; **76**: 74.e1-74. e14 [PMID: 33109350 DOI: 10.1016/j.crad.2020.09.025]

106 **Arnold DT**, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, Noel A, Gunning S, Hatrick J, Hamilton S, Elvers KT, Hyams C, Bibby A, Moran E, Adamali HI, Dodd JW, Maskell NA, Barratt SL. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax* 2020 [PMID: 33273026 DOI: 10.1136/thoraxjnl-2020-216086]

107 **Alharthy A**, Abuhamdah M, Balhamar A, Faqihi F, Nasim N, Ahmad S, Noor A, Tamim H, Alqahtani SA, Abdulaziz Al Saud AAASB, Kutsogiannis DJ, Brindley PG, Memish ZA, Karakitsos D, Blaivas M. Residual Lung Injury in Patients Recovering From COVID-19 Critical Illness: A Prospective Longitudinal Point-of-Care Lung Ultrasound Study. *J Ultrasound Med* 2020 [PMID: 33185316 DOI: 10.1002/jum.15563]

108 **Stephanie S**, Shum T, Cleveland H, Challa SR, Herring A, Jacobson FL, Hatabu H, Byrne SC, Shashi K, Araki T, Hernandez JA, White CS, Hossain R, Hunsaker AR, Hammer MM. Determinants of Chest X-Ray Sensitivity for COVID- 19: A Multi-Institutional Study in the United States. *Radiol Cardiothorac Imaging* 2020; **2**: e200337 [PMID: 33778628 DOI: 10.1148/ryct.2020200337]

109 **Wen Z**, Chi Y, Zhang L, Liu H, Du K, Li Z, Chen J, Cheng L, Wang D. Coronavirus Disease 2019: Initial Detection on Chest CT in a Retrospective Multicenter Study of 103 Chinese Patients. *Radiol Cardiothorac Imaging* 2020; **2**: e200092 [PMID: 33778564 DOI: 10.1148/ryct.2020200092]

110 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

World Journal of Radiology

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

World J Radiol 2021 May 28; 13(5): 137-148

DOI: 10.4329/wjr.v13.i5.137

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Prospective Study

Comparison of point and two-dimensional shear wave elastography of the spleen in healthy subjects

Friederike Nowotny, Julian Schmidberger, Patrycja Schlingeloff, Andreas Binzberger, Wolfgang Kratzer

ORCID number: Friederike Nowotny 0000-0003-4248-6304; Julian Schmidberger 0000-0002-9960-9574; Patrycja Schlingeloff 0000-0003-3514-7347; Andreas Binzberger 0000-0002-3220-2833; Wolfgang Kratzer 0000-0002-9727-3843.

Author contributions: Kratzer W und Nowotny F designed the study; Nowotny F, Binzberger A, and Kratzer W performed the research; Schmidberger J und Schlingeloff P analyzed the data; Nowotny F and Kratzer W wrote the paper; and all authors revised the manuscript for final submission.

Institutional review board statement: The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki (No. 415/15). All data were analyzed anonymously.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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

Data sharing statement: No additional data are available.

Friederike Nowotny, Julian Schmidberger, Patrycja Schlingeloff, Andreas Binzberger, Wolfgang Kratzer, Department of Internal Medicine I, University Hospital Ulm, Ulm 89081, Germany

Corresponding author: Wolfgang Kratzer, MD, Professor, Department of Internal Medicine I, University Hospital Ulm, Albert-Einstein-Allee 23, Ulm 89081, Germany. wolfgang.kratzer@uniklinik-ulm.de

Abstract

BACKGROUND

Few systematic comparative studies of the different methods of physical elastography of the spleen are currently available.

AIM

To compare point shear wave and two-dimensional elastography of the spleen considering the anatomical location (upper, hilar, and lower pole).

METHODS

As part of a prospective clinical study, healthy volunteers were examined for splenic elasticity using four different ultrasound devices between May 2015 and April 2017. The devices used for point shear wave elastography were from Siemens (S 3000) and Philips (Epiq 7), and those used for two-dimensional shear wave elastography were from GE (Logiq E9) and Toshiba (Aplio 500). In addition, two different software versions (5.0 and 6.0) were evaluated for the Toshiba ultrasound device (Aplio 500). The study consisted of three arms: A, B, and C.

RESULTS

In study arm A, 200 subjects were evaluated (78 males and 122 females, mean age 27.9 ± 8.1 years). In study arm B, 113 subjects were evaluated (38 men and 75 women, mean age 26.0 ± 6.3 years). In study arm C, 44 subjects were enrolled. A significant correlation of the shear wave velocities at the upper third of the spleen (r = 0.33088, P < 0.0001) was demonstrated only for the Philips Epiq 7 device compared to the Siemens Acuson S 3000. In comparisons of the other ultrasound devices (GE, Siemens, Toshiba), no comparable results could be obtained for any anatomical position of the spleen. The influencing factors age, gender, and body mass index did not show a clear correlation with the measured shear wave velocities.

CONCLUSION

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

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

Received: February 19, 2021
Peer-review started: February 19, 2021
First decision: March 28, 2021
Revised: March 31, 2021
Accepted: May 22, 2021
Article in press: May 22, 2021
Published online: May 28, 2021

P-Reviewer: Treeprasertsuk S
S-Editor: Liu M
L-Editor: A
P-Editor: Wang LL

The absolute values of the shear wave elastography measurements of the spleen and the two different elastography methods are not comparable between different manufacturers or models.

Key Words: Ultrasonography; Elastography; Spleen; Healthy subjects; Acoustic radiation force impulse; Two-dimensional shear-wave elastography; Point shear wave elastography

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Measurement of shear wave velocity in the spleen has been increasingly used in prognostic assessment of esophageal varices and as a marker of portal hypertension. The current recommendations of medical societies for splenic elastography note methodological limitations in transient elastography. Currently, whether the different elastography methods and shear wave measurements with different ultrasonic devices provide comparable results has not been clarified. Our results show that the most reliable measurements for all devices were obtained at the lower pole of the spleen. However, absolute values of splenic shear wave elastography measurements are not transferable between manufacturers or models.

Citation: Nowotny F, Schmidberger J, Schlingeloff P, Binzberger A, Kratzer W. Comparison of point and two-dimensional shear wave elastography of the spleen in healthy subjects. *World J Radiol* 2021; 13(5): 137-148
URL: https://www.wjgnet.com/1949-8470/full/v13/i5/137.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i5.137

INTRODUCTION

Ultrasound shear wave elastography is gaining importance in diagnostics for a variety of diseases[1-4]. In recent years, several ultrasound-based elastography techniques have been developed for non-invasive quantitative assessment of tissue elasticity, primarily liver stiffness[5]. The first method in this field was transient elastography (TE) by FibroScan. A newer generation of elastography techniques that do not require mechanical pulses to generate shear waves, but instead use high-intensity ultrasound waves, is summarized as acoustic radiation force impulse (ARFI) elastography. Compared to TE, ARFI techniques are more precise and allow more valid measurements, even in patients with high body mass index (BMI) or ascites[6].

Currently, there are two different techniques that work on the basis of this principle, both of which can be generally summarized under the term shear wave elastography: point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE)[5]. Different manufacturers have increasingly integrated p-SWE and 2D-SWE techniques into their ultrasound scanners. In a meta-analysis, the pSWE and 2D-SWE techniques showed significantly better results than FibroScan with respect to the rate of unreliable measurements in healthy subjects and in patients with chronic liver disease[6]. However, some of the study populations examined in the comparative studies were small and, often, only two different ultrasound devices from different manufacturers were compared[7-9]. Recent studies with larger samples have shown good agreement between the p-SWE and 2D-SWE techniques for different manufacturers, with slightly lower shear wave velocities for 2D-SWE depending on the software version used[10-12]. Furthermore, various factors, such as fasting time, breathing, and BMI, can substantially affect the measurement of shear wave velocities and, therefore, must be taken into account when interpreting the results[5]. A recent meta-analysis of 2D-SWE reconfirmed the higher reliability of the method compared to the other ultrasound elastography methods as demonstrated in various studies[6].

In recent years, the measurement of splenic stiffness has increasingly become the focus of scientific investigations, especially for prognostic assessment of esophageal varices and as a marker of portal hypertension[13-15]. In a recent meta-analysis, Song *et al*[16] demonstrated a good correlation between splenic stiffness and blood pressure measured by hepatic venous pressure gradient. The current recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)

note obvious methodological limitations for transient splenic ultrasonography, especially in patients with high BMI, the detection of ascites and pulmonary or colonic gas overlays, and in patients with a splenic diameter < 4 cm. The successful application of TE in measuring splenic elasticity has been reported to be approximately 70%[15]. With few studies currently available on 2D-SWE, the technology has been viewed critically in the assessment of splenic stiffness[15,17]. For p-SWE, recent studies report sensitivity of up to 97% for the measurement of splenic stiffness, but spleen size, adiposity, and abdominal wall thickness seem to affect reproducibility in p-SWE[15,18-21]. In addition to the above parameters, the anatomical position for measurement in splenic elastography seems to influence the results. To date, most elastography studies on the spleen have performed measurements at undefined anatomic positions or different splenic poles[22-26].

To the best of our knowledge, no comparative studies are currently available on different elastography methods (*e.g.*, pSWE, 2D-SWE) for sonoelastographic measurement of splenic stiffness taking into account the anatomical location of the measurement in healthy volunteers. The aim of the present study was to compare 2D-SWE to p-SWE in healthy volunteers taking into account whether the measurement is performed in the upper, middle, or lower third of the spleen.

MATERIALS AND METHODS

Study process

The study consisted of three arms: A, B, and C (Figure 1). Arm A tested four ultrasound devices: the Siemens Acuson S3000, Toshiba Aplio 500 (software version 5.0), Philips Epiq 7, and GE Logiq E9. We chose the Siemens S3000 ultrasound scanner as the reference device because the largest number of studies exist for this ultrasound scanner or its predecessor, the Siemens S2000[27-29]. The Siemens S3000 and Philips Epiq 7 devices use p-SWE technology, and the Aplio 500 Toshiba and GE Logiq E9 devices use 2D-SWE technology. Study arm A showed that the Toshiba Aplio 500 device (software version 5.0) generated strongly deviating results compared to the other ultrasound devices tested. Due to the divergent results between Toshiba Aplio 500 (version 5.0) and the other tested devices, especially the reference device, the Toshiba Aplio 500 was tested using software version 6.0 against the Siemens Acuson S3000 in study arm B. In study arm C, the results of study arms A and B were compared to investigate the differences between the two different software versions of the Toshiba Aplio 500. Study arm A was conducted from May 2015 to September 2015 and study arm B from November 2016 to April 2017.

Subjects

Initially, 282 subjects were included in study arm A. Due to incomplete measurements and invalid data and measurements, the data sets of 200 subjects could be evaluated. In study arm B, 151 subjects were initially recruited, but because of missing or incomplete data 113 subjects could be analyzed. The characteristics of the subjects in study arms A and B are given in Table 1. Study arm C included 44 subjects. The same study protocol applied to both study arms. Only subjects who met the inclusion criteria and provided informed written consent to participate in the study were recruited. The study had a positive vote from the local ethics committee (No. 415/15) and was conducted according to the guidelines of the Declaration of Helsinki[30]. The inclusion criteria in the study were age ≥ 18 years; no history of hepatopathies (viral hepatides, hemacromatosis, autoimmune hepatitis, toxic hepatides, Wilson's disease) or other chronic diseases, such as diabetes or arterial hypertension; fasting period ≥ 3 h before ultrasound examination; BMI < 30 kg/m² and > 18 kg/m²; normal findings on previous abdominal ultrasonography, specifically normal echogenicity, texture, and size of the liver (≤ 16 cm) and normal echogenicity and size of the spleen (up to 14 cm length allowed); and alcohol consumption < 40 g/d in men and < 20 g/d in women.

Ultrasound and elastography examinations of the spleen

Before elastography, standardized abdominal ultrasonography of the liver and spleen in B-mode was performed in each subject to document the liver size, echogenicity, and parenchymal structure and the spleen size, shape, and parenchymal and vascular status. Subjects with pathological findings on focused abdominal ultrasonography were excluded from the study. One subject at a time was examined by one investigator using all devices. Study arm A had 6 investigators and study arm B had 2 investigators; an experienced supervisor (> 5000 examinations/year) was available in case of

Table 1 Characteristics of subjects included in study arms A and B and their overlap, *n* (%)

	Study arm A (*n* = 200)		Study arm B (*n* = 113)		Overlap C (*n* = 44)	
	Frequency	mean ± SD	Frequency	mean ± SD	Frequency	mean ± SD
Gender						
Male	78 (39.00)		38 (30.6)		10 (22.73)	
Female	122 (61.00)		75 (66.4)		34 (77.27)	
Age		27.93 ± 8.13		25.95 ± 6.26		27.11 ± 5.64
< 30 yr	154 (77.00)		98 (86.7)		34 (77.27)	
≥ 30 yr	46 (23.00)		15 (13.3)		10 (22.73)	
BMI		22.56 ± 2.57		21.64 ± 2.24		21.60 ± 2.67
BMI < 25	166 (83.0)		103 (91.2)		38 (86.36)	
BMI ≥25	34 (17.00)		10 (8.9)		6 (13.64)	
Alcohol consumption		8.17 ± 9.70		6.73 ± 8.35		6.22 ± 7.95
None	18 (9.00)		9 (8.0)		9 (20.45)	
Less 1/mo	28 (14.00)		17 (15.0)		3 (6.82)	
Several times per month	106 (53.00)		71 (62.8)		28 (63.64)	
Several times per week	48 (24.00)		16 (14.2)		4 (9.09)	
Fasting time		3.74 ± 1.84		4.47 ± 2.80		4.11 ± 1.65
Spleen length (mm)		105.44 ± 14.80		105.53 ± 14.16		101.66 ± 13.78
Median (min-max)		105.50 (61-144)		106.00 (65-144)		100.50 (75-137)
Spleen depth (mm)		35.38 ± 6.19		35.28 ± 6.38		34.25 ± 5.59
Median (min-max)		35.50 (21-56)		35.00 (21-56)		34.00 (24-48)

BMI: Body mass index.

unclear findings. Splenic elastography was performed in all subjects in the supine position with the left arm maximally abducted and in expiration. Care was taken to place the transducer at right angles to the splenic capsule as much as possible. Shear wave velocity measurements were obtained in meters per second at each of three anatomic positions: the upper, middle, and lower thirds of the spleen (Figure 2). Five valid measurements were obtained per anatomic position using the Philips Epiq 7 and Siemens Acuson S3000 to calculate a median and mean value. A total of 15 measurements per spleen were performed using p-SWE. Elastographic studies on the Toshiba Aplio 500, GE Logiq E9, and Siemens Acuson S3000 were performed with convex transducers (6C1HD, 1.5-5.5 MHz) and on the Philips Epiq 7 with one transducer (5C1 HD, 1-5 MHz). The preset region of interest (ROI) was 10 mm × 5 mm for Siemens. The ROI for the other manufacturers was set to 10 mm × 10 mm. As the quality of the generated shear waves can be visualized with the Toshiba Aplio 500 and GE Logiq E9, the investigator could directly assess the reliability of the measurement; therefore, with these devices only one measurement was made per measurement site (three measurements per spleen). The measurements were considered reliable as soon as the shear waves could be displayed in parallel in the defined ROI. If this was not the case, the measurement was repeated until the required quality was achieved. If this was not successful, the subject was excluded from the study (Figure 1).

Statistical analysis

All statistical analyses were performed using SAS Version 9.4 software (SAS Institute, Cary, North Carolina, United States). Normal distribution was tested with the Shapiro-Wilk test. Differences were determined using the non-parametric Wilcoxon rank sum test. Potential confounding variables, such as age and BMI, were taken into account with partial correlation analyses. The inter-observer reliability (ICC) was used to determine the reliability of the agreement of measurements between the examiners. All tests were two-sided. $P < 0.05$ was considered significant according to the specified

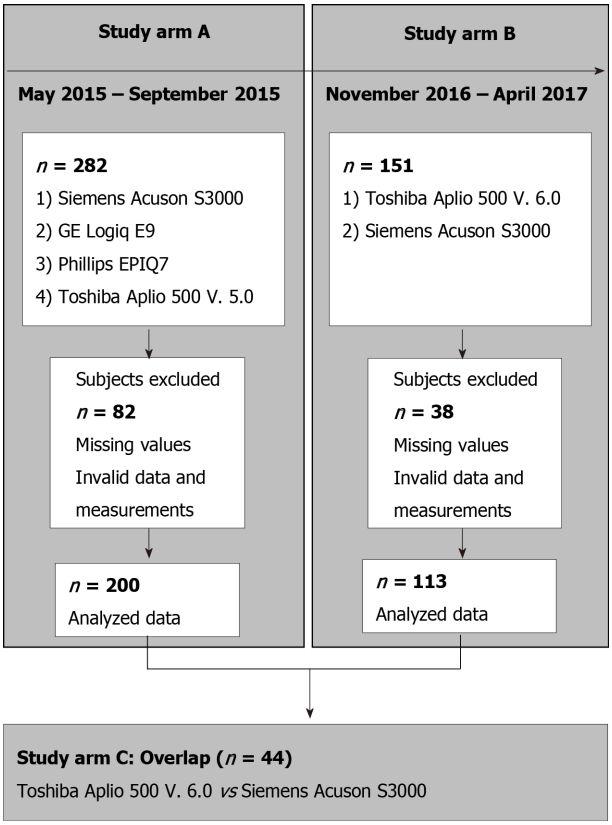


Figure 1 Flow chart of study arm inclusion and exclusion.

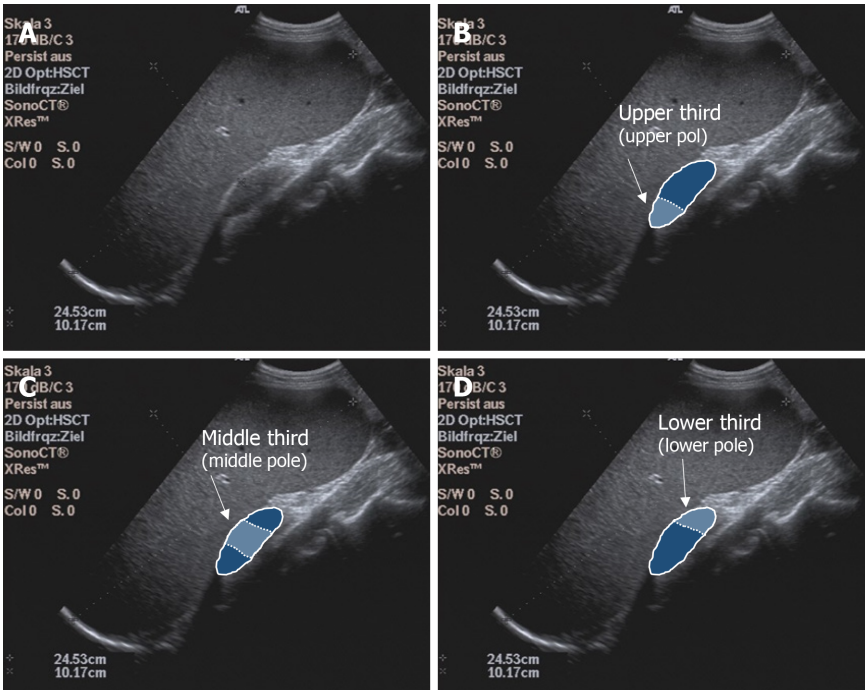


Figure 2 Illustration of the examination of the spleen. A: B-Mode Ultrasound image of the spleen; B: Upper spleen pole; C: Middle spleen pole; and D: Lower spleen pole.

$\alpha = 0.05$, with a probability of error of 5%.

Biostatistics

The statistical methods of this study were reviewed by Dr. Julian Schmidberger, MPH, Ph.D., from the Department of Internal Medicine I, University Hospital Ulm, Albert-

Einstein-Allee 2389081 Ulm, Germany.

RESULTS

Ultrasound device comparison depending on the anatomical measurement position in study arm A

In our study the ICC was 0.83 (95%-KI 0.74-0.89), being comparable to similar studies[31,32]. The comparison between the Siemens Acuson S3000 and GE Logiq E9, taking into account age, BMI, and gender, showed no correlation of the collected measurements at any of the three anatomical measurement positions (Tables 2 and 3). Comparison of the Philips Epiq 7 with the Siemens Acuson S3000 demonstrated a significant correlation of the shear wave velocity of the two devices as a function of age, BMI, and gender at the upper third of the spleen (r = 0.33088, P < 0.0001). We found no correlation of the measurements at the lower or middle third of the spleen (Table 4). Examination of the splenic elastography by the Toshiba Aplio 500 compared to the Siemens Acuson S3000 revealed no correlation of the measured results at any of the three anatomical positions (Table 4). With overall poor correlations between the measurements by the different ultrasound devices, higher agreement was found between devices using identical shear wave technology, especially p-SWE.

Influence of age, sex, and BMI on shear wave velocities in the spleen in study arm A

For the Siemens Acuson S3000 (p-SWE), GE Logiq E9 (2D-SWE), and Philips Epiq 7 (p-SWE), no significant correlation was detected between age and splenic elasticity. For the Toshiba Aplio 500 (version 5.0; 2D-SWE), we found a significant correlation at the lower and middle third of the spleen (P < 0.05). A correlation was also found between gender and spleen elasticity for the Siemens Acuson S3000 at all anatomical positions (P < 0.05). For the Toshiba Aplio 500 (software version 5.0), an influence of gender was determined for the anatomical location (upper and lower third; P < 0.05). For the GE Logiq E9, there was a significant correlation with gender at the upper third of the spleen (P < 0.05). For the Philips Epiq 7, no significant correlation with gender was detected at any position. A significant correlation with BMI was demonstrated for the Toshiba Aplio 500 (version 5.0) at the lower third of the spleen (P < 0.05) and for the GE Logiq E9 at the middle third of the spleen (P < 0.05). No correlation between BMI and changed shear wave velocities at the spleen were detected for the Siemens and Philips devices.

Ultrasound device comparison depending on the anatomical measurement position in study arm B

In study arm B, the Siemens device was compared against a newer software version (6.0) of the Toshiba Aplio 500 device. Using the mean values an controlling for age, BMI, and gender, a significant correlation of the shear wave velocities of the two devices was shown for the upper and lower thirds of the spleen (Tables 2 and 4, Figure 3).

Influence of age, sex, and BMI on shear wave velocities in the spleen in study arm B

In study arm B, no correlation was found between the measured heavy-wave velocities and gender or BMI for both devices tested. In addition, no correlation could be demonstrated for age and shear wave velocity with the Siemens device. Only for the Toshiba Aplio 500 (version 6.0) did we find a significant correlation between age and the measured shear wave velocities, but only for the lower third of the spleen (P < 0.05).

Study arm C

With the help of the subgroup of 44 subjects, we compared the measurements made with the two software versions of the Toshiba Aplio 500 (Tables 1 and 3). All shear wave values obtained with the version 6.0 were significantly lower than those obtained with version 5.0 (P < 0.0001). The mean values differed by 33.0% in the upper third (3.46 m/s *vs* 2.32 m/s), by 14.0% in the middle third (2.94 m/s *vs* 2.53 m/s), and by 25.4% in the lower third (3.38 m/s *vs* 2.52 m/s).

Table 2 Location and dispersion measures of shear wave velocity at the spleen measured with the Toshiba Aplio 500 version 5.0 and version 6.0, Siemens S3000, GE Logiq E9, and Philips Epiq 7 devices, *n* (%)

	Study arm A (*n* = 200)			Study arm B (*n* = 131)		
	Upper pole	Middle pole	Lower pole	Upper pole	Middle pole	Lower pole
Toshiba Aplio 500, mean ± SD	3.35 ± 0.92	2.90 ± 0.45	3.38 ± 0.65	2.34 ± 0.29	2.48 ± 0.26	2.48 ± 0.28
Median (Min-Max)	3.12 (2.20-6.94)	2.84 (1.94-4.86)	3.36 (1.50-5.92)	2.36 (1.42-3.36)	2.48 (1.82-3.02)	2.45 (1.84-3.25)
Siemens S3000, mean ± SD	2.05 ± 0.54	2.53 ± 0.44	2.53 ± 0.58	2.39 ± 0.33	2.63 ± 0.28	2.49 ± 0.34
Median (Min-Max)	2.04 (0.73-3.77)	2.49 (1.27-3.73)	2.47 (1.39-4.59)	2.39 (1.52-3.86)	2.62 (1.97-3.36)	2.50 (1.53-3.58)
GE Logiq E9, mean ± SD	2.20 ± 0.51	1.86 ± 0.44	1.53 ± 0.44	-	-	-
Median (Min-Max)	2.23 (1.10-6.26)	1.88 (0.71-3.02)	1.48 (0.77-2.84)			
Philips Epiq 7, mean ± SD	1.88 ± 0.40	1.89 ± 0.38	2.30 ± 0.87	-	-	-
Median (Min-Max)	1.90 (0.88-3.10)	1.91 (0.93-3.12)	2.17 (0.99-10.62)			

Table 3 Position and stress measurements of shear wave velocities measured with the Toshiba Aplio 500 version 5.0 and version 6.0

Overlap C (*n* = 44)	Upper pole	Middle pole	Lower pole
Toshiba Aplio 500 V.5.0, mean ± SD	3.46 ± 0.52	2.94 ± 0.52	3.38 ± 1.02
Median (Min-Max)	3.45 (2.54-5.13)	2.80 (2.27-4.86)	3.14 (2.25-6.53)
Toshiba Aplio 500 V.6.0, mean ± SD	2.32 ± 0.34	2.53 ± 0.25	2.52 ± 0.29
Median (Min-Max)	2.36 (1.42-3.36)	2.56 (1.85-2.94)	2.46 (1.93-3.25)

Table 4 Correlation of the heavy wave velocities of the Toshiba Aplio 500 version 5.0 and version 6.0, GE Logiq E9, and Philips Epiq 7 devices with the Siemens S3000

		Siemens S3000			
		Study arm A (*n* = 200)		Study arm B (*n* = 131)	
Device	Pole	*R* value	*P* value	*R* value	*P* value
Toshiba Aplio 500	Lower pole	-0.08792	0.2193	0.19863	0.0375
	Middle pole	0.13632	0.0561	0.13438	0.1616
	Upper pole	0.03951	0.5815	0.24951	0.0086
GE Logiq E9	Lower pole	-0.03307	0.6446	-	-
	Middle pole	-0.04941	0.4905	-	-
	Upper pole	0.04744	0.5079	-	-
Philips Epiq 7	Lower pole	0.04894	0.4947	-	-
	Middle pole	0.12321	0.0845	-	-
	Upper pole	0.33088	< 0.0001	-	-

DISCUSSION

This study is the first to compare four ARFI-based ultrasound elastography methods, two pSWE techniques and two 2D-SWE techniques, from different manufacturers in healthy volunteers taking into account the anatomical location of the measurement of the spleen. Our results show that the anatomical position must be taken into account for splenic elastography. The best results were obtained with the lower pole of the spleen. Furthermore, when interpreting the results using different elastography techniques, attention must be paid to possible limitations in device compatibility. The absolute values of the shear wave elastography measurements of the spleen are not transferable between different manufacturers or models.

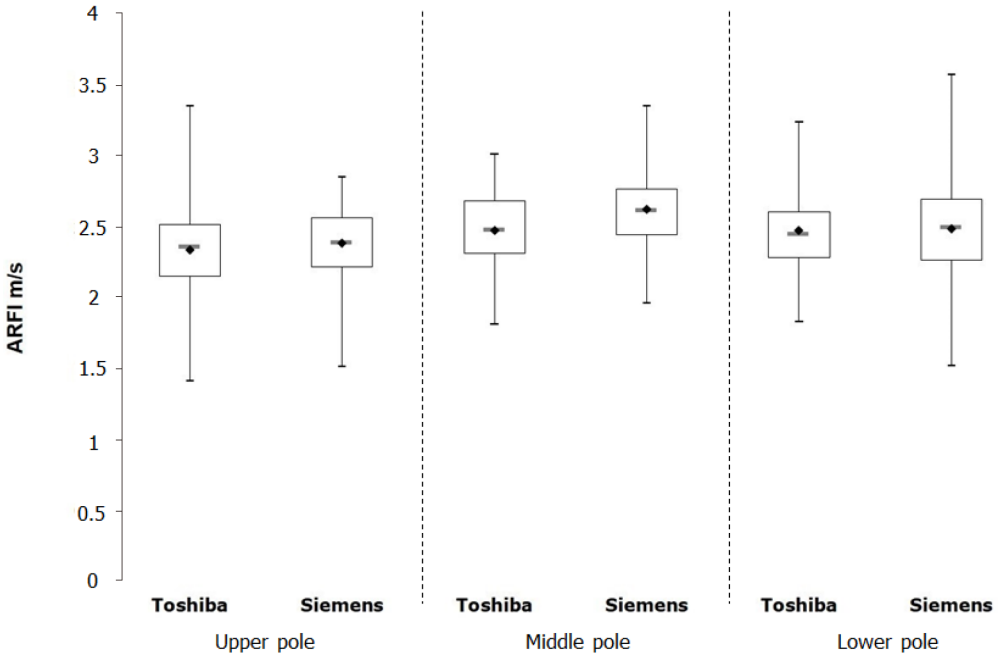


Figure 3 Boxplot diagram illustrating the measurements on the Toshiba Aplio 400 version 6.0 and Siemens devices for the different splenic sections. ARFI: Acoustic radiation force impulse.

In previous studies of the spleen, the measurements were performed at undefined areas or different splenic poles (upper, middle, lower third)[22-26]. Giuffrè *et al*[33] preferably investigated the lower pole, Albayrak *et al*[21] performed shear wave elastography of the middle third of the spleen, and Karlas *et al*[34] performed measurements in an insufficiently defined area between the middle and lower thirds of the spleen. Our results show that the lower third of the spleen is the best anatomical measurement position due to good visibility, as shown by other research groups[26,35-37]. Our results also confirm the recommendations of the EFSUMB to perform elastography on the lower third of the spleen[16]. The upper third does not seem to be suitable for measurements because its anatomical position often makes it difficult or impossible to see by inspiration, as it is partly overlapped by the lung or intestinal segments and located far away from the transducer. Our results confirm that readings should not be assumed to be transferable from one anatomic region of the spleen to another. Whether this is due to the tissue itself or to the examination conditions, such as poor visibility of the upper third, is currently not clear. A previous study reported that the measurement differences between devices and investigators can be up to 15%[38]. In a recent study patients with chronic hepatitis C virus infection show a good agreement of p-SWE and 2D-SWE in patients with F2-F4 fibrosis[39]. Since only healthy subjects were examined in our collective, these results cannot simply be transferred to the situation in patients with chronic hepatitis C and to the spleen[39]. In addition, our results show that without considering the anatomic site of measurement for splenic elastography, reliable measurement results cannot be obtained, regardless of the method used. Again, our results confirm the recommendations of medical societies that the absolute shear wave values are not comparable between different systems and manufacturers[5].

We could not demonstrate any correlation between age and the measured shear wave velocities. This finding is in accordance with the results of recent publications that could not demonstrate any influence of age on the measured shear wave velocities regardless of the shear wave elastography technique used[20,21,33,40,41]. However, an age-related correlation was previously demonstrated in children and adolescents younger than 18 years[42,43]. Independent of the shear wave technique, our study showed a contradictory picture regarding the influence of gender on the measured heavy wave velocities. For both the Siemens device (p-SWE) and the GE device (2D-SWE), gender-specific shear wave velocities were detected. This was not possible for the Philips device (p-SWE). Most of the available studies could not prove any gender-specific influence on the shear wave velocities[21,35,42,44]. A study of healthy children and adolescents concluded that gender influences elastography at the spleen[43]. The influence of BMI on spleen shear wave velocity was not clear according to other

research groups[21,33,44]. The influence of abdominal wall thickness on shear wave velocities has not yet been clarified[17,19,20,26] and this parameter was not assessed in our study. Future studies investigating BMI and abdominal wall thickness as influencing factors seem to be necessary.

A limitation of our study is that the defined exclusion criteria were only inquired about anamnestically, and advanced or still undiagnosed diseases could only be excluded by abdominal ultrasonography. Here, in contrast to other studies, no laboratory parameters were determined[22,24]. Also no information on unsuccessful mesaurements was collected during the study. However, due to the predominantly healthy young and slim probands, a low number of unsuccessful measurements can be assumed[45]. Histological examination could not be performed either, as this was ethically unacceptable in young healthy subjects. Compared to current studies and recommendations regarding liver elastography, the low number of measurements in our study is a major limitation. At each position, one measurement was performed with 2D-SWE and five measurements with pSWE. The EFSUMB currently recommends three to five measurements for 2D-SWE in order to obtain good measurements[40]. Karlas *et al*[34] also recommend between eight and ten measurements for pSWE of the spleen in order to obtain the most accurate shear wave velocities.

CONCLUSION

In conclusion, the absolute values of the shear wave elastography measurements of the spleen and the two different elastography methods are not comparable between different manufacturers or models. Further studies are needed to confirm the present study results.

ARTICLE HIGHLIGHTS

Research background

Measurement of shear wave velocity in the spleen has been increasingly used in prognostic assessment of esophageal varices and as a marker of portal hypertension. Few systematic comparative studies of the different methods of physical elastography of the spleen are currently available.

Research motivation

Currently, whether the different elastography methods and shear wave measurements with different ultrasonic devices provide comparable results have not been clarified.

Research objectives

The objective of the study was to compare point shear wave and two-dimensional elastography of the spleen considering the anatomical location (upper, hilar, and lower pole).

Research methods

As part of a prospective clinical study, healthy volunteers were examined for splenic elasticity using four different ultrasound devices between May 2015 and April 2017. The devices used for point shear wave elastography were from Siemens (S 3000) and Philips (Epiq 7), and those used for two-dimensional shear wave elastography were from GE (Logiq E9) and Toshiba (Aplio 500). In addition, two different software versions (5.0 and 6.0) were evaluated for the Toshiba ultrasound device (Aplio 500). The study consisted of three arms: A, B, and C.

Research results

In study arm A, 200 subjects were evaluated (78 males and 122 females, mean age 27.9 ± 8.1 years). In study arm B, 113 subjects were evaluated (38 men and 75 women, mean age 26.0 ± 6.3 years). In study arm C, 44 subjects were enrolled. A significant correlation of the shear wave velocities at the upper third of the spleen (r = 0.33088, P < 0.0001) was demonstrated only for the Philips Epiq 7 device compared to the Siemens Acuson S 3000. In comparisons of the other ultrasound devices (GE, Siemens, Toshiba), no comparable results could be obtained for any anatomical position of the

spleen. The influencing factors age, gender, and body mass index did not show a clear correlation with the measured shear wave velocities.

Research conclusions

The absolute values of the shear wave elastography measurements of the spleen and the two different elastography methods are not comparable between different manufacturers or models.

Research perspectives

However, absolute values of splenic shear wave elastography measurements are not transferable between manufacturers or models.

ACKNOWLEDGEMENTS

Members of the Elastography Study Group: Hadeel Gamal El-Deen Abd El-Moniem, Gräter Tilmann, Hesse Julian, Klimesch Benjamin, Maaß Marie, Schall Katrin.

REFERENCES

1 **Li J**, Chen M, Cao CL, Zhou LQ, Li SG, Ge ZK, Zhang WH, Xu JW, Cui XW, Dietrich CF. Diagnostic Performance of Acoustic Radiation Force Impulse Elastography for the Differentiation of Benign and Malignant Superficial Lymph Nodes: A Meta-analysis. *J Ultrasound Med* 2020; **39**: 213-222 [PMID: 31343772 DOI: 10.1002/jum.15096]

2 **Dietrich CF**, Hocke M. Elastography of the Pancreas, Current View. *Clin Endosc* 2019; **52**: 533-540 [PMID: 31311914 DOI: 10.5946/ce.2018.156]

3 **Wee TC**, Simon NG. Ultrasound elastography for the evaluation of peripheral nerves: A systematic review. *Muscle Nerve* 2019; **60**: 501-512 [PMID: 31269240 DOI: 10.1002/mus.26624]

4 **Cornelson SM**, Ruff AN, Perillat M, Kettner NW. Sonoelastography of the trunk and lower extremity muscles in a case of Duchenne muscular dystrophy. *J Ultrasound*2019 epub ahead of print [PMID: 31256365 DOI: 10.1007/s40477-019-00394-1]

5 **Dietrich CF**, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, Cosgrove D, Ferraioli G, Friedrich-Rust M, Gilja OH, Goertz RS, Karlas T, de Knegt R, de Ledinghen V, Piscaglia F, Procopet B, Saftoiu A, Sidhu PS, Sporea I, Thiele M. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). *Ultraschall Med* 2017; **38**: e16-e47 [PMID: 28407655 DOI: 10.1055/s-0043-103952]

6 **Kim DW**, Park C, Yoon HM, Jung AY, Lee JS, Jung SC, Cho YA. Technical performance of shear wave elastography for measuring liver stiffness in pediatric and adolescent patients: a systematic review and meta-analysis. *Eur Radiol* 2019; **29**: 2560-2572 [PMID: 30617493 DOI: 10.1007/s00330-018-5900-6]

7 **Bota S**, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, Peck-Radosavljevic M. Meta-analysis: ARFI elastography *vs* transient elastography for the evaluation of liver fibrosis. *Liver Int* 2013; **33**: 1138-1147 [PMID: 23859217 DOI: 10.1111/Liv.12240]

8 **Sporea I**, Bota S, Jurchis A, Sirli R, Grădinaru-Tascău O, Popescu A, Ratiu I, Szilaski M. Acoustic radiation force impulse and supersonic shear imaging *vs* transient elastography for liver fibrosis assessment. *Ultrasound Med Biol* 2013; **39**: 1933-1941 [PMID: 23932281 DOI: 10.1016/j.ultrasmedbio.2013.05.003]

9 **Mulazzani L**, Salvatore V, Ravaioli F, Allegretti G, Matassoni F, Granata R, Ferrarini A, Stefanescu H, Piscaglia F. Point shear wave ultrasound elastography with Esaote compared to real-time 2D shear wave elastography with supersonic imagine for the quantification of liver stiffness. *J Ultrasound* 2017; **20**: 213-225 [PMID: 28900522 DOI: 10.1007/s40477-017-0260-7]

10 **Gress VS**, Glawion EN, Schmidberger J, Kratzer W. Comparison of Liver Shear Wave Elastography Measurements using Siemens Acuson S3000, GE LOGIQ E9, Philips EPIQ7 and Toshiba Aplio 500 (Software Versions 5.0 and 6.0) in Healthy Volunteers. *Ultraschall Med* 2019; **40**: 504-512 [PMID: 30352452 DOI: 10.1055/a-0651-0542]

11 **Ferraioli G**, De Silvestri A, Lissandrin R, Maiocchi L, Tinelli C, Filice C, Barr RG. Evaluation of Inter-System Variability in Liver Stiffness Measurements. *Ultraschall Med* 2019; **40**: 64-75 [PMID: 29566420 DOI: 10.1055/s-0043-124184]

12 **Mjelle AB**, Mulabecirovic A, Havre RF, Rosendahl K, Juliusson PB, Olafsdottir E, Gilja OH, Vesterhus M. Normal Liver Stiffness Values in Children: A Comparison of Three Different Elastography Methods. *J Pediatr Gastroenterol Nutr* 2019; **68**: 706-712 [PMID: 30889132 DOI: 10.1097/MPG.0000000000002320]

13 **Mazur R**, Celmer M, Silicki J, Hołownia D, Pozowski P, Międzybrodzki K. Clinical applications of spleen ultrasound elastography - a review. *J Ultrason* 2018; **18**: 37-41 [PMID: 29844939 DOI: 10.15557/JoU.2018.0006]

14 **Gibiino G**, Garcovich M, Ainora ME, Zocco MA. Spleen ultrasound elastography: state of the art and future directions - a systematic review. *Eur Rev Med Pharmacol Sci* 2019; **23**: 4368-4381 [PMID: 31173311 DOI: 10.26355/eurrev_201905_17944]

15 **Săftoiu A**, Gilja OH, Sidhu PS, Dietrich CF, Cantisani V, Amy D, Bachmann-Nielsen M, Bob F, Bojunga J, Brock M, Calliada F, Clevert DA, Correas JM, D'Onofrio M, Ewertsen C, Farrokh A, Fodor D, Fusaroli P, Havre RF, Hocke M, Ignee A, Jenssen C, Klauser AS, Kollmann C, Radzina M, Ramnarine KV, Sconfienza LM, Solomon C, Sporea I, Ștefănescu H, Tanter M, Vilmann P. The EFSUMB Guidelines and Recommendations for the Clinical Practice of Elastography in Non-Hepatic Applications: Update 2018. *Ultraschall Med* 2019; **40**: 425-453 [PMID: 31238377 DOI: 10.1055/a-0838-9937]

16 **Song J**, Huang J, Huang H, Liu S, Luo Y. Performance of spleen stiffness measurement in prediction of clinical significant portal hypertension: A meta-analysis. *Clin Res Hepatol Gastroenterol* 2018; **42**: 216-226 [PMID: 29223365 DOI: 10.1016/j.clinre.2017.11.002]

17 **Cassinotto C**, Charrie A, Mouries A, Lapuyade B, Hiriart JB, Vergniol J, Gaye D, Hocquelet A, Charbonnier M, Foucher J, Laurent F, Chermak F, Montaudon M, de Ledinghen V. Liver and spleen elastography using supersonic shear imaging for the non-invasive diagnosis of cirrhosis severity and oesophageal varices. *Dig Liver Dis* 2015; **47**: 695-701 [PMID: 25959234 DOI: 10.1016/j.dld.2015.04.008]

18 **Takuma Y**, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, Matsueda K, Yamamoto H. Portal Hypertension in Patients with Liver Cirrhosis: Diagnostic Accuracy of Spleen Stiffness. *Radiology* 2016; **279**: 609-619 [PMID: 26588019 DOI: 10.1148/radiol.2015150690]

19 **Balakrishnan M**, Souza F, Muñoz C, Augustin S, Loo N, Deng Y, Ciarleglio M, Garcia-Tsao G. Liver and Spleen Stiffness Measurements by Point Shear Wave Elastography *via* Acoustic Radiation Force Impulse: Intraobserver and Interobserver Variability and Predictors of Variability in a US Population. *J Ultrasound Med* 2016; **35**: 2373-2380 [PMID: 27663656 DOI: 10.7863/ultra.15.10056]

20 **Cho YS**, Lim S, Kim Y, Sohn JH, Jeong JY. Spleen Stiffness Measurement Using 2-Dimensional Shear Wave Elastography: The Predictors of Measurability and the Normal Spleen Stiffness Value. *J Ultrasound Med* 2019; **38**: 423-431 [PMID: 30039572 DOI: 10.1002/jum.14708]

21 **Albayrak E**, Server S. The relationship of spleen stiffness value measured by shear wave elastography with age, gender, and spleen size in healthy volunteers. *J Med Ultrason (2001)* 2019; **46**: 195-199 [PMID: 30689067 DOI: 10.1007/s10396-019-00929-3]

22 **Ferraioli G**, Tinelli C, Lissandrin R, Zicchetti M, Bernuzzi S, Salvaneschi L, Filice C; Elastography Study Group. Ultrasound point shear wave elastography assessment of liver and spleen stiffness: effect of training on repeatability of measurements. *Eur Radiol* 2014; **24**: 1283-1289 [PMID: 24643497 DOI: 10.1007/s00330-014-3140-y]

23 **Gallotti A**, D'Onofrio M, Pozzi Mucelli R. Acoustic Radiation Force Impulse (ARFI) technique in ultrasound with Virtual Touch tissue quantification of the upper abdomen. *Radiol Med* 2010; **115**: 889-897 [PMID: 20082227 DOI: 10.1007/s11547-010-0504-5]

24 **Gao J**, Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG. The stiffness of the liver and spleen on ARFI Imaging pre and post TIPS placement: a preliminary observation. *Clin Imaging* 2012; **36**: 135-141 [PMID: 22370134 DOI: 10.1016/j.clinimag.2011.11.014]

25 **Grgurevic I**, Cikara I, Horvat J, Lukic IK, Heinzl R, Banic M, Kujundzic M, Brkljacic B. Noninvasive assessment of liver fibrosis with acoustic radiation force impulse imaging: increased liver and splenic stiffness in patients with liver fibrosis and cirrhosis. *Ultraschall Med* 2011; **32**: 160-166 [PMID: 21104600 DOI: 10.1055/s-0029-1245807]

26 **Kaminuma C**, Tsushima Y, Matsumoto N, Kurabayashi T, Taketomi-Takahashi A, Endo K. Reliable measurement procedure of virtual touch tissue quantification with acoustic radiation force impulse imaging. *J Ultrasound Med* 2011; **30**: 745-751 [PMID: 21632988 DOI: 10.7863/jum.2011.30.6.745]

27 **Dong Y**, Sirli R, Ferraioli G, Sporea I, Chiorean L, Cui X, Fan M, Wang WP, Gilja OH, Sidhu PS, Dietrich CF. Shear wave elastography of the liver - review on normal values. *Z Gastroenterol* 2017; **55**: 153-166 [PMID: 28192849 DOI: 10.1055/s-0042-117226]

28 **Galgenmueller S**, Jaeger H, Kratzer W, Schmidt SA, Oeztuerk S, Haenle MM, Mason RA, Graeter T. Parameters affecting different acoustic radiation force impulse applications in the diagnosis of fibrotic liver changes. *World J Gastroenterol* 2015; **21**: 8425-8432 [PMID: 26217095 DOI: 10.3748/wjg.v21.i27.8425]

29 **Keller J**, Kaltenbach TE, Haenle MM, Oeztuerk S, Graeter T, Mason RA, Seufferlein T, Kratzer W. Comparison of Acoustic Structure Quantification (ASQ), shearwave elastography and histology in patients with diffuse hepatopathies. *BMC Med Imaging* 2015; **15**: 58 [PMID: 26637242 DOI: 10.1186/s12880-015-0100-1]

30 **General Assembly of the World Medical Association**. . World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent* 2014; **81**: 14-18 [PMID: 25951678]

31 **Serra C**, Grasso V, Conti F, Felicani C, Mazzotta E, Lenzi M, Verucchi G, D'errico A, Andreone P. A New Two-Dimensional Shear Wave Elastography for Noninvasive Assessment of Liver Fibrosis in Healthy Subjects and in Patients with Chronic Liver Disease. *Ultraschall Med* 2018; **39**: 432-439 [PMID: 29458217 DOI: 10.1055/s-0043-119356]

32 **Fang C**, Konstantatou E, Romanos O, Yusuf GT, Quinlan DJ, Sidhu PS. Reproducibility of 2-Dimensional Shear Wave Elastography Assessment of the Liver: A Direct Comparison With Point Shear Wave Elastography in Healthy Volunteers. *J Ultrasound Med* 2017; **36**: 1563-1569 [PMID:

28370146 DOI: 10.7863/ultra.16.07018]
33 **Giuffrè M**, Macor D, Masutti F, Abazia C, Tinè F, Patti R, Buonocore MR, Colombo A, Visintin A, Campigotto M, Crocè LS. Evaluation of spleen stiffness in healthy volunteers using point shear wave elastography. *Ann Hepatol* 2019; **18**: 736-741 [PMID: 31054978 DOI: 10.1016/j.aohep.2019.03.004]
34 **Karlas T**, Lindner F, Tröltzsch M, Keim V. Assessment of spleen stiffness using acoustic radiation force impulse imaging (ARFI): definition of examination standards and impact of breathing maneuvers. *Ultraschall Med* 2014; **35**: 38-43 [PMID: 24510458 DOI: 10.1055/s-0033-1356230]
35 **Goertz RS**, Amann K, Heide R, Bernatik T, Neurath MF, Strobel D. An abdominal and thyroid status with Acoustic Radiation Force Impulse Elastometry--a feasibility study: Acoustic Radiation Force Impulse Elastometry of human organs. *Eur J Radiol* 2011; **80**: e226-e230 [PMID: 20971591 DOI: 10.1016/j.ejrad.2010.09.025]
36 **Mori K**, Arai H, Abe T, Takayama H, Toyoda M, Ueno T, Sato K. Spleen stiffness correlates with the presence of ascites but not esophageal varices in chronic hepatitis C patients. *Biomed Res Int* 2013; **2013**: 857862 [PMID: 23984413 DOI: 10.1155/2013/857862]
37 **Procopet B**, Berzigotti A, Abraldes JG, Turon F, Hernandez-Gea V, García-Pagán JC, Bosch J. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. *J Hepatol* 2015; **62**: 1068-1075 [PMID: 25514554 DOI: 10.1016/j.jhep.2014.12.007]
38 **Hall TJ**, Milkowski A, Garra B, Carson P, Palmeri M, Nightingale K, Lynch T, Alturki A, Andre M, Audiere S, Bamber J, Barr R, Bercoff J, Bernal M, Brum J, Cohen-Bacrie C, Couade M, Daniels A, DeWall R, Dillman J, Ehman R, Franchi-Abella SF, Fromageau J, Gennisson J, Henry JP, Ivancevich N, Kalin J, Kohn S, Kugel J, Liu N L, Loupas T, Mazernik J, McAleavey S, Miette V, Metz S, Morel BM, Nelson T, Nordberg E, Oudry J, Padwal M, Rouze N, Samir A, Sandrin L, Schaccitti J, Schmitt C, Shamdasani V, Switalski P, Wang M, Wear K. RSNA/QIBA: Shear wave speed as a biomarker for liver fibrosis staging. 2013 IEEE International Ultrasonics Symposium (IUS); 2013 July 21-25; Prague, Czech Republic [DOI: 10.1109/ULTSYM.2013.0103]
39 **Bâldea V**, Lupușoru R, Dănilă M, Șirli R, Popescu A, Sporea I. Comparison between the performance of Two-Dimensional and Point Shear Wave elastography for the noninvasive assessment of liver cirrhosis. *Ultrasound Med Biol* 2019; **45**: S119 [DOI: 10.1016/j.ultrasmedbio.2019.07.391]
40 **Arda K**, Ciledag N, Aktas E, Aribas BK, Köse K. Quantitative assessment of normal soft-tissue elasticity using shear-wave ultrasound elastography. *AJR Am J Roentgenol* 2011; **197**: 532-536 [PMID: 21862792 DOI: 10.2214/AJR.10.5449]
41 **Pawluś A**, Inglot MS, Szymańska K, Kaczorowski K, Markiewicz BD, Kaczorowska A, Gąsiorowski J, Szymczak A, Inglot M, Bladowska J, Zaleska-Dorobisz U. Shear wave elastography of the spleen: evaluation of spleen stiffness in healthy volunteers. *Abdom Radiol (NY)* 2016; **41**: 2169-2174 [PMID: 27389244 DOI: 10.1007/s00261-016-0834-4]
42 **Cañas T**, Fontanilla T, Miralles M, Maciá A, Malalana A, Román E. Normal values of spleen stiffness in healthy children assessed by acoustic radiation force impulse imaging (ARFI): comparison between two ultrasound transducers. *Pediatr Radiol* 2015; **45**: 1316-1322 [PMID: 25796383 DOI: 10.1007/s00247-015-3306-z]
43 **Lee MJ**, Kim MJ, Han KH, Yoon CS. Age-related changes in liver, kidney, and spleen stiffness in healthy children measured with acoustic radiation force impulse imaging. *Eur J Radiol* 2013; **82**: e290-e294 [PMID: 23433651 DOI: 10.1016/j.ejrad.2013.01.018]
44 **Kassym L**, Nounou MA, Zhumadilova Z, Dajani AI, Barkibayeva N, Myssayev A, Rakhypbekov T, Abuhammour AM. New combined parameter of liver and splenic stiffness as determined by elastography in healthy volunteers. *Saudi J Gastroenterol* 2016; **22**: 324-330 [PMID: 27488328 DOI: 10.4103/1319-3767.187607]
45 **Petzold G**, Hofer J, Ellenrieder V, Neesse A, Kunsch S. Liver Stiffness Measured by 2-Dimensional Shear Wave Elastography: Prospective Evaluation of Healthy Volunteers and Patients With Liver Cirrhosis. *J Ultrasound Med* 2019; **38**: 1769-1777 [PMID: 30536601 DOI: 10.1002/jum.14866]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 June 28; 13(6): 149-222

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 6 June 28, 2021

MINIREVIEWS

REVIEW

World Journal of Radiology

Monthly Volume 13 Number 6 June 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Milan Vošmik, MD, PhD, Associated Professor, Department of Oncology and Radiotherapy, Charles University, Medical School in Hradec Králové and University Hospital Hradec Králové, Hradec Králové 500-05, Czech Republic. milan.vosmik@fnhk.cz

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
June 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 June 28; 13(6): 149-156

DOI: 10.4329/wjr.v13.i6.149

ISSN 1949-8470 (online)

MINIREVIEWS

Thoracic imaging outcomes in COVID-19 survivors

Jaber S Alqahtani, Saeed M Alghamdi, Abdulelah M Aldhahir, Malik Althobiani, Reynie Purnama Raya, Tope Oyelade

ORCID number: Jaber S Alqahtani 0000-0003-1795-5092; Saeed M Alghamdi 0000-0002-6677-1110; Abdulelah M Aldhahir 0000-0002-4270-9494; Malik Althobiani 0000-0002-2230-5708; Reynie Purnama Raya 0000-0002-4548-6820; Tope Oyelade 0000-0003-1151-0295.

Author contributions: Alqahtani JS contributed conceptualization, data collection, formal analysis, project administration, wrote original draft, reviewed and edited the manuscript; Alghamdi SM, Aldhahir AM and Oyelade T contributed data collection, formal analysis, reviewed and edited the manuscript; Althobiani M and Raya RP reviewed and edited the manuscript.

Conflict-of-interest statement: The authors have nothing to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License

Jaber S Alqahtani, Department of Respiratory Care, Prince Sultan Military College of Health Sciences, Dammam 3431, Saudi Arabia

Jaber S Alqahtani, Malik Althobiani, Department of Respiratory Medicine, Division of Medicine, University College London, London NW3 2PF, United Kingdom

Saeed M Alghamdi, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah 21990, Saudi Arabia

Abdulelah M Aldhahir, Respiratory Care Department, Faculty of Applied Medical Sciences, Jazan University, Jazan 4514, Saudi Arabia

Malik Althobiani, Department of Respiratory Therapy, King Abdulaziz University, Jeddah 21589, Saudi Arabia

Reynie Purnama Raya, Faculty of Science, Universitas 'Aisyiyah Bandung, Bandung 40264, Indonesia

Reynie Purnama Raya, Institute for Global Health, Division of Medicine, University College London, London NW3 2PF, United Kingdom

Tope Oyelade, Institute for Liver and Digestive Health, Division of Medicine, University College London, London NW3 2PF, United Kingdom

Corresponding author: Jaber S Alqahtani, MSc, Academic Research, Lecturer, Department of Respiratory Care, Prince Sultan Military College of Health Sciences, Dhahran, Dammam 3431, Saudi Arabia. Alqahtani-Jaber@hotmail.com

Abstract

The coronavirus disease 2019 (COVID-19) pandemic presents a significant global public health challenge. One in five individuals with COVID-19 presents with symptoms that last for weeks after hospital discharge, a condition termed “long COVID”. Thus, efficient follow-up of patients is needed to assess the resolution of lung pathologies and systemic involvement. Thoracic imaging is multimodal and involves using different forms of waves to produce images of the organs within the thorax. In general, it includes chest X-ray, computed tomography, lung ultrasound and magnetic resonance imaging techniques. Such modalities have been useful in the diagnosis and prognosis of COVID-19. These tools have also allowed for the follow-up and assessment of long COVID. This review provides insights on the effectiveness of thoracic imaging techniques in the follow-up of

s/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: United Kingdom

Peer-review report's scientific quality classification

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

Received: January 28, 2021
Peer-review started: January 28, 2021
First decision: May 6, 2021
Revised: May 13, 2021
Accepted: June 2, 2021
Article in press: June 2, 2021
Published online: June 28, 2021

P-Reviewer: Liang XH, Tong MY
S-Editor: Gao CC
L-Editor: A
P-Editor: Yuan YY

COVID-19 survivors who had long COVID.

Key Words: Long COVID; COVID-19; SARS-CoV-2; Thoracic imaging; Computed tomography; Survivors; Chest X-ray; Lung ultrasound

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic presents a significant global public health challenge. One in five individuals with COVID-19 presents with symptoms that last for weeks after hospital discharge, a condition termed "long COVID". This review provides insights on findings of thoracic imaging techniques in the follow-up of COVID-19 survivors who had long COVID.

Citation: Alqahtani JS, Alghamdi SM, Aldhahir AM, Althobiani M, Raya RP, Oyelade T. Thoracic imaging outcomes in COVID-19 survivors. *World J Radiol* 2021; 13(6): 149-156
URL: https://www.wjgnet.com/1949-8470/full/v13/i6/149.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i6.149

INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic continues to cause significant morbidity and mortality worldwide[1-3]. To date, the focus of research communication has been on the management of acute respiratory complications, particularly in critically ill patients[4,5]. However, since June 2020 increased attention has been paid to the experiences of COVID-19 survivors whose symptoms continue for four or more weeks[6]. According to the Office for National Statistics, one in five individuals has symptoms that continue after five weeks, and one in ten has symptoms for 12 wk or longer after acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[7]. This is called "long COVID" and is defined as a condition in which infected people do not fully recover for several weeks or months after signs indicative of SARS-CoV-2 infection[8]. Studies on long COVID exploring the underlying pathology and sequelae, as well as rehabilitation for patients, are increasing. Data shows that many patients with long COVID develop serious clinical complications[9-11] and require follow-up to confirm full resolution of symptoms.

An imaging test refers to the generation of image results that are clinically relevant for clinical diagnosis, guiding management, triage, and therapy. Chest radiography, computed tomography (CT), lung ultrasound (LUS), and magnetic resonance imaging (MRI) provide additional clinical insights on COVID-19 patients to better understand long COVID complications. Early and accurate diagnosis, as well as guided management of COVID-19-related complications, is important[12]. Further, because of the tendency toward extended sequelae of COVID-19 symptoms, some of which include multi-organ involvement, there is an increasing need to develop follow-up strategies to prevent further deterioration of patients. Therefore, this review provides an update on the effectiveness of thoracic imaging techniques in the follow-up of COVID-19 survivors who suffer from long COVID.

THE USE OF THORACIC IMAGING IN COVID-19 PATIENTS

Using diagnostic thoracic imaging techniques on patients diagnosed with COVID-19 can sometimes be challenging due to the strict infection control measures that are required to prevent or reduce the spread of infection to healthcare providers and other patients[13]. However, various imaging modalities have been used due to the value of thoracic imaging in detection and monitoring of disease progression. Generally, chest radiography and CT of the chest are used with COVID-19, while the use of MRI and LUS is limited in the literature[14].

In the early stages of COVID-19 infection, chest radiography is insensitive especially in mild cases[15], whereas CT is more sensitive for early parenchymal lung disease, disease progression, and alternative diagnoses, including acute heart failure[16]. Nevertheless, concerning the importance of chest radiography or CT for diagnosing viral pneumonia, experiences and decisions vary widely based on cultural standards and public health recommendations[17]. This is exemplified in China where patients are encouraged to present themselves early in the course of their disease when chest radiography has limited clinical value. CT has therefore proved a more efficient tool in detecting COVID-19 and guiding public health measures such as self-isolation[16]. In contrast, patients in the US have been instructed to stay at home until they suffer severe symptoms and so, as expected, a chest radiograph is generally abnormal at the time of presentation. In some countries, chest radiography is preferred in certain groups of patients because of portability; therefore, imaging can be performed in an infected patient's isolation room, thus reducing the risk of SARS-CoV-2 transmission that may result from in-hospital transportation[17]. Although chest radiography can be beneficial for evaluating disease progress and alternative diagnoses, many hospitals rely on CT scan findings when clinical management decisions are needed, such as discharge from hospital or the need for intensive care unit[18]. Generally, the choice of thoracic imaging will depend on available equipment (chest radiography, CT, MRI or LUS), expertise, and the judgment of the healthcare staff at the points of care, with the final decision based on appropriate and reasonable assessment of related risks.

CHEST RADIOGRAPHY IN COVID-19 SURVIVORS

Chest radiography, also referred to as chest X-ray (CXR), involves using short wavelength electromagnetic radiation to produce images of the chest's internal organs. With moderate ease of use and interpretation and low side effects, CXR remains one of the oldest and most used non-invasive chest imaging techniques[19]. However, in the context of COVID-19, the use of CXR has been reported to vary in importance and usefulness in both diagnosis and prognostication of disease course. Common CXR findings that have been described in COVID-19 patients are pulmonary lesions associated with inflammatory injuries, ground-glass opacity (GGO), linear opacity consolidation, crazy-paving pattern and vacuolar sign[20].

GGO remains the major structural change indicative of COVID-19 infection, with a majority of patients developing bilateral CXR findings of this nature[21,22]. A combination of GGO and consolidation of the lung image usually occurs in the periphery of the lung[23] and is scored from 0-4 based on the percentage of the lung affected[24]. In a study by Wong *et al*[15], the sensitivity of baseline CXRs in the diagnosis of COVID-19 was 62%, with 9% of patients showing abnormal CT findings before reverse transcription polymerase chain reaction (RT-PCR) confirmation of SARS-CoV-2 infection. A significant majority of patients with COVID-19 infection show CXR abnormalities indicative of damage to the lung tissue, which is attributable to systemic inflammatory response syndrome[22,25].

In most patients who survive severe COVID-19, there is a significant tendency to develop fibrotic lung tissue after recovery. However, while CRX is promising in diagnosing COVID-19, its use as a marker for pulmonary tissue recovery in patients with long COVID-19 remains unclear. For instance, in a study assessing 119 COVID-19 patients, D'cruz *et al*[26] found that follow-up CRX did not correlate with abnormal CT findings or prolonged functional disability in infected patients, while another study involving 134 patients concluded that CXR findings were an independent risk factor for poorer prognosis in COVID-19 patients[20]. Liao *et al*[22], in another study of 172 COVID-19 survivors, showed that 86% of patients had abnormal CT findings three months after discharge. In this study, change in CXR findings was associated with recovery duration, and abnormal lung findings were reported to correlate significantly with severity of COVID-19. Generally, the effectiveness of CXR as a prognostic marker or in tracking lung tissue regeneration in patients with long COVID remains uncertain.

CT IN COVID-19 SURVIVORS

CT scans have been extensively used in the diagnosis of COVID-19. In a series of 51 patients, the sensitivity of CT scan in detecting SARS-CoV-2 infection was reported to be higher (98%) compared to RT-PCR (71%)[27,28]. In another study involving 167 patients considered at high risk for SARS-CoV-2 infection, chest CT scan confirming

viral pneumonia correlated significantly with positive RT-PCR results[29]. Generally, chest CT findings of lung tissue pathology are similar to those of CXR scans in COVID-19 and are scored based on bilateral lung involvement, including GGO, consolidation, vacuolar sign, linear opacity and crazy-paving pattern[30,31]. However, while the sensitivity of CT is high in detecting lung tissue pathology associated with pneumonic infections, the specificity for SARS-CoV-2 infection is relatively low (25%-56%)[31].

Because of its sensitivity, the first point of call and the reference technique for chest imaging has been CT. Although CT is expensive, less portable and available, and requires well-trained and experienced radiographers for standard operation and interpretation of findings[32], it has been extensively used in the prognosis and follow-up of COVID-19 patients. In a study involving 55 COVID-19 survivors followed up for three months after discharge, abnormal CT findings were detected in 71% of patients [33]. Another study in which final CT scans were obtained from 70 COVID-19 survivors at discharge showed unresolved lung tissue pathology in 94% of the patients, mainly in the form of residual GGO (60%)[34]. Tabatabaei *et al*[35] studied 52 patients who had recovered from COVID-19 and reported residual CT abnormalities in 42% of the survivors. These findings showed significant correlation with disease severity. Generally, CT is a useful and more sensitive tool in the follow-up of patients recovered from COVID-19. It may be helpful in the assessment of treatment effects.

LUS IN COVID-19 SURVIVORS

LUS provides a faster, safer and more sensitive assessment of lung tissue pathology compared to radiation-based CXR and has been extensively used in the monitoring of patients with COVID-19. LUS is also relatively more accessible because of the inherent portability and bedside availability, making it a technique of choice where timely assessment of lung complications is needed, especially in COVID-19 patients with severe or unstable health conditions[36]. Further, the ability to delineate alterations in superficial lung tissue through the air and tissue ratio (using A- and B-lines) makes LUS unique and more sensitive in characterizing the nature, topography, and size of lung tissue lesions[37,38]. In general, irregular thickening of the pleural line, heterogeneous B-lines and consolidations, pleural effusions, and recovery-phase A-lines in the lung image have been detected in COVID-19 patients using ultrasonography[39-41]. LUS has been reported to correlate strongly with systemic inflammation and severity of COVID-19, although not with survival[42].

In the follow-up of COVID-19 survivors with long-persisting symptoms, LUS findings have shown promising outcomes. In a case series of long COVID patients by Tung-Chen *et al*[43], LUS findings correlated with chest CT and accurately assessed the resolution of residual lung tissue abnormalities. LUS findings, specifically the frequency of B-lines, which measures the thickening of pleural lines, were also reported to correlate with the duration of COVID-19 symptoms in patients[44]. Further, LUS was successfully used in the assessment of the progression of COVID-19 in a 35-year-old survivor for up to three weeks in a home setting[45]. These highlights both the sensitivity and availability of LUS for the assessment of both short- and long-term effects of SARS-CoV-2 infection.

MRI IN COVID-19 SURVIVORS

MRI was first introduced in the United Kingdom in 1980, and since that time, it has become widely used in clinical practice[46,47]. It is extremely effective, particularly in the diagnosis of patients without exposing them to dangerous ionising radiation[48]. Angiotensin-converting enzyme 2 (ACE2) is the path for SARS-CoV-2 to attack thoracic organs, including lung and cardiac systems. MRI has been used regularly to assess cardiac involvement in patients who have recovered from COVID-19[11,49]. Huang *et al*[49] conducted a study on patients who reported cardiac symptoms during their hospitalization due to COVID-19 to assess whether there was continued cardiac involvement after the patients' recovery from COVID-19. This study found that 58% of the recovered patients had abnormal MRI findings, including myocardial oedema (54%) and late gadolinium enhancement (31%). Further, fibrosis and compromised right ventricle function have also been found in patients who have recovered from COVID-19. In another study conducted by Puntmann *et al*[11], independent of pre-existing comorbidities, severity and overall course of the acute illness, cardiac involvement was reported in 78% of patients and around 60% had ongoing myocardial

Table 1 Findings of thoracic imaging tools in coronavirus disease 2019 survivors

Thoracic imaging tools	Imaging findings in COVID-19 survivors
Chest X-ray (CXR)	(1) CRX does not correlate with abnormal CT findings or prolonged functional disability in infected patients; (2) Changes in CXR findings are associated with recovery duration and severity of COVID-19; and (3) The overall effectiveness of CRX is uncertain
CT scan	(1) Abnormal CT findings were detected in 71% of COVID-19 survivors; Unresolved lung tissue pathology presents mainly in the form of residual GGO; and (2) CT findings show a significant correlation with disease severity
Lung ultrasound (LUS)	(1) LUS findings correlate with chest CT and accurately assess the resolution of residual lung tissue abnormalities; and (2) LUS findings correlate with the duration of COVID-19 symptoms in COVID-19 survivors and can be used in home settings
MRI	(1) This is used to assess cardiac involvement in patients recovered from COVID-19; (2) 58% of recovered patients had abnormal MRI findings, including myocardial oedema (54%) and late gadolinium enhancement (31%); and (3) Fibrosis and compromised right ventricle function have also been found in patients who have recovered from COVID-19

COVID-19: Coronavirus disease 2019; CT: Computed tomography; MRI: Magnetic resonance imaging; GGO: Ground-glass opacity.

inflammation. The abnormal findings included elevated myocardial native T1 and myocardial native T2 and pericardial enhancement. Cardiac involvement in patients recovered from COVID-19 is common and has the potential to affect the overall prognosis. Although rarely used, MRI is effective in detecting cardiac involvement in patients and provides a holistic diagnostic assessment of residual symptoms in COVID-19 survivors. Further studies are essential to explore the long-term cardiopulmonary burden of long COVID.

In summary, Table 1 shows the major findings of thoracic imaging tools in COVID-19 survivors.

KEY POINTS

(1) COVID-19 survivors sometimes develop long-term sequelae, generally termed "long COVID", which can be assessed by different imaging tests; (2) Various imaging modes have been used as diagnostic, prognostic, and follow-up tools in COVID-19. However, sensitivity and specificity, as well as modes and ease of use, vary; (3) The effectiveness of CRX as a prognostic marker or in tracking lung tissue regeneration in patients with long COVID remains uncertain; (4) CT is a relatively more sensitive tool in the follow up of COVID-19 survivors and could be used for the assessment of treatment effects; (5) LUS is sensitive and relatively more portable than radiology-based imaging tools, allowing for use in out-of-hospital settings, and it may be the best tool for the follow-up of COVID-19 survivors; and (6) Although rarely used, MRI is effective in detecting cardiac involvement in patients and provides a holistic diagnostic assessment of residual symptoms in COVID-19 survivors.

CONCLUSION

COVID-19 survivors, especially those with a severe clinical course, have residual lung tissue abnormalities and suffer extensive sequelae, currently termed "long COVID". Fibrotic lung tissue from systemic inflammatory response to SARS-CoV-2 infection is characteristic of severe COVID-19 and can be picked up in follow-up scans. Various imaging techniques have been extensively used for the follow-up of long COVID, including CXR, CT, LUS and MRI with varying efficiency. However, CT remains the most commonly used because of its sensitivity, while LUS is favoured because of its accessibility and portability.

REFERENCES

1 **Alqahtani JS**, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, Quaderi S, Mandal S, Hurst JR. Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. *PLoS One* 2020; **15**: e0233147 [PMID: 32392262 DOI: 10.1371/journal.pone.0233147]

2 **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]

3 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

4 **Alhazzani W**, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020; **46**: 854-887 [PMID: 32222812 DOI: 10.1007/s00134-020-06022-5]

5 **Alqahtani JS**, Mendes RG, Aldhahir A, Rowley D, AlAhmari MD, Ntoumenopoulos G, Alghamdi SM, Sreedharan JK, Aldabayan YS, Oyelade T, Alrajeh A, Olivieri C, AlQuaimi M, Sullivan J, Almeshari MA, Esquinas A. Global Current Practices of Ventilatory Support Management in COVID-19 Patients: An International Survey. *J Multidiscip Healthc* 2020; **13**: 1635-1648 [PMID: 33239884 DOI: 10.2147/JMDH.S279031]

6 **Shah W**, Heightman M, O'Brien S. UK guidelines for managing long-term effects of COVID-19. *Lancet* 2021; **397**: 1706 [PMID: 33965081 DOI: 10.1016/S0140-6736(21)00847-3]

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

8 **Nabavi N**. Long covid: How to define it and how to manage it. *BMJ* 2020; **370**: m3489 [PMID: 32895219 DOI: 10.1136/bmj.m3489]

9 **Greenhalgh T**, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020; **370**: m3026 [PMID: 32784198 DOI: 10.1136/bmj.m3026]

10 **Mandal S**, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, Heightman M, Hillman TE, Jacob J, Jarvis HC, Lipman MCI, Naidu SB, Nair A, Porter JC, Tomlinson GS, Hurst JR; ARC Study Group. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2020 [PMID: 33172844 DOI: 10.1136/thoraxjnl-2020-215818]

11 **Puntmann VO**, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265-1273 [PMID: 32730619 DOI: 10.1001/jamacardio.2020.3557]

12 **Gorna R**, MacDermott N, Rayner C, O'Hara M, Evans S, Agyen L, Nutland W, Rogers N, Hastie C. Long COVID guidelines need to reflect lived experience. *Lancet* 2021; **397**: 455-457 [PMID: 33357467 DOI: 10.1016/S0140-6736(20)32705-7]

13 **Mossa-Basha M**, Meltzer CC, Kim DC, Tuite MJ, Kolli KP, Tan BS. Radiology Department Preparedness for COVID-19: *Radiology* Scientific Expert Review Panel. *Radiology* 2020; **296**: E106-E112 [PMID: 32175814 DOI: 10.1148/radiol.2020200988]

14 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? *J Ultrasound Med* 2020; **39**: 1459-1462 [PMID: 32198775 DOI: 10.1002/jum.15284]

15 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

16 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

17 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin J, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest* 2020; **158**: 106-116 [PMID: 32275978 DOI: 10.1016/j.chest.2020.04.003]

18 **Orsi MA**, Oliva AG, Cellina M. Radiology Department Preparedness for COVID-19: Facing an Unexpected Outbreak of the Disease. *Radiology* 2020; **295**: E8 [PMID: 32228364 DOI: 10.1148/radiol.2020201214]

19 **Pezzotti W**. Chest X-ray interpretation: not just black and white. *Nursing* 2014; **44**: 40-7; quiz 47-8

[PMID: 24281317 DOI: 10.1097/01.NURSE.0000438704.82227.44]

20 **Zhou S**, Chen C, Hu Y, Lv W, Ai T, Xia L. Chest CT imaging features and severity scores as biomarkers for prognostic prediction in patients with COVID-19. *Ann Transl Med* 2020; **8**: 1449 [PMID: 33313194 DOI: 10.21037/atm-20-3421]

21 **Cleverley J**, Piper J, Jones MM. The role of chest radiography in confirming covid-19 pneumonia. *BMJ* 2020; **370**: m2426 [PMID: 32675083 DOI: 10.1136/bmj.m2426]

22 **Liao X**, Wang Y, He Z, Yun Y, Hu M, Ma Z, Huang L, Cai Q, Xu L, Hao Y, Liu L. Three-month pulmonary function and radiological outcomes in COVID-19 survivors: a longitudinal patient cohort study. *Open Forum Infect Dis* 2020; ofaa540 [DOI: 10.1093/ofid/ofaa540]

23 **Jacobi A**, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. *Clin Imaging* 2020; **64**: 35-42 [PMID: 32302927 DOI: 10.1016/j.clinimag.2020.04.001]

24 **Warren MA**, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, Rice TW, Matthay MA, Calfee CS, Ware LB. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax* 2018; **73**: 840-846 [PMID: 29903755 DOI: 10.1136/thoraxjnl-2017-211280]

25 **Sun D**, Li X, Guo D, Wu L, Chen T, Fang Z, Chen L, Zeng W, Yang R. CT Quantitative Analysis and Its Relationship with Clinical Features for Assessing the Severity of Patients with COVID-19. *Korean J Radiol* 2020; **21**: 859-868 [PMID: 32524786 DOI: 10.3348/kjr.2020.0293]

26 **D'Cruz RF**, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, Patrick T, Walder D, Heitmann A, Lee K, Madula R, McNulty W, Macedo P, Lyall R, Warwick G, Galloway JB, Birring SS, Patel A, Patel I, Jolley CJ. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res* 2021; **7** [PMID: 33575312 DOI: 10.1183/23120541.00655-2020]

27 **Fang Y**, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296**: E115-E117 [PMID: 32073353 DOI: 10.1148/radiol.2020200432]

28 **Kim H**, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse Transcriptase Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. *Radiology* 2020; **296**: E145-E155 [PMID: 32301646 DOI: 10.1148/radiol.2020201343]

29 **Xie X**, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* 2020; **296**: E41-E45 [PMID: 32049601 DOI: 10.1148/radiol.2020200343]

30 **Zhao W**, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol* 2020; **214**: 1072-1077 [PMID: 32125873 DOI: 10.2214/AJR.20.22976]

31 **Jalaber C**, Lapotre T, Morcet-Delattre T, Ribet F, Jouneau S, Lederlin M. Chest CT in COVID-19 pneumonia: A review of current knowledge. *Diagn Interv Imaging* 2020; **101**: 431-437 [PMID: 32571748 DOI: 10.1016/j.diii.2020.06.001]

32 **Fred HL**. Drawbacks and limitations of computed tomography: views from a medical educator. *Tex Heart Inst J* 2004; **31**: 345-348 [PMID: 15745283]

33 **Zhao YM**, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; **25**: 100463 [PMID: 32838236 DOI: 10.1016/j.eclinm.2020.100463]

34 **Wang Y**, Dong C, Hu Y, Li C, Ren Q, Zhang X, Shi H, Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296**: E55-E64 [PMID: 32191587 DOI: 10.1148/radiol.2020200843]

35 **Tabatabaei SMH**, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? *Emerg Radiol* 2020; **27**: 711-719 [PMID: 33165674 DOI: 10.1007/s10140-020-01869-z]

36 **Wang B**, Zhang L, Zhang D, Yuan H, Wu C, Zhang Y, He L, Wang R, Wang J, Xie M. Bedside ultrasound in assessment of 510 severe and critical patients with COVID-19 pneumonia in Wuhan, China. *AUDT* 2020; **4**: 60-66 [DOI: 10.37015/AUDT.2020.200018]

37 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for International Standardization of the Use of Lung Ultrasound for Patients With COVID-19: A Simple, Quantitative, Reproducible Method. *J Ultrasound Med* 2020; **39**: 1413-1419 [PMID: 32227492 DOI: 10.1002/jum.15285]

38 **Alqahtani JS**, Oyelade T, Sreedharan J, Aldhahir AM, Alghamdi SM, Alrajeh AM, Alqahtani AS, Alsulayyim A, Aldabayan YS, Alobaidi NY, AlAhmari MD. Diagnostic and clinical values of non-cardiac ultrasound in COPD: A systematic review. *BMJ Open Respir Res* 2020; **7** [PMID: 32978244 DOI: 10.1136/bmjresp-2020-000717]

39 **Peng QY**, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; **46**: 849-850 [PMID: 32166346 DOI: 10.1007/s00134-020-05996-6]

40 **Denault AY**, Delisle S, Canty D, Royse A, Royse C, Serra XC, Gebhard CE, Couture ÉJ, Girard M, Cavayas YA, Peschanski N, Langevin S, Ouellet P. A proposed lung ultrasound and phenotypic algorithm for the care of COVID-19 patients with acute respiratory failure. *Can J Anaesth* 2020; **67**: 1393-1404 [PMID: 32440906 DOI: 10.1007/s12630-020-01704-6]

41 **Gil-Rodrigo A**, Llorens P, Martínez-Buendía C, Luque-Hernández MJ, Espinosa B, Ramos-Rincón JM. Diagnostic yield of point-of-care ultrasound imaging of the lung in patients with COVID-19. *Emergencias* 2020; **32**: 340-344 [PMID: 33006834]

42 **Rojatti M**, Regli IB, Zanforlin A, Ferretti E, Falk M, Strapazzon G, Gamper M, Zanon P, Bock M, Rauch S. Lung Ultrasound and Respiratory Pathophysiology in Mechanically Ventilated COVID-19 Patients-an Observational Trial. *SN Compr Clin Med* 2020; 1-8 [PMID: 32995708 DOI: 10.1007/s42399-020-00536-1]

43 **Tung-Chen Y**, Martí de Gracia M, Parra-Gordo ML, Díez-Tascón A, Agudo-Fernández S, Ossaba-Vélez S. Usefulness of Lung Ultrasound Follow-up in Patients Who Have Recovered From Coronavirus Disease 2019. *J Ultrasound Med* 2020 [PMID: 33159704 DOI: 10.1002/jum.15556]

44 **Zhang Y**, Xue H, Wang M, He N, Lv Z, Cui L. Lung Ultrasound Findings in Patients With Coronavirus Disease (COVID-19). *AJR Am J Roentgenol* 2021; **216**: 80-84 [PMID: 32755198 DOI: 10.2214/AJR.20.23513]

45 **Tung-Chen Y**. Lung ultrasound in the monitoring of COVID-19 infection. *Clin Med (Lond)* 2020; **20**: e62-e65 [PMID: 32398268 DOI: 10.7861/clinmed.2020-0123]

46 **Hawkes RC**, Holland GN, Moore WS, Worthington BS. Nuclear magnetic resonance (NMR) tomography of the brain: a preliminary clinical assessment with demonstration of pathology. *J Comput Assist Tomogr* 1980; **4**: 577-586 [PMID: 6967878 DOI: 10.1097/00004728-198010000-00001]

47 **Smith FW**, Hutchison JM, Mallard JR, Johnson G, Redpath TW, Selbie RD, Reid A, Smith CC. Oesophageal carcinoma demonstrated by whole-body nuclear magnetic resonance imaging. *Br Med J (Clin Res Ed)* 1981; **282**: 510-512 [PMID: 6780102 DOI: 10.1136/bmj.282.6263.510]

48 **Grover VP**, Tognarelli JM, Crossey MM, Cox IJ, Taylor-Robinson SD, McPhail MJ. Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians. *J Clin Exp Hepatol* 2015; **5**: 246-255 [PMID: 26628842 DOI: 10.1016/j.jceh.2015.08.001]

49 **Huang L**, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020; **13**: 2330-2339 [PMID: 32763118 DOI: 10.1016/j.jcmg.2020.05.004]

World Journal of Radiology

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

World J Radiol 2021 June 28; 13(6): 157-170

DOI: 10.4329/wjr.v13.i6.157

ISSN 1949-8470 (online)

MINIREVIEWS

Imaging spectrum of abdominal manifestations of COVID-19

Tanvi Vaidya, Avinash Nanivadekar, Rajan Patel

ORCID number: Tanvi Vaidya 0000-0002-6290-5628; Avinash Nanivadekar 0000-0001-5025-5157; Rajan Patel 0000-0002-6199-055X.

Author contributions: All authors have participated sufficiently in the drafting of this manuscript and take responsibility for the scientific content; Vaidya T and Nanivadekar A were involved in the study conceptualization; Vaidya T and Patel R took part in data acquisition; Patel R drafted the manuscript; Nanivadekar A designed the literature search and reviewed the manuscript; Nanivadekar A and Patel R performed final editing of the manuscript; all authors have read and approved the final manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: htt

Tanvi Vaidya, Avinash Nanivadekar, Rajan Patel, Department of Radiology, Ruby Hall Clinic, Pune 411001, Maharashtra, India

Corresponding author: Tanvi Vaidya, DNB, Attending Doctor, Department of Radiology, Ruby Hall Clinic, Sasoon Road, Pune 411001, Maharashtra, India. tanvivaidya5@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) has posed a serious threat to global public health with its rapid spread, high fatality, and severe burden on health care providers all over the world. Although COVID-19 has been established as a respiratory tract infection, it can manifest with gastrointestinal symptoms as a consequence of direct infection by the virus or due to inflammation-mediated cytotoxicity. It has been observed that COVID-19 patients presenting with gastrointestinal symptoms tend to progress to a severe form of disease with increased morbidity and mortality, thus indicating the need for timely management. COVID-19 manifests with a wide spectrum of radiologic findings on gastrointestinal tract imaging, encompassing bowel abnormalities, hepato-biliary and pancreatic involvement, vascular occlusion, and solid organ infarction. Early recognition of these imaging features can facilitate timely treatment of COVID-19 associated gastrointestinal tract complications and may prompt the diagnosis of COVID-19 in patients with atypical disease manifestations. The aim of this article is to provide an overview of the various gastrointestinal imaging manifestations that can be encountered in patients with COVID-19, with an emphasis on early diagnosis of the disease as well as treatment related complications.

Key Words: COVID-19; Imaging; Gastrointestinal; Hepato-biliary; Vascular; Thrombosis

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The gastrointestinal manifestations of coronavirus disease 2019 are being increasingly recognized. A variety of imaging features can be encountered, either due to direct infection by the virus or as a result of viral-mediated cytotoxicity and tissue damage. Imaging can play a key role in the early recognition of gastrointestinal tract involvement and its potentially fatal complications.

Citation: Vaidya T, Nanivadekar A, Patel R. Imaging spectrum of abdominal manifestations of COVID-19. *World J Radiol* 2021; 13(6): 157-170

p://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: India

Peer-review report's scientific quality classification

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

Received: February 3, 2021
Peer-review started: February 3, 2021
First decision: March 31, 2021
Revised: April 11, 2021
Accepted: May 24, 2021
Article in press: May 24, 2021
Published online: June 28, 2021

P-Reviewer: Jiang Y, Zhang L
S-Editor: Liu M
L-Editor: Wang TQ
P-Editor: Yuan YY

URL: https://www.wjgnet.com/1949-8470/full/v13/i6/157.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i6.157

INTRODUCTION

Since December 2019, the world has witnessed the emergence and unrelenting spread of coronavirus disease 2019 (COVID-19) with its devastating impact on global public health. As of February 3, 2021, there have been 103 million confirmed cases worldwide and over 2.2 million deaths[1]. Although in the majority of cases, the disease manifests with respiratory symptoms such as fever, cough, and dyspnea, its extra-pulmonary manifestations due to multi-system involvement are being increasingly recognized[2]. Particularly, the incidence of gastrointestinal (GI) manifestations such as abdominal pain, nausea, vomiting, and diarrhea has varied from 12% to as much as 61% in patients with COVID-19[3-5]. GI tract involvement in COVID-19 is believed to be a direct consequence of tissue damage mediated by the virus and additionally due to inflammation-mediated cytotoxicity[6,7]. About 10% of patients with COVID-19 could manifest only with GI symptoms without co-existing respiratory symptoms, which could result in delayed diagnosis. Moreover, COVID-19 patients presenting with GI symptoms tend to progress to a severe form of disease with poor outcomes. This subset of patients requires greater attention for early identification of complications[5].

The pulmonary imaging features of COVID-19 have been extensively described in the literature, an understanding of which has provided a greater insight into the pathophysiology of the disease. In comparison, there is a paucity of literature with respect to the various GI imaging manifestations of COVID-19. Considering the high likelihood of GI tract involvement in COVID-19, it is becoming increasingly important for radiologists to be aware of the variety of abdominal imaging findings in patients with COVID-19. Early recognition of these features can facilitate timely management of COVID-19 associated complications as well as alert the treating physician to consider a diagnosis of COVID-19 in patients presenting with atypical symptoms. Moreover, knowledge of these imaging findings may enhance our understanding of the pathophysiology of GI phenomena in the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

The aim of this article is to share our experience with the spectrum of GI manifestations that can be encountered in patients with COVID-19.

METHODOLOGY OF LITERATURE SEARCH

We performed a systematic review of the literature, in order to identify all published articles on patients with abdominal manifestations due to COVID-19. We conducted literature searches in PubMed/MEDLINE, EMBASE, and Google Scholar bibliographic databases, spanning the years 2019 to 2021. The keywords "abdominal", "COVID-19", "imaging", and "radiology" were used in all possible combinations. We also performed specific searches pertaining to involvement of particular organs/systems, using keywords such as "colonic", "small bowel", "pancreas", "gall bladder", and "renal" in combination with "COVID-19" and "imaging". Additionally, since thrombotic events are recognized as a major complication of the infection, we also searched for the literature pertaining to these, in the context of GI involvement, using the keywords "thrombosis", "abdomen", "imaging", "infarction", "gangrene", and "COVID-19" in various combinations. Moreover, the reference lists of all relevant publications were reviewed for additional articles.

All publications pertinent to our research subject such as scientific studies, review articles, case series, and case reports were included in our literature search. These were carefully evaluated by two of the authors, to identify the relevant radiologic findings in these cases for inclusion in our literature review. Articles without full-text availability and those without details of radiologic evaluation were excluded.

With regards to our experience, considering this was an in-between pandemic, single-centre, imaging review of the GI manifestations of COVID-19 infection, we had a small cohort of patients under investigation. As compared to the large sample of COVID-19 RT-PCR positive patients presenting with respiratory complaints, fewer COVID-19 cases presented with GI symptoms. This small cohort was investigated by means of imaging and biochemical tests and appropriate treatment was instituted. The

data pertaining to this particular cohort was retrieved from the patient database and was studied retrospectively. The imaging studies for each of these cases were reviewed. The relevant radiologic findings and clinical details were compiled for the purpose of this review. This review article is thus, based on our experience in a COVID centre as well as that of other researchers, elucidated by means of scientific studies and case reports. Based on all of these observations, we recommend a large-scale multicentre study based on a bigger sample size, to ascertain the statistical significance of our findings and to understand whether GI affection constitutes a statistically significant percentage in patients with COVID-19.

We will review the GI imaging manifestations of COVID-19 under the following sub-headings: Small and large bowel abnormalities; vascular occlusion and solid organ infarction; hepato-biliary involvement; pancreatic involvement; and bleeding complications.

SMALL AND LARGE BOWEL ABNORMALITIES

Large bowel thickening/colitis

The occurrence of GI symptoms in a COVID-19 patient, such as diarrhoea, hematochezia, or abdominal pain, may warrant a computed tomography (CT) evaluation for GI tract assessment. Various mechanisms have been implicated in GI tract involvement by the SARS-CoV-2[8]. Direct infection of the GI tract epithelial cells by binding to the angiotensin-converting enzyme-2 (ACE-2) surface receptors followed by viral replication and cell destruction and alternatively, cell injury resulting from an inflammatory response to the virus-infected cells could account for the GI manifestations of COVID-19[9,10]. A few cases of large bowel infection with SARS-CoV-2 have been reported, which on imaging, manifest with diffuse, circumferential, homogeneously enhancing bowel wall thickening in a variable distribution[11,12]. The wall thickening may involve one or more segments of the colon. In our experience and as described by other researchers, the bowel wall thickening is not associated with pericolic lymphadenopathy, pneumatosis, or ileus. In our institute, we encountered a patient with bloody diarrhea in whom contrast-enhanced CT (CECT) revealed homogeneously enhancing wall thickening involving the sigmoid colon (Figure 1). Owing to the rarity of isolated viral colitis, it is important to exclude signs of ischemia such as decreased/ absent wall enhancement, poor opacification of the mesenteric vascular arcade, and filling defects suggestive of thrombi in the abdominal arteries, so as to enable early identification of ischemic colitis. The absence of classical imaging features of inflammatory bowel disease like the "comb" sign, mural stratification, fibrofatty proliferation could prompt the consideration of infection as a probable cause of colitis[13]. The detection of SARS-CoV-2 RNA in the stool may conclusively establish the diagnosis. Colonoscopy is generally not indicated in uncomplicated infectious colitis, unless the patient presents with unusual manifestations such as severe GI bleeding[14].

Acute mesenteric ischemia and enteric perforation

Patients with COVID-19 presenting with severe GI symptoms associated with abdominal distention, decreased bowel sounds, or worsening systemic status should alert the treating physician to the possibility of acute mesenteric ischemia, a potentially fatal complication of the disease[15]. Ischemia may occur as a result of hypercoagulability as a consequence of systemic inflammation, elevation of von Willebrand Factor levels secondary to endothelial damage induced by viral binding to ACE-2 surface receptors, or direct insult to enterocytes by the coronavirus itself[16,17]. An increase in D-dimer and lactate levels in the blood could indicate an ischemic complication, but these lack specificity[18]. Radiologic evaluation has a crucial role in the timely detection of acute mesenteric ischemia (AMI) and is the cornerstone of diagnosis. Abdominal radiography has a limited role in the evaluation of bowel ischemia, owing to its low sensitivity and specificity[19]. Ultrasonography (US), despite its ready availability and absence of radiation exposure, is also relatively non-specific for the diagnosis. Screening US may reveal decreased peristalsis, inter-bowel fluid, and/or excessive intra-luminal contents indicating stasis. However, its utility is limited if the patient is obese or has pneumoperitoneum or an excessive amount of bowel gas[20]. Moreover, these findings lack sensitivity and specificity for the diagnosis.

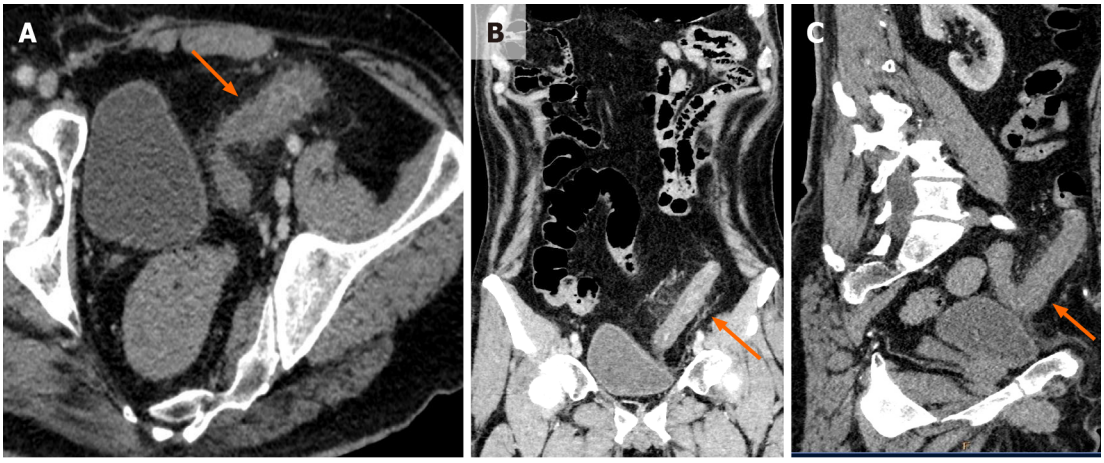


Figure 1 Contrast enhanced computed tomography imaging in a patient with coronavirus disease 2019 presenting with bloody diarrhea. A: Axial; B: Coronal; C: Sagittal. Contrast enhanced computed tomography images of the abdomen and pelvis show diffuse edematous wall thickening involving the sigmoid colon (orange arrows in A, B, and C). Associated pericolic fat stranding is seen. In the absence of other causes of bowel wall thickening, a diagnosis of viral colitis was considered.

Computed tomography angiography remains the mainstay for definitive diagnosis of AMI[21]. Thrombi or emboli manifest as filling defects within the lumen of the abdominal aorta and its branches, namely, the celiac axis, superior mesenteric artery (SMA), and inferior mesenteric artery. Poor contrast opacification of the mesenteric vascular arcade on angiography images is indicative of hypoperfusion[22]. In our experience, this finding is well seen on maximum intensity projection (MIP) coronal images (Figure 2). Accordingly, the segment of the injured small bowel reveals wall thickening secondary to mural edema; this is the most frequently observed CT finding in AMI[23]. A very specific finding for AMI is absent or decreased contrast enhancement of the bowel wall. A target appearance of the bowel wall, representing mucosal hyperemia with surrounding mural edema, can be seen in ischemic colitis and after reperfusion following arterial occlusion. Disruption of normal bowel peristalsis leads to dilatation of the bowel lumen (> 3 cm); the dilated bowel may contain fluid, air, or both. In the late phase, thinning of the bowel wall is evident; the wall may not be discernible in some segments, thus appearing "paper thin" and featureless due to loss of normal tone. Eventually, transmural infarction leads to pneumatosis intestinalis/air in the bowel wall, followed by porto-mesenteric venous gas, pneumoperitoneum, and free fluid in the peritoneal cavity, due to extravasation of intra-luminal fluid and as a result of the peritoneal reaction to the bowel ischemia[24].

Various investigators have reported AMI in critically ill patients with COVID-19, and the vast majority of patients were diagnosed in the late phase of AMI manifesting with frank perforation and pneumoperitoneum[25-29].

We encountered two cases of AMI as a complication of COVID-19 in our practice. Both patients were being treated for severe viral pneumonia in the intensive care unit. During the course of their treatment, they presented with abdominal distension, vomiting, and intractable abdominal pain. Clinical examination revealed diffuse abdominal tenderness, hypotension, and tachycardia, prompting the need for urgent imaging. On CT imaging, our first patient presented with frank jejunal perforation with pneumoperitoneum (Figure 3), thus requiring emergent laparotomy. In the second case, CT angiography revealed absent mural enhancement of distal ileal loops with barely discernible walls, suggestive of bowel gangrene (Figure 4). The proximal small bowel loops appeared dilated with air-fluid levels within. Thrombotic macrovascular arterial occlusion was detected in the form of non-opacification of the ileocolic branches of the SMA (Figure 2). Consequently, superior mesenteric artery thrombectomy with resection of the gangrenous bowel was performed. Both patients required prolonged supportive care but survived. Based on this experience, we believe that a high index of suspicion for AMI accompanied by prompt imaging play a key role in decreasing morbidity and mortality. Owing to the high mortality rate in the event of this devastating complication, a thorough understanding of the pathophysiology and clinical presentation of AMI as well as familiarity with the imaging features is of utmost importance to make a timely diagnosis so as to decrease morbidity and mortality.

THROMBO-EMBOLIC PHENOMENA AND SOLID ORGAN INFARCTION

Over the past couple of months, an increasing number of reports have emerged highlighting the high incidence of thrombotic events in patients with coronavirus disease[30,31]. The state of hypercoagulability occurring in COVID-19 patients is believed to be mediated by a combination of inflammation, endothelial damage, and/or vascular injury[6]. Considering the likelihood of pro-thrombotic complications, it is justifiable to perform a contrast enhanced CT scan of the thorax and the abdomen, including the arterial and venous phases, in case of suspected pulmonary embolism or patients presenting with unexplained abdominal pain[32]. Many venous thromboembolic events have been documented in association with COVID-19 (Figure 5), whereas arterial thrombosis has been described in relatively fewer cases and could possibly be underestimated[33]. COVID-19 associated arterial thrombosis has been frequently observed in non-atherosclerotic vessels on CT imaging[34], suggesting that patients with a severe inflammatory reaction as indicated by elevation of D-dimer, fibrin degradation products, and platelet count coupled with decreased antithrombin values are at greater risk for thrombo-embolic phenomena[35].

Solid organ infarction in COVID-19 could either be incidentally detected on CT imaging or could manifest with abdominal pain or features of organ dysfunction. Few reports of COVID-19 associated renal infarction have emerged; some of these manifesting with acute kidney injury. CECT that includes the arterial and venous phases is the study of choice for the recognition of kidney infarction. Ultrasound of the kidneys has a limited role in the detection of infarction due to its lower sensitivity and specificity[36].

Renal infarcts are well demonstrated preferably in the arterial phase; they manifest as solitary or multiple, discrete, wedge-shaped parenchymal defects involving both the cortex and medulla, with the apex pointing toward the medulla and base parallel to the subcapsular region[37,38] (Figure 6). A subcapsular enhancing cortical rim may be visualized a few days later, reflecting perfusion of capsular collaterals. In case of total renal infarction, CT demonstrates a non-enhancing kidney with non-opacification of the collecting system in the excretory phase. CT angiography may demonstrate filling defects in the aorta or the renal arterial vasculature suggestive of thrombi; however, these may not always be evident due to the occurrence of microthrombi, which may remain occult on imaging[39,40]. The presence of microthrombi in this setting has been previously documented on histopathologic evaluation of the glomerular capillaries of the infarcted parenchyma[41].

Reports of splenic infarction in COVID-19 are scarce in the published literature, since these are usually detected incidentally on chest CECT scans that extend to the upper abdomen[42]. These are usually silent but may occasionally manifest with left upper quadrant pain and abdominal guarding. CT imaging reveals sharply marginated, wedge shaped, hypodense areas with absent post contrast enhancement; these are well depicted in the porto-venous phase. Global splenic infarction appears as hypo/non enhancement of the entire parenchyma[43] (Figure 7). CT angiography may demonstrate filling defects in the splenic artery or its hilar branches, representing thrombi.

In our experience, solid organ infarction was always incidentally detected during imaging performed for suspected pulmonary thromboembolism, particularly in association with raised D-dimer levels. Thus, a combination of relevant serum biomarkers and judicious use of imaging, particularly contrast enhanced CT scans, plays a crucial role in the detection of COVID-19-related coagulopathy, thereby facilitating timely management to reduce morbidity and mortality.

HEPATO-BILIARY INVOLVEMENT

The association of hepato-biliary dysfunction with COVID-19 is being increasingly recognized[44]. As many as 40% of COVID-positive patients are found to have abnormal liver function tests (LFTs) on admission, suggesting hepatocyte injury either due to a severe inflammatory response or possibly as a result of ACE-2-mediated viral infection of hepatocytes[45].

Very few studies have investigated the role of abdominal imaging in the evaluation of COVID-19 related hepato-biliary dysfunction. The predominant abnormalities seen in these studies on CT/US imaging were distension of the gallbladder and gallbladder sludge (Figure 8), which are indicative of cholestasis[46-48]. Additional imaging features such as gallbladder wall thickening/mural edema were detected in fewer

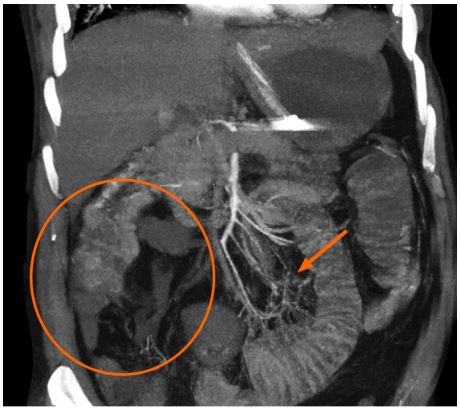


Figure 2 Acute mesenteric ischemia diagnosed on computed tomography mesenteric angiography performed in a critical patient with coronavirus disease 2019 presenting with severe abdominal pain. The coronal maximum intensity projection image reveals a lack of opacification of the right sided branches of the superior mesenteric artery (SMA), namely, the ileo-colic and right colic branches (orange circle). The distal branches of the SMA also appear hypoperfused (orange arrow). Imaging features are consistent with SMA thrombosis.

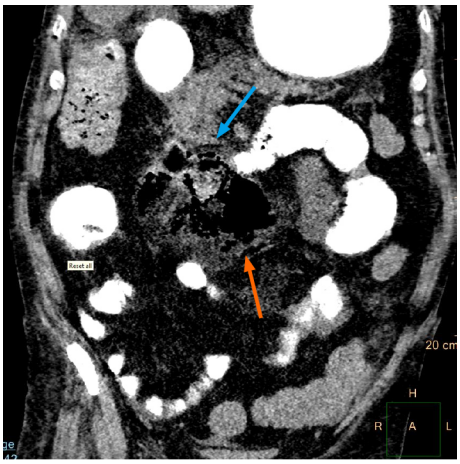


Figure 3 Bowel perforation detected on a computed tomography scan of the abdomen and pelvis performed for evaluation of severe abdominal pain and abdominal distension in a critical patient with coronavirus disease 2019. Positive oral contrast is seen to opacify small and large bowel loops. There is evidence of jejunal perforation with a localized air collection in the mesentery (orange arrow) at the site and adjacent inflammation (blue arrow). The proximal jejunal loops appear dilated. The patient underwent emergency laparotomy with resection and anastomosis.

cases. Since these findings are commonly seen in acute hepatitis, they may serve as a useful clue to indicate hepatocellular dysfunction; however, further research is essential to establish the true significance of these observations.

Hepatomegaly with increased parenchymal echogenicity is reported to be the most commonly encountered liver abnormality on abdominal US, possibly indicative of a diffuse parenchymal disease[46-48]. These findings may also be seen in COVID-19 patients with obesity and non-alcoholic fatty liver disease, which serve as potential risk factors for the increase in COVID-19 disease severity[49].

We did not encounter cases of isolated hepato-biliary involvement in COVID-19. However, we did observe increased severity of infection in patients with pre-existing chronic liver parenchymal disease, detected on imaging. The majority of patients presenting with deranged LFTs had no significant abnormality on screening abdominal US, while a small proportion of patients were found to have diffusely increased hepatic echogenicity. This subgroup of patients had associated co-morbidities such as obesity and type 2 diabetes mellitus, thus the US findings were highly suggestive of hepatic steatosis in the given setting. The definite imaging features on US indicating hepatic involvement in COVID-19 have not been ascertained so far.

PANCREATIC INVOLVEMENT

Viral pancreatitis is a well-known clinical entity. Although an accurate understanding of the spectrum of pancreatic injury is not established at present, recent reports have emerged highlighting acute pancreatitis (AP) as a possible manifestation of COVID-19

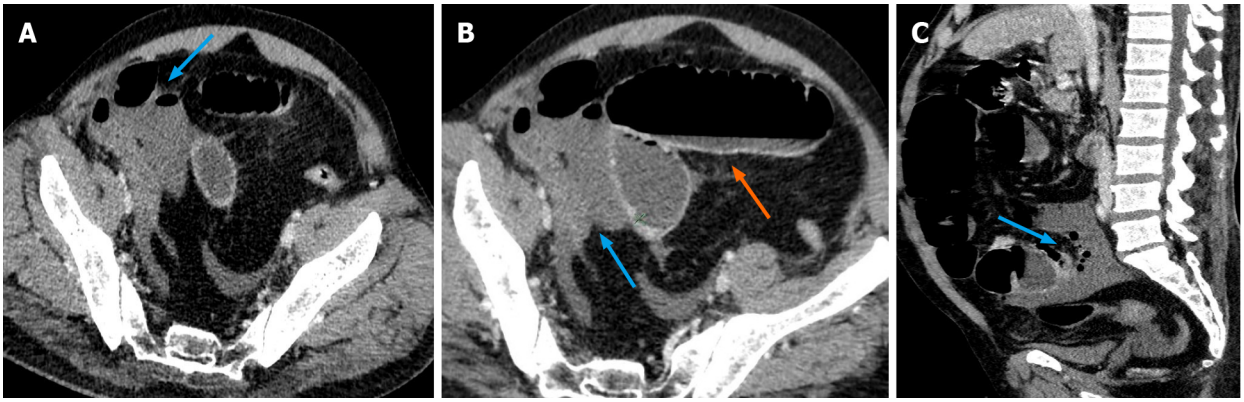


Figure 4 Small bowel ischemia detected on computed tomography mesenteric angiography study performed in a coronavirus disease 2019 patient presenting with severe abdominal pain and abdominal distension. A and B: Axial contrast enhanced computed tomography (CT) images of the abdomen and pelvis; C: Sagittal contrast enhanced CT images of the abdomen and pelvis, showing dilated distal ileal loops in the right iliac fossa with non-enhancing, barely discernible walls suggestive of bowel gangrene (blue arrows in A, B, and C). The proximal small bowel loops appear dilated with air-fluid levels within, suggestive of stasis (orange arrow in B).

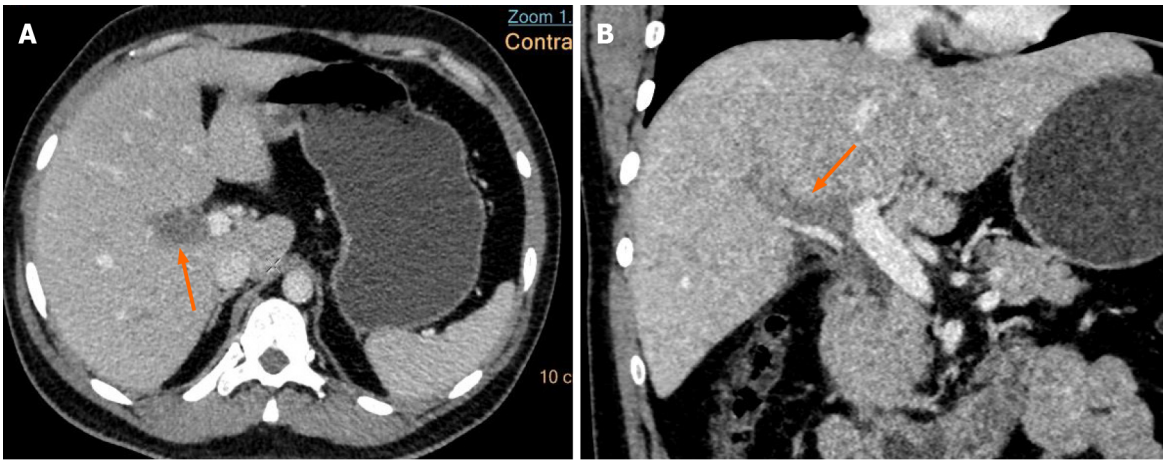


Figure 5 Venous thrombosis diagnosed in a coronavirus disease 2019 patient presenting with abdominal pain. A: Axial; B: Coronal. Contrast enhanced computed tomography (CT) images of the abdomen show a hypodense filling defect in the main portal vein at the hilum extending into the right branch (orange arrows in A and B), suggestive of portal vein thrombosis. There were no features of mesenteric ischemia seen on the CT.

[50-52]. COVID-19 induced pancreatic injury is believed to be a consequence of SARS-CoV-2 cytotoxicity mediated by viral binding to ACE-2 receptors expressed on pancreatic islet cells or possibly due to the severe immune response triggered by viral infection[53].

The initial diagnosis for AP is usually based on clinical parameters that include signs and symptoms of acute abdomen associated with an elevation of serum pancreatic enzymes, such as amylase and lipase; however, imaging plays a valuable role in aiding the diagnosis whenever the clinical presentation is unclear. Moreover, imaging is essential for diagnosing the etiology, staging disease severity, and evaluating complications[54,55]. Various researchers have elucidated the imaging features of COVID-induced AP based on isolated cases encountered by them in practice. Radiologically, it appears to be a mild form of disease, also termed as interstitial/edematous pancreatitis, with CT imaging features ranging from a normal-appearing pancreas and peripancreatic soft tissues to diffuse enlargement coupled with heterogeneous enhancement of the parenchyma with ill-defined or fuzzy borders. Peripancreatic inflammation appears as hazy stranding of the surrounding fat and streak of fluid along the anterior conal fascia and in the retro-mesenteric plane (Figure 9). To the best of our knowledge, no case of necrotizing pancreatitis in the setting of COVID-19 has been reported so far. Considering the possible occurrence of mild pancreatic injury in patients with COVID-19 pneumonia, it may be prudent to evaluate pancreatic enzymes in patients presenting with GI symptoms[56]. CT imaging could be used in conjunction with the clinical parameters in order to establish

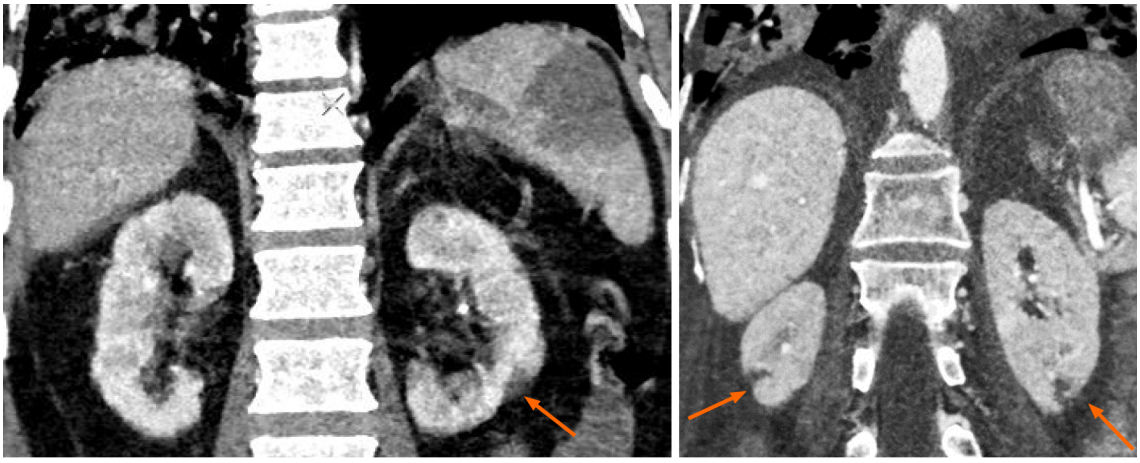


Figure 6 Solid organ infarction in a patient with coronavirus disease 2019. Coronal contrast enhanced computed tomography (CT) images of the abdomen show discrete, wedge-shaped non-enhancing renal parenchymal defects, with their apex pointing towards the medulla and base parallel to the subcapsular region (orange arrows), suggestive of renal infarcts. These were incidentally detected during CT pulmonary angiography.

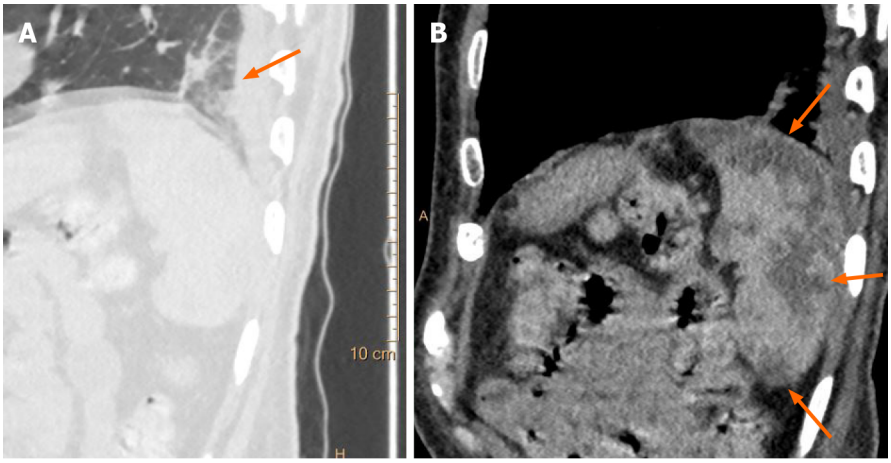


Figure 7 Incidentally detected splenic infarction in a patient with coronavirus disease 2019. A: Sagittal chest computed tomography (CT) image shows subpleural ground glass opacities in the lung fields in a case of coronavirus disease 2019 (orange arrow); B: Sagittal contrast enhanced CT image of the abdomen in the same patient show incidentally detected, sharply marginated, wedge shaped, hypodense areas in the spleen, suggestive of splenic infarcts (orange arrows).

a correct diagnosis or provide an alternative diagnosis when in doubt. In the absence of other etiologies like gallstones, trauma, alcohol, or drug intake, viral infection can be considered as the causative factor for pancreatitis in patients with COVID-19.

BLEEDING MANIFESTATIONS

Clinicians involved in the treatment of COVID-19 are familiar with the high tendency to develop a hypercoagulable state in patients with a severe form of the illness. The acute thrombotic complications in critically ill patients affecting different organ systems are being increasingly recognized by imaging[18]. However, there is a paucity of literature with respect to the occurrence of bleeding events in COVID-19, either as a result of coagulopathy or secondary to anti-coagulation therapies[57]. The increased risk of bleeding in COVID-19 patients is believed to result from an imbalance between production and destruction of platelets secondary to infection[58]. More importantly, the possibility of bleeding complications is increased by the use of therapeutic/prophylactic anticoagulation to combat the COVID-19 associated hypercoagulable state, as evidenced by elevated D-dimer levels[59]. A sudden drop in the hemoglobin level coupled with features of hypovolemia such as hypotension and tachycardia serves as clinical indicators for the development of major bleeding and warrants CT imaging to identify the site of bleed[60]. The majority of researchers, including us,

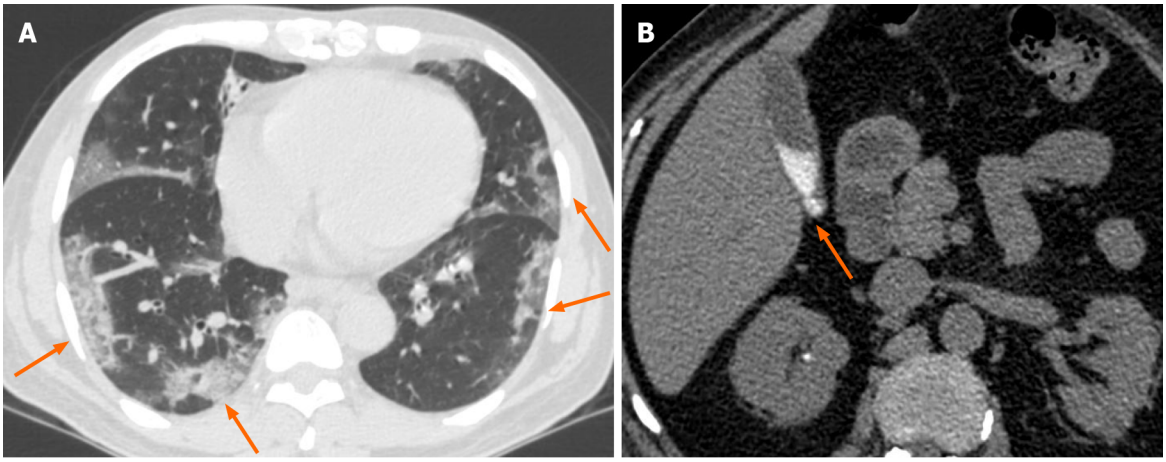


Figure 8 Evidence of cholestasis in a critically ill coronavirus disease 2019 patient. A: Axial chest computed tomography (CT) image shows multiple peripheral ground glass opacities associated with interstitial thickening in both lung fields (orange arrows in A); B: Axial non-contrast CT image of the abdomen shows incidentally detected hyperdense sludge within the gall bladder lumen (orange arrow in B), suggesting cholestasis.

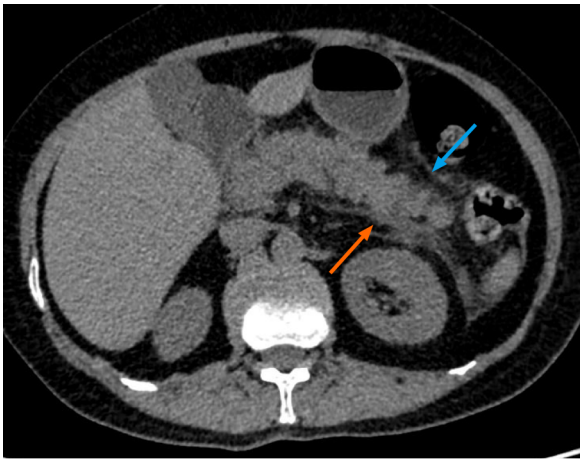


Figure 9 Acute viral pancreatitis in a coronavirus disease 2019 patient presenting with abdominal pain. Non-contrast axial computed tomography image of the abdomen in a case of suspected viral pancreatitis (intravenous contrast could not be administered due to a history of renal parenchymal disease with elevated creatinine) is shown. The distal body and tail of pancreas reveal fuzzy margins with peri-pancreatic fat stranding (blue arrow). Thickening of the left anterior conal fascia is noted with a streak of fluid in the left retro-mesenteric plane (orange arrow). Elevated serum amylase and lipase levels, in conjunction with these imaging findings, were highly suggestive of a diagnosis of acute viral pancreatitis in a patient with coronavirus disease 2019 presenting with abdominal pain.

have encountered abdominal hematomas as the most bleeding manifestation in critically ill COVID-19 patients, of these the ilio-psoas compartment appears to be the most frequent site of bleeding[61-64]. Non-contrast CT scans in these cases reveal diffuse enlargement of the ilio-psoas compartment with a hyperdense intra-muscular collection (Figure 10); sometimes a blood-fluid level may be noted within it, indicative of active bleeding. CT angiography may provide confirmatory evidence of active bleeding, presenting as a blush or extravasation of intravenously administered contrast seen in the arterial phase; this finding would necessitate immediate treatment [65]. Digital subtraction angiography may then be performed to identify the bleeding vessels followed by selective transarterial embolization. In the absence of radiologic evidence of active bleeding or hemodynamic instability, conservative treatment may be instituted[66]. In our experience, minimally invasive intervention in the form of pigtail catheter insertion is useful for drainage of large hematomas; this offers symptomatic relief by decompression of adjacent structures.

Abdominal manifestations of COVID-19: Roadmap for future research

A limitation that we encountered while working on this review was that our work was based primarily on observations and experiences in a single tertiary care institute. Moreover, obtaining the relevant literature pertaining to imaging of abdominal complications of COVID-19 was an uphill task owing to the paucity of studies with

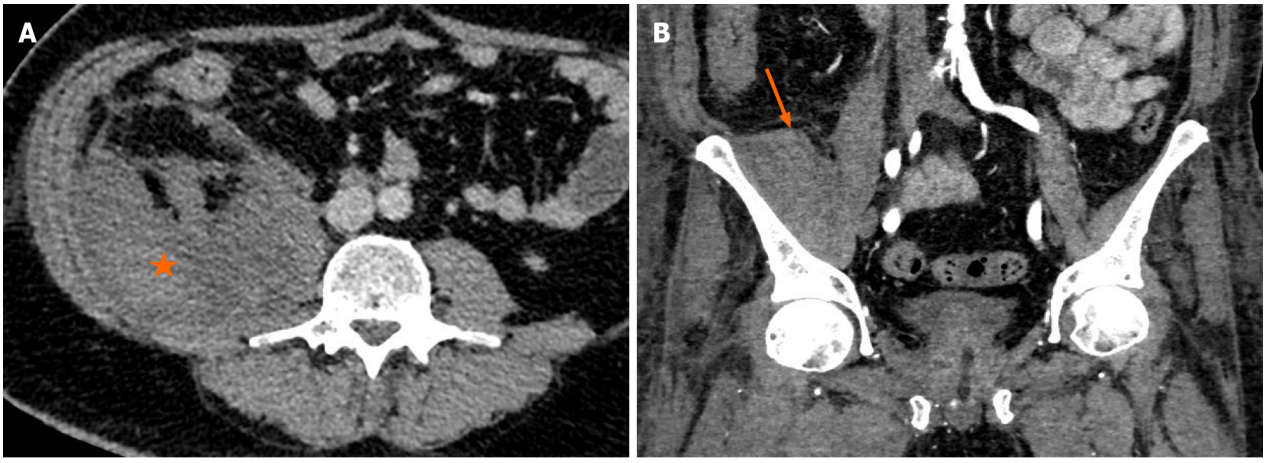


Figure 10 Bleeding manifestations encountered in treated cases of coronavirus disease 2019. A: Contrast enhanced axial computed tomography (CT) image of the abdomen shows a hyperdense collection in the right ilio-psoas compartment (orange asterisk in A), suggestive of a hematoma; B: Contrast enhanced coronal CT image of the abdomen shows a hyperdense collection in the right iliacus muscle (orange arrow in B) in another patient. Both patients were being treated with anticoagulants for coronavirus disease 2019 associated hypercoagulable state evidenced by elevated D-dimer levels. CT imaging was performed to evaluate the cause of a sudden fall in hemoglobin.

large sample sizes with particular focus on imaging. Thus, with regards to future research, we believe that a multi-centre collaboration can result in higher rates of patient enrolment than single-centre studies, thereby generating a larger data pool and bigger sample sizes, in a shorter duration, in order to investigate the research question of interest. In this manner, it is possible to obtain statistically significant results which can be representative of the whole population, thereby leading to more accurate insights into the pathophysiology and imaging findings of GI tract involvement in COVID-19, and enable researchers to draw evidence-based conclusions.

Another advantage of multi-centre studies is that owing to the heterogeneity of available data, it may be possible to understand the chronology or temporal evolution of the abdominal imaging manifestations of COVID-19, as findings may vary depending on the timing of imaging during the course of infection. These results could aid our understanding of the timelines for the various abdominal complications in COVID-19, based on which standardized protocols can be developed to guide clinicians regarding the clinical red flags and worrisome biochemical parameters that require close attention in a COVID-19 patient presenting with GI symptoms, the indications and timing of abdominal imaging in COVID-19, the choice of imaging modality, particular imaging findings that need evaluation, and appropriate interventions for each complication. The formulation of standardized protocols for diagnosis and treatment could play a major role in the timely identification and management of devastating GI complications associated with COVID-19.

Artificial intelligence: Future directions and potential role in the COVID-19 era

Artificial intelligence (AI) based on radiologic evaluation appears to have a promising role in the diagnosis, severity assessment, and prognosis of COVID-19 pneumonia. Several researchers have demonstrated the utility of AI algorithms, particularly deep learning techniques, in the diagnosis of COVID-19 pneumonia based on chest CT images, differentiation of COVID-19 pneumonia from other non-COVID pneumonias, and quantification of the extent of lung parenchymal involvement using segmentation masks[67-69].

With increasing awareness and recognition of the extra-pulmonary manifestations of COVID-19, particularly the thrombotic complications, the corresponding imaging findings could also serve as appropriate targets for AI systems[67]. A subtype of the deep learning technology, namely, convolutional neural networks, has generated great interest amongst the radiology community owing to their varied applications[70] and could have a potential role in the detection of extra-pulmonary thrombotic complications of COVID-19 such as multi-organ infarction and arterial and venous thrombi on CT imaging. This technique of machine learning, however, would require the availability of large amounts of input data for adequate 'training'. Typical data sets required for training could range from hundreds to thousands of patient's scans. The data also needs accurate labels/annotations, which could be binary, meaning whether a study is positive or negative for COVID-19, or using segmentation labels to identify

the extent of the abnormality. Training data sets may also be augmented further with the addition of clinical data, vital parameters, and blood test values. Moreover, it is advisable to include external test data sets of patients from a different demographic from the one used for training, so as to ascertain if the AI algorithm can be applied to various patient populations. Thus, multi-institutional collaboration and global data sharing are a must to generate data sets satisfactory for machine learning[70,71]. The availability of high-quality data sets of thrombotic complications in COVID-19 patients, detected on CT angiography images, could be used to develop innovative machine learning models for detection and quantification of extra-pulmonary disease severity. Thus, AI could certainly serve as a valuable tool to triage COVID-19 patients presenting to the emergency department, reduce radiologist workload, improve diagnostic accuracy, and facilitate prognostication and management decisions[72].

CONCLUSION

To conclude, GI manifestations of COVID-19 can present at the time of diagnosis or can occur anytime during the course of disease; this may necessitate imaging especially in critically ill patients. Hypercoagulability is one of the hallmarks of COVID-19, with multi-systemic implications. Our experience suggests that a high index of suspicion for abdominal visceral infarction and bowel ischemia should be maintained in COVID-19 patients presenting with severe GI symptoms. Timely imaging with CT angiography in these patients with clinical and biochemical markers of ischemia could play a major role in decreasing mortality. In patients with abdominal pain, CT imaging can also aid the diagnosis of viral-mediated inflammation of abdominal viscera, such as colitis and pancreatitis, thereby guiding appropriate management. With regards to treatment-related complications, prompt radiological investigations, such as non-contrast CT scans, are crucial for the diagnosis of occult bleeding associated with anticoagulant therapy in COVID-19 patients presenting with hypovolemia. Thus, in this COVID-19 era, radiologists could play a pivotal role in the detection of various GI tract abnormalities associated with the infection and in the timely recognition of thrombotic and treatment-related complications. An awareness of the COVID-19 associated abdominal imaging manifestations can enable radiologists to guide treating physicians for optimal disease management.

REFERENCES

1 **World Health Organization**. Coronavirus disease 2019 (COVID-19) Situation Report – 94. 2020 Apr 23 [cited 3 February 2021]. In: World Health Organization [Internet]. Available from: https://reliefweb.int/report/world/coronavirus-disease-2019-covid-19-situation-report-94-23-april-2020

2 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]

3 **Tian Y**, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther* 2020; **51**: 843-851 [PMID: 32222988 DOI: 10.1111/apt.15731]

4 **Redd WD**, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, Shen L, Chan WW. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. *Gastroenterology* 2020; **159**: 765-767.e2 [PMID: 32333911 DOI: 10.1053/j.gastro.2020.04.045]

5 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]

6 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

7 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

8 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms

in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]

9 **Patel KP**, Patel PA, Vunnam RR, Hewlett AT, Jain R, Jing R, Vunnam SR. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. *J Clin Virol* 2020; **128**: 104386 [PMID: 32388469 DOI: 10.1016/j.jcv.2020.104386]

10 **Xiao F**, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020; **158**: 1831-1833.e3 [PMID: 32142773 DOI: 10.1053/j.gastro.2020.02.055]

11 **Carvalho A**, Alqusairi R, Adams A, Paul M, Kothari N, Peters S, DeBenedet AT. SARS-CoV-2 Gastrointestinal Infection Causing Hemorrhagic Colitis: Implications for Detection and Transmission of COVID-19 Disease. *Am J Gastroenterol* 2020; **115**: 942-946 [PMID: 32496741 DOI: 10.14309/ajg.0000000000000667]

12 **Sattar Y**, Connerney M, Rauf H, Saini M, Ullah W, Mamtani S, Syed U, Luddington S, Walfish A. Three Cases of COVID-19 Disease With Colonic Manifestations. *Am J Gastroenterol* 2020; **115**: 948-950 [PMID: 32427677 DOI: 10.14309/ajg.0000000000000692]

13 **Childers BC**, Cater SW, Horton KM, Fishman EK, Johnson PT. CT Evaluation of Acute Enteritis and Colitis: Is It Infectious, Inflammatory, or Ischemic? *Radiographics* 2015; **35**: 1940-1941 [PMID: 26562230 DOI: 10.1148/rg.2015150125]

14 **Tse F**, Borgaonkar M, Leontiadis GI. COVID-19: Advice from the Canadian Association of Gastroenterology for Endoscopy Facilities, as of March 16, 2020. *J Can Assoc Gastroenterol* 2020; **3**: 147-149 [PMID: 32395690 DOI: 10.1093/jcag/gwaa012]

15 **Parry AH**, Wani AH, Yaseen M. Acute Mesenteric Ischemia in Severe Coronavirus-19 (COVID-19): Possible Mechanisms and Diagnostic Pathway. *Acad Radiol* 2020; **27**: 1190 [PMID: 32475635 DOI: 10.1016/j.acra.2020.05.016]

16 **Lodigiani C**, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT, Barco S; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020; **191**: 9-14 [PMID: 32353746 DOI: 10.1016/j.thromres.2020.04.024]

17 **Escher R**, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. *Thromb Res* 2020; **190**: 62 [PMID: 32305740 DOI: 10.1016/j.thromres.2020.04.014]

18 **Klok FA**, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; **191**: 145-147 [PMID: 32291094 DOI: 10.1016/j.thromres.2020.04.013]

19 **Stoker J**, van Randen A, Laméris W, Boermeester MA. Imaging patients with acute abdominal pain. *Radiology* 2009; **253**: 31-46 [PMID: 19789254 DOI: 10.1148/radiol.2531090302]

20 **Reginelli A**, Genovese E, Cappabianca S, Iacobellis F, Berritto D, Fonio P, Coppolino F, Grassi R. Intestinal Ischemia: US-CT findings correlations. *Crit Ultrasound J* 2013; **5** Suppl 1: S7 [PMID: 23902826 DOI: 10.1186/2036-7902-5-S1-S7]

21 **Furukawa A**, Kanasaki S, Kono N, Wakamiya M, Tanaka T, Takahashi M, Murata K. CT diagnosis of acute mesenteric ischemia from various causes. *AJR Am J Roentgenol* 2009; **192**: 408-416 [PMID: 19155403 DOI: 10.2214/AJR.08.1138]

22 **Klein HM**, Lensing R, Klosterhalfen B, Töns C, Günther RW. Diagnostic imaging of mesenteric infarction. *Radiology* 1995; **197**: 79-82 [PMID: 7568858 DOI: 10.1148/radiology.197.1.7568858]

23 **Taourel PG**, Deneuville M, Pradel JA, Régent D, Bruel JM. Acute mesenteric ischemia: diagnosis with contrast-enhanced CT. *Radiology* 1996; **199**: 632-636 [PMID: 8637978 DOI: 10.1148/radiology.199.3.8637978]

24 **Chou CK**, Mak CW, Tzeng WS, Chang JM. CT of small bowel ischemia. *Abdom Imaging* 2004; **29**: 18-22 [PMID: 15160748 DOI: 10.1007/s00261-003-0073-3]

25 **Corrêa Neto IJ**, Viana KF, Silva MB, Silva LM, Oliveira GD, Cecchini AR, Rolim AS, Robles L. Perforated acute abdomen in a patient with COVID-19: an atypical manifestation of the disease. *J Coloproctology* 2020; **40**: 269-272 [DOI: 10.1016/j.jcol.2020.05.011]

26 **Kangas-Dick A**, Prien C, Rojas K, Pu Q, Hamshow M, Wan E, Chawla K, Wiesel O. Gastrointestinal perforation in a critically ill patient with COVID-19 pneumonia. *SAGE Open Med Case Rep* 2020; **8**: 2050313X20940570 [PMID: 32728444 DOI: 10.1177/2050313X20940570]

27 **De Nardi P**, Parolini DC, Ripa M, Racca S, Rosati R. Bowel perforation in a Covid-19 patient: case report. *Int J Colorectal Dis* 2020; **35**: 1797-1800 [PMID: 32458395 DOI: 10.1007/s00384-020-03627-6]

28 **de Barry O**, Mekki A, Diffre C, Seror M, El Hajjam M, Carlier RY. Arterial and venous abdominal thrombosis in a 79-year-old woman with COVID-19 pneumonia. *Radiol Case Rep* 2020; **15**: 1054-1057 [PMID: 32351657 DOI: 10.1016/j.radcr.2020.04.055]

29 **Farina D**, Rondi P, Botturi E, Renzulli M, Borghesi A, Guelfi D, Ravanelli M. Gastrointestinal: Bowel ischemia in a suspected coronavirus disease (COVID-19) patient. *J Gastroenterol Hepatol* 2021; **36**: 41 [PMID: 32450607 DOI: 10.1111/jgh.15094]

30 **Helms J**, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study.

Intensive Care Med 2020; **46**: 1089-1098 [PMID: 32367170 DOI: 10.1007/s00134-020-06062-x]
31 **Miesbach W**, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. *Clin Appl Thromb Hemost* 2020; **26**: 1076029620938149 [PMID: 32677459 DOI: 10.1177/1076029620938149]
32 **Zhang Y**, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, Zhou X, Jiang W, Zhao YQ, Zhang SY, Li TS. [Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia]. *Zhonghua Xue Ye Xue Za Zhi* 2020; **41**: E006 [PMID: 32220276 DOI: 10.3760/cma.j.issn.0253-2727.2020.0006]
33 **de Roquetaillade C**, Chousterman BG, Tomasoni D, Zeitouni M, Houdart E, Guedon A, Reiner P, Bordier R, Gayat E, Montalescot G, Metra M, Mebazaa A. Unusual arterial thrombotic events in Covid-19 patients. *Int J Cardiol* 2021; **323**: 281-284 [PMID: 32918938 DOI: 10.1016/j.ijcard.2020.08.103]
34 **Stefanini GG**, Montorfano M, Trabattoni D, Andreini D, Ferrante G, Ancona M, Metra M, Curello S, Maffeo D, Pero G, Cacucci M, Assanelli E, Bellini B, Russo F, Ielasi A, Tespili M, Danzi GB, Vandoni P, Bollati M, Barbieri L, Oreglia J, Lettieri C, Cremonesi A, Carugo S, Reimers B, Condorelli G, Chieffo A. ST-Elevation Myocardial Infarction in Patients With COVID-19: Clinical and Angiographic Outcomes. *Circulation* 2020; **141**: 2113-2116 [PMID: 32352306 DOI: 10.1161/CIRCULATIONAHA.120.047525]
35 **Han H**, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020; **58**: 1116-1120 [PMID: 32172226 DOI: 10.1515/cclm-2020-0188]
36 **Hazanov N**, Somin M, Attali M, Beilinson N, Thaler M, Mouallem M, Maor Y, Zaks N, Malnick S. Acute renal embolism. Forty-four cases of renal infarction in patients with atrial fibrillation. *Medicine (Baltimore)* 2004; **83**: 292-299 [PMID: 15342973 DOI: 10.1097/01.md.0000141097.08000.99]
37 **Glazer GM**, Francis IR, Brady TM, Teng SS. Computed tomography of renal infarction: clinical and experimental observations. *AJR Am J Roentgenol* 1983; **140**: 721-727 [PMID: 6601378 DOI: 10.2214/ajr.140.4.721]
38 **Suzer O**, Shirkhoda A, Jafri SZ, Madrazo BL, Bis KG, Mastromatteo JF. CT features of renal infarction. *Eur J Radiol* 2002; **44**: 59-64 [PMID: 12350414 DOI: 10.1016/s0720-048x(01)00476-4]
39 **Basara Akin I**, Altay C, Eren Kutsoylu O, Secil M. Possible radiologic renal signs of COVID-19. *Abdom Radiol (NY)* 2021; **46**: 692-695 [PMID: 32725482 DOI: 10.1007/s00261-020-02671-8]
40 **Post A**, den Deurwaarder ESG, Bakker SJL, de Haas RJ, van Meurs M, Gansevoort RT, Berger SP. Kidney Infarction in Patients With COVID-19. *Am J Kidney Dis* 2020; **76**: 431-435 [PMID: 32479921 DOI: 10.1053/j.ajkd.2020.05.004]
41 **Su H**, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X, Zhang C. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; **98**: 219-227 [PMID: 32327202 DOI: 10.1016/j.kint.2020.04.003]
42 **Santos Leite Pessoa M**, Franco Costa Lima C, Farias Pimentel AC, Godeiro Costa JC, Bezerra Holanda JL. Multisystemic Infarctions in COVID-19: Focus on the Spleen. *Eur J Case Rep Intern Med* 2020; **7**: 001747 [PMID: 32665933 DOI: 10.12890/2020_001747]
43 **Balcar I**, Seltzer SE, Davis S, Geller S. CT patterns of splenic infarction: a clinical and experimental study. *Radiology* 1984; **151**: 723-729 [PMID: 6718733 DOI: 10.1148/radiology.151.3.6718733]
44 **Ye Q**, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *Am J Physiol Gastrointest Liver Physiol* 2020; **319**: G245-G252 [PMID: 32639848 DOI: 10.1152/ajpgi.00148.2020]
45 **Fan Z**, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]
46 **Abdelmohsen MA**, Alkandari BM, Gupta VK, ElBeheiry AA. Diagnostic value of abdominal sonography in confirmed COVID-19 intensive care patients. *Egypt J Radiol Nucl Med* 2020; **51**: 198 [DOI: 10.1186/s43055-020-00317-9]
47 **Bhayana R**, Som A, Li MD, Carey DE, Anderson MA, Blake MA, Catalano O, Gee MS, Hahn PF, Harisinghani M, Kilcoyne A, Lee SI, Mojtahed A, Pandharipande PV, Pierce TT, Rosman DA, Saini S, Samir AE, Simeone JF, Gervais DA, Velmahos G, Misdraji J, Kambadakone A. Abdominal Imaging Findings in COVID-19: Preliminary Observations. *Radiology* 2020; **297**: E207-E215 [PMID: 32391742 DOI: 10.1148/radiol.2020201908]
48 **Goldberg-Stein S**, Fink A, Paroder V, Kobi M, Yee J, Chernyak V. Abdominopelvic CT findings in patients with novel coronavirus disease 2019 (COVID-19). *Abdom Radiol (NY)* 2020; **45**: 2613-2623 [PMID: 32761402 DOI: 10.1007/s00261-020-02669-2]
49 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]
50 **Wang F**, Wang H, Fan J, Zhang Y, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. *Gastroenterology* 2020; **159**: 367-370 [PMID: 32247022 DOI: 10.1053/j.gastro.2020.03.055]
51 **Aloysius MM**, Thatti A, Gupta A, Sharma N, Bansal P, Goyal H. COVID-19 presenting as acute pancreatitis. *Pancreatology* 2020; **20**: 1026-1027 [PMID: 32444169 DOI: 10.1016/j.pan.2020.05.003]
52 **Hadi A**, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, Gluud LL. Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family

members. *Pancreatology* 2020; **20**: 665-667 [PMID: 32387082 DOI: 10.1016/j.pan.2020.04.021]
53 **Liu F**, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clin Gastroenterol Hepatol* 2020; **18**: 2128-2130.e2 [PMID: 32334082 DOI: 10.1016/j.cgh.2020.04.040]
54 **Koo BC**, Chinogureyi A, Shaw AS. Imaging acute pancreatitis. *Br J Radiol* 2010; **83**: 104-112 [PMID: 20139261 DOI: 10.1259/bjr/13359269]
55 **Mazrouei SSA**, Saeed GA, Al Helali AA. COVID-19-associated acute pancreatitis: a rare cause of acute abdomen. *Radiol Case Rep* 2020; **15**: 1601-1603 [PMID: 32685078 DOI: 10.1016/j.radcr.2020.06.019]
56 **Meireles PA**, Bessa F, Gaspar P, Parreira I, Silva VD, Mota C, Alvoeiro L. Acalculous Acute Pancreatitis in a COVID-19 Patient. *Eur J Case Rep Intern Med* 2020; **7**: 001710 [PMID: 32523925 DOI: 10.12890/2020_001710]
57 **Conti CB**, Henchi S, Coppeta GP, Testa S, Grassia R. Bleeding in COVID-19 severe pneumonia: The other side of abnormal coagulation pattern? *Eur J Intern Med* 2020; **77**: 147-149 [PMID: 32414639 DOI: 10.1016/j.ejim.2020.05.002]
58 **Tang N**, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; **18**: 844-847 [PMID: 32073213 DOI: 10.1111/jth.14768]
59 **Al-Samkari H**, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020; **136**: 489-500 [PMID: 32492712 DOI: 10.1182/blood.2020006520]
60 **Patel I**, Akoluk A, Douedi S, Upadhyaya V, Mazahir U, Costanzo E, Flynn D. Life-Threatening Psoas Hematoma due to Retroperitoneal Hemorrhage in a COVID-19 Patient on Enoxaparin Treated With Arterial Embolization: A Case Report. *J Clin Med Res* 2020; **12**: 458-461 [PMID: 32655742 DOI: 10.14740/jocmr4256]
61 **Mazzitelli M**, Serapide F, Tassone B, Laganà D, Trecarichi EM, Torti C. Spontaneous and Severe Haematomas in Patients with COVID-19 on Low- Molecular-Weight Heparin for Paroxysmal Atrial Fibrillation. *Mediterr J Hematol Infect Dis* 2020; **12**: e2020054 [PMID: 32670532 DOI: 10.4084/MJHID.2020.054]
62 **Scialpi M**, Russo P, Piane E, Gallo E, Scalera GB. First case of retroperitoneal hematoma in COVID-19. *Turk J Urol* 2020; **46**: 407-409 [PMID: 32915717 DOI: 10.5152/tud.2020.20302]
63 **Zhang J**, He X, Hu J, Li T. Retroperitoneal Hemorrhage During Veno-Venous Extracorporeal Membrane Oxygenation in COVID-19 Patients: Clinical Experience and Review of Literature. 2020 Preprint. Available from: Research Square [DOI: 10.21203/rs.3.rs-32685/v1]
64 **Erdinc B**, Raina JS. Spontaneous Retroperitoneal Bleed Coincided With Massive Acute Deep Vein Thrombosis as Initial Presentation of COVID-19. *Cureus* 2020; **12**: e9772 [PMID: 32953290 DOI: 10.7759/cureus.9772]
65 **Scialpi M**, Scaglione M, Angelelli G, Lupattelli L, Resta MC, Resta M, Rotondo A. Emergencies in the retroperitoneum: assessment of spread of disease by helical CT. *Eur J Radiol* 2004; **50**: 74-83 [PMID: 15093238 DOI: 10.1016/j.ejrad.2003.11.020]
66 **Chan YC**, Morales JP, Reidy JF, Taylor PR. Management of spontaneous and iatrogenic retroperitoneal haemorrhage: conservative management, endovascular intervention or open surgery? *Int J Clin Pract* 2008; **62**: 1604-1613 [PMID: 17949429 DOI: 10.1111/j.1742-1241.2007.01494.x]
67 **Summers RM**. Artificial Intelligence of COVID-19 Imaging: A Hammer in Search of a Nail. *Radiology* 2021; **298**: E162-E164 [PMID: 33350895 DOI: 10.1148/radiol.2020204226]
68 **Zhang K**, Liu X, Shen J, Li Z, Sang Y, Wu X, Zha Y, Liang W, Wang C, Wang K, Ye L, Gao M, Zhou Z, Li L, Wang J, Yang Z, Cai H, Xu J, Yang L, Cai W, Xu W, Wu S, Zhang W, Jiang S, Zheng L, Zhang X, Wang L, Lu L, Li J, Yin H, Wang W, Li O, Zhang C, Liang L, Wu T, Deng R, Wei K, Zhou Y, Chen T, Lau JY, Fok M, He J, Lin T, Li W, Wang G. Clinically Applicable AI System for Accurate Diagnosis, Quantitative Measurements, and Prognosis of COVID-19 Pneumonia Using Computed Tomography. *Cell* 2020; **181**: 1423-1433.e11 [PMID: 32416069 DOI: 10.1016/j.cell.2020.04.045]
69 **Li L**, Qin L, Xu Z, Yin Y, Wang X, Kong B, Bai J, Lu Y, Fang Z, Song Q, Cao K, Liu D, Wang G, Xu Q, Fang X, Zhang S, Xia J. Using Artificial Intelligence to Detect COVID-19 and Community-acquired Pneumonia Based on Pulmonary CT: Evaluation of the Diagnostic Accuracy. *Radiology* 2020; **296**: E65-E71 [PMID: 32191588 DOI: 10.1148/radiol.2020200905]
70 **Desai SB**, Pareek A, Lungren MP. Deep learning and its role in COVID-19 medical imaging. *Intell Based Med* 2020; **3**: 100013 [PMID: 33169117 DOI: 10.1016/j.ibmed.2020.100013]
71 **McBee MP**, Awan OA, Colucci AT, Ghobadi CW, Kadom N, Kansagra AP, Tridandapani S, Auffermann WF. Deep Learning in Radiology. *Acad Radiol* 2018; **25**: 1472-1480 [PMID: 29606338 DOI: 10.1016/j.acra.2018.02.018]
72 **Kanne JP**, Bai H, Bernheim A, Chung M, Haramati LB, Kallmes DF, Little BP, Rubin G, Sverzellati N. COVID-19 Imaging: What We Know Now and What Remains Unknown. *Radiology* 2021; 204522 [PMID: 33560192 DOI: 10.1148/radiol.2021204522]

World Journal of Radiology

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

World J Radiol 2021 June 28; 13(6): 171-191

DOI: 10.4329/wjr.v13.i6.171

ISSN 1949-8470 (online)

REVIEW

COVID-19 imaging: Diagnostic approaches, challenges, and evolving advances

Dante L Pezzutti, Vibhor Wadhwa, Mina S Makary

ORCID number: Dante L Pezzutti 0000-0002-4800-5607; Vibhor Wadhwa 0000-0003-2597-5042; Mina S Makary 0000-0002-2498-7132.

Author contributions: Pezzutti DL, Wadhwa V, and Makary MS performed the literature review, wrote the manuscript, prepared the figures and tables, made the requested revisions, and provided final approval of the final version of the manuscript to be published.

Conflict-of-interest statement: The authors have no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear

Dante L Pezzutti, Mina S Makary, Department of Radiology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Vibhor Wadhwa, Department of Radiology, Weill Cornell Medical Center, New York City, NY 10065, United States

Corresponding author: Mina S Makary, MD, Assistant Professor, Attending Doctor, Director, Department of Radiology, The Ohio State University Wexner Medical Center, 395 W. 12th Ave, 4th Floor, Columbus, OH 43210, United States. mina.makary@osumc.edu

Abstract

The role of radiology and the radiologist have evolved throughout the coronavirus disease-2019 (COVID-19) pandemic. Early on, chest computed tomography was used for screening and diagnosis of COVID-19; however, it is now indicated for high-risk patients, those with severe disease, or in areas where polymerase chain reaction testing is sparsely available. Chest radiography is now utilized mainly for monitoring disease progression in hospitalized patients showing signs of worsening clinical status. Additionally, many challenges at the operational level have been overcome within the field of radiology throughout the COVID-19 pandemic. The use of teleradiology and virtual care clinics greatly enhanced our ability to socially distance and both are likely to remain important mediums for diagnostic imaging delivery and patient care. Opportunities to better utilize of imaging for detection of extrapulmonary manifestations and complications of COVID-19 disease will continue to arise as a more detailed understanding of the pathophysiology of the virus continues to be uncovered and identification of predisposing risk factors for complication development continue to be better understood. Furthermore, unidentified advancements in areas such as standardized imaging reporting, point-of-care ultrasound, and artificial intelligence offer exciting discovery pathways that will inevitably lead to improved care for patients with COVID-19.

Key Words: COVID-19; Coronavirus; Pandemic; Diagnostic imaging; Radiography; Computed tomography; Outcomes; Future trends

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

medicine and medical imaging

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: February 7, 2021
Peer-review started: February 7, 2021
First decision: May 6, 2021
Revised: May 15, 2021
Accepted: June 23, 2021
Article in press: June 23, 2021
Published online: June 28, 2021

P-Reviewer: Tumminello G
S-Editor: Zhang H
L-Editor: A
P-Editor: Li X

Core Tip: The role of both radiology and the radiologist has evolved throughout the coronavirus disease-2019 (COVID-19) pandemic. Detecting extrapulmonary manifestations as well as complications of COVID-19 disease with imaging remain important areas for further research. The development of COVID-19 severity scoring systems and standardized reporting methods has begun to lay the foundations for artificial intelligence systems. Furthermore, teleradiology and virtual care clinics were important components of the response to the COVID-19 pandemic and will remain important mediums for diagnostic imaging delivery and patient care. Finally, the emergence of point of care ultrasound is an exciting yet underexplored area of imaging applications for COVID-19.

Citation: Pezzutti DL, Wadhwa V, Makary MS. COVID-19 imaging: Diagnostic approaches, challenges, and evolving advances. *World J Radiol* 2021; 13(6): 171-191
URL: https://www.wjgnet.com/1949-8470/full/v13/i6/171.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i6.171

INTRODUCTION

In December 2019, the first reports of respiratory-related infections with a novel coronavirus emerged[1]. This virus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it causes, coronavirus disease-2019 (COVID-19), then quickly spread across the globe and the World Health Organization officially announced a global pandemic on March 11, 2020[2]. At the time of this writing, there have been more than 100000000 confirmed cases and 2200000 deaths worldwide from COVID-19. It is now the third leading cause of death within the United States, behind cancer and cardiovascular disease, accounting for nearly 27000000 cases in the United States and more than 440000 deaths in the United States [3]. In individuals over the age of 35, it is the leading cause of death in the United States[4].

From the pandemic's inception, radiological imaging has played a critical role in the diagnosis and management of COVID-19. However, the role of imaging has evolved throughout the pandemic. The purpose of this review is to address the evolving role of imaging in the diagnosis and management of COVID-19. In addition, we aim to discuss the current state of COVID-19 severity scoring systems in imaging, the operational challenges and preparedness response to COVID-19 in regard to the field of radiology, as well as the opportunities and future directions of radiological imaging in COVID-19.

ROLE OF RADIOLOGISTS

At the onset of the pandemic, the use of imaging, specifically chest radiography (CXR) and chest computed tomography (CT), served primarily as diagnostic and screening tools for COVID-19[5]. This is because the development of real time-polymerase chain reaction (RT-PCR) assays was still in process and the availability of these tests was not yet widespread[6,7]. Chest CT was shown to be more sensitive than CXR (95% *vs* 69%), but the use of either was not solely dependent on their sensitivities, but also the availability of each technology and the risk of subsequent exposure to other staff during each study[5]. Furthermore, early reports suggested a high sensitivity for chest CT for patients with COVID-19, and thus argued for its use as a screening tool[8]. In contrast, a later study conducted by Bernheim *et al*[9], revealed that in a study of 121 patients that examined CT findings in patients within two days of symptom onset, all but one patient tested positive with RT-PCR but had negative chest CT findings.

As testing kits became more widely available across communities, the role of imaging as a primary diagnostic and screening tool for COVID-19 became secondary to RT-PCR[7]. Although still a topic of debate, the Fleischner Society released a consensus statement indicating various scenarios where imaging in COVID-19 patients may be utilized and the radiologist be called upon, with each scenario being dependent upon the severity of disease, the pre-test probability, and the availability of

resources [*i.e.*, personal protective equipment (PPE), testing kits, staff, *etc.*].

These scenarios where imaging is indicated in patients with confirmed or suspected COVID-19 are specific for CXR and chest CT and include the following: (1) patients with a positive RT-PCR test or high pre-test probability in the absence of a RT-PCR test with evidence of risk factors for disease progression (*i.e.*, > 65 years of age, immunocompromised, comorbidities such as diabetes mellitus, hypertension, chronic lung disease, cardiovascular disease); (2) patients with moderate to severe features of COVID-19, regardless of RT-PCR test results; and (3) patients with moderate-to-severe symptoms within a high prevalence of disease environment and with limited testing resources, regardless of a RT-PCR result[7]. A modified algorithm based on the Fleischner Society's recommendations for imaging in the workup and management of COVID-19 disease is detailed in Figures 1 and 2.

Radiologists and medical imaging in general have been important not only in the screening and diagnosis of patients with COVID-19, but also in monitoring disease progression, predicting prognosis, monitoring treatment response, and determining disease severity[10]. In addition to CXR and chest CT, the use of imaging modalities such as ultrasound, magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) have been reported in the management of COVID-19 patients. Hereafter, the various imaging modalities used for COVID-19 patients, along with their indications, advantages and disadvantages, and the various features of disease present on each is described.

CURRENT STATE OF AFFAIRS

CXR

CXR is widely known to be a cost-effective and easily accessible imaging modality and is thus often used initially in the assessment of a patient with suspected COVID-19. The overall sensitivity of CXR is 69%-74%, with a lower sensitivity at earlier points in the course of the disease[1]. It is also easily portable, which makes it useful in patients that are immobile or bedridden. CXR can also be used to easily monitor disease progression and may be employed for those patients who are showing signs of worsening clinical status in the hospital[11]. The utility of CXR is also in evaluating for alternative diagnoses which may present with symptoms similar to COVID-19.

Pulmonary imaging findings on CXR are similar to those found on CT, and are often bilateral, posterior and peripheral, with a predominance in the lower lung fields. The most commonly reported interstitial abnormalities are reticular and reticulonodular patterns and the most commonly reported alveolar findings include hazy pulmonary opacities similar to the ground-glass opacities (GGOs) identified on CT. These can be accompanied with or without consolidation[12,13]. Progression of disease can be identified by the pulmonary opacities becoming more diffuse and thickening of the interstitial markings. The most severe signs of disease are present 10-12 d after symptom onset[14].

CT

Chest CT for COVID-19 has been shown to have a sensitivity of 94% and a specificity of 37%, with a positive predictive value of 1.5%-30.7% and a negative predictive value of 95.4%–99.8%[15]. Thus, in areas of low prevalence with COVID-19, using CT will equate to an increased number of false positives[1]. However, because of this high sensitivity, its use may be warranted in the setting of a high prevalence of disease and a negative or unavailable PCR test[16].

The high sensitivity of chest CT also allows for radiologists to detect COVID-19 disease on those patients receiving CT for other indications. This allows for early detection and containment in an otherwise asymptomatic patient, which are thought to be 18%-33% of those infected with SARS-CoV-2[17-19]. Furthermore, CT can be used in the evaluation of certain complications from COVID-19 that may not be discernible on CXR, such as pulmonary thromboembolism, lung abscesses, acute respiratory distress syndrome (ARDS), myocarditis, and acute lung edema[20,21]. Despite the augmented sensitivity, higher resolution and improved clarity in identifying both pulmonary and extrapulmonary manifestations with CT, it is important to note that the use of CT leads to involvement of more staff within the hospital and the use of more personal protective equipment, leading to increased cost and heightened risk of spread to hospital employees[22].

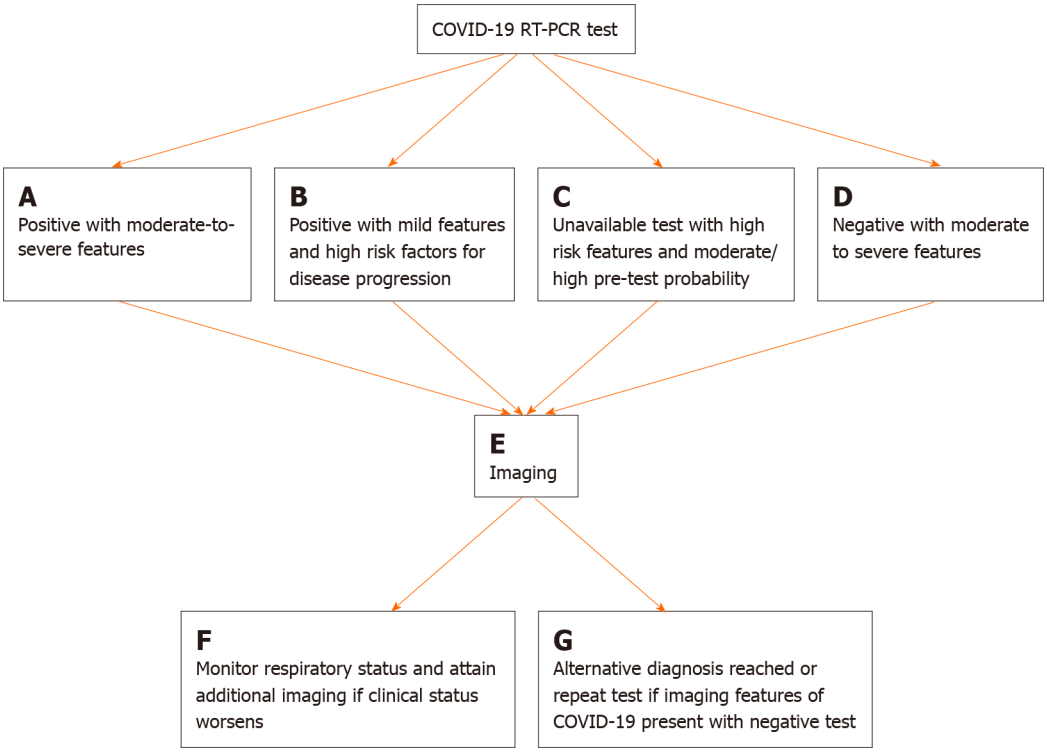


Figure 1 Flowchart depicting four scenarios in which imaging is indicated in the diagnostic work up and management of coronavirus disease-2019. A: Moderate to severe features are defined as the presence marked pulmonary damage and dysfunction; B: Mild features are defined as the absence of marked pulmonary damage and dysfunction & high risk factors for disease progression are defined as the presence of underlying comorbidities such as cardiovascular disease, diabetes, hypertension, and an immunocompromised status; C: Moderate/high pre-test probability is defined as a high background prevalence of disease in the surrounding area and a likely scenario of exposure to severe acute respiratory syndrome coronavirus 2; D: Moderate to severe features are defined as the presence marked pulmonary damage and dysfunction; E: Imaging refers to either the use of chest radiography (CXR) or chest computed tomography (CT). The employment of either is dependent upon time of presentation (early = chest CT, late = CXR), resources (CT scanner availability), and clinical expertise (preference of physician for a particular imaging modality); F: Additional imaging would ideally be CXR as it allows for rapid assessment of an evolving clinical status; G: Repeat test includes RT-PCR. Imaging features of COVID-19 disease on CXR include a bilateral, posterior and peripheral pattern, with a predominance in the lower lung fields; the most commonly reported interstitial abnormalities are reticular and reticulonodular patterns and the most commonly reported alveolar findings are hazy pulmonary opacities. This flow chart was adapted and modified based on the Fleischner Society's article from April of 2020 (Rubin). COVID-19: Coronavirus disease-2019; RT-PCR: Real time-polymerase chain reaction.

The two most commonly identified pulmonary findings on chest CT are GGOs and reticular opacities, typically with bilateral involvement and a multifocal pattern in a peripheral, sub-pleural, and posterior distribution[9,15,23-26]. Consolidations are also frequently observed, and can be present alone or alongside GGOs, in which case they are known as "mixed lesions". Finally, GGOs with superimposed intralobular lines and interlobular septal thickening–known as the crazy paving pattern–is a common finding on chest CT[27]. Other notable findings of disease include adjacent pleural thickening, intralobular septal thickening, air bronchograms, reverse halo sign, and a variant of the reverse halo sign known as the bullseye sign[28-30]. Findings such as pleural effusions and lymphadenopathy are normally absent[24].

The CT findings of patients with COVID pneumonia are dynamic and progress through a series of four stages marked from the time of symptom onset[31]. The early phase (0-4 d) is characterized mainly by the emergence of GGOs. The progressive phase (5-8 d) is characterized by an increase in the size and number of GGOs with the gradual transformation of GGOs into multifocal, consolidative areas and the development of a crazy-paving pattern. The peak stage (9-13 d) is characterized by more extensive lung involvement and the presence of more dense consolidations. Following the peak stage, an absorption stage can be identified where consolidations are slowly reabsorbed and fibrotic bands, a sign of repaired lungs, begin to appear[25,31]. Evidence of lung abnormalities persist long beyond symptom resolution, with one study reporting 94% of patients having residual CT findings 25 d following symptom onset[32]. Over the course of recovery, it is common to observe traction bronchiectasis, as well as peribronchovascular thickening[33].

Ultrasound

Ultrasound is well known to have advantages in the realm of medical imaging in that

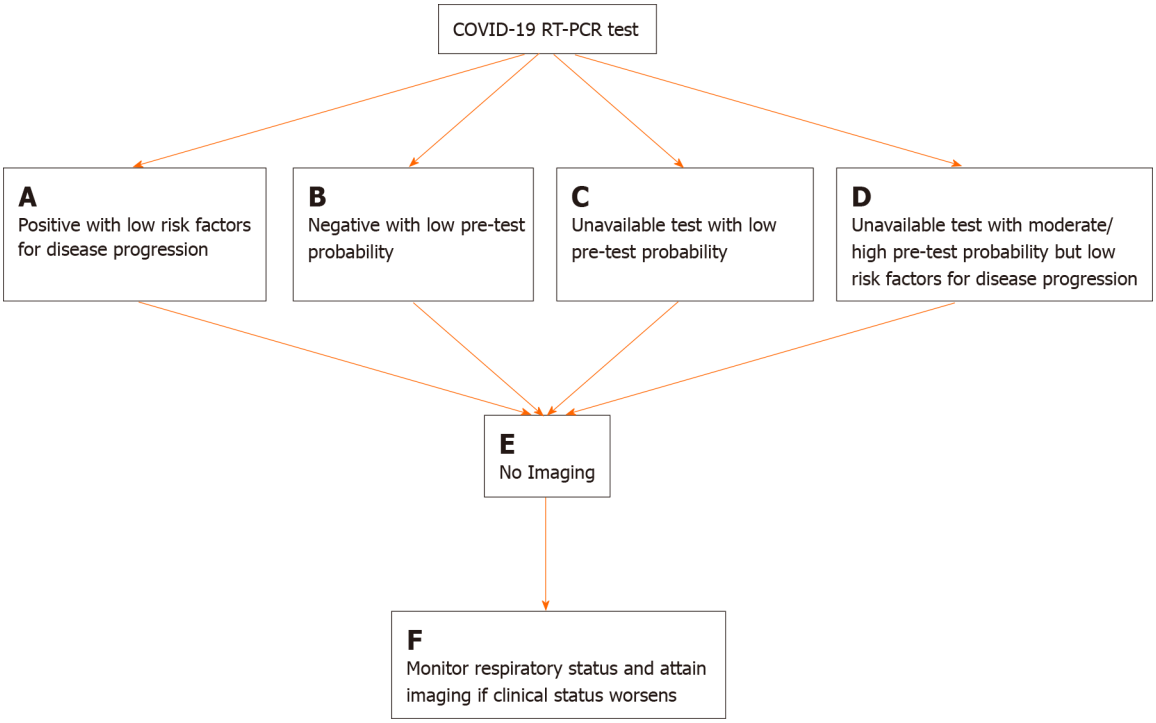


Figure 2 Flowchart depicting four scenarios in which imaging is not indicated in the diagnostic work up and management of coronavirus disease-2019. A: Low risk factors for disease progression are defined as the absence of underlying comorbidities such as cardiovascular disease, diabetes, hypertension, and an immunocompromised status; B: Low pre-test probability is defined as a low background prevalence of disease in the surrounding area and an unlikely scenario of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); C: Low pre-test probability is defined as a low background prevalence of disease in the surrounding area and an unlikely scenario of exposure to SARS-CoV-2; D: Moderate/high pre-test probability is defined as a high background prevalence of disease in the surrounding area and a likely scenario of exposure to SARS-CoV-2; E: Imaging refers to either the use of chest radiography (CXR) or chest computed tomography (CT). The employment of either is dependent upon time of presentation (early = chest CT, late = CXR), resources (CT scanner availability), and clinical expertise (preference of physician for a particular imaging modality); F: Imaging would ideally be chest radiography as it allows for rapid assessment of an evolving clinical status. This flow chart was adapted and modified based on the Fleischner Society's article from April of 2020 (Rubin). COVID-19: Coronavirus disease-2019; RT-PCR: Real time-polymerase chain reaction.

it does not expose patients to ionizing radiation and is easily accessible in terms of its portability and the ability to perform bedside examinations[34]. In the age of a pandemic, being able to perform ultrasound at the bedside offers advantages in that one does not need to transfer the patient to another part of the hospital and risk spreading the virus to other members in the hospital, especially other patients. This also frees up those staff involved in the transfer of the patient to attend to their other responsibilities. Furthermore, ultrasound is well known to be extremely affordable, results are available instantly, and it can be performed on patients who otherwise should not be exposed to radiation (*i.e.*, pregnant patients)[22,34-36].

Common findings identified on lung ultrasound in patients with COVID-19 include non-specific findings such as the presence of B-line artifacts, an irregularly thickened pleura, and sub-pleural consolidations. B-line artifacts are vertically oriented hyperechoic artifacts that originate from the pleura or from areas of consolidation. These lines indicate accumulation of fluid in the pulmonary interstitial space or alveoli[12,37]. A-lines can then be seen in the recovery phase of the disease[38].

Despite showing promise as a useful imaging modality in COVID-19 patients, the main evidence for the use of ultrasound come from small case series, tutorials, and opinion articles, and there are no large-scale studies examining its utility. The current guidelines from the major radiological societies for lung imaging in COVID-19 state no official role for the use of ultrasound and it is mainly an investigational tool at this time[39]. The use of point of care ultrasound (POCUS) will be further discussed in a later section.

Nuclear medicine

In imaging of COVID-19 patients, 18F-FDG PET has a high sensitivity but a poor specificity and has mainly been reported as an imaging modality that incidentally detects evidence of COVID-19 disease[23,40]. For example, a report of a patient who underwent 18F-FDG PET/CT for suspected recurrence of non-small cell lung cancer,

was noted to have incidental foci consistent with GGO in the lower lobes of the lungs bilaterally, determined to likely be related to an acute-inflammatory process. The patient then tested positive for SARS-CoV-2, and clinically deteriorated and required intensive-care unit (ICU) level care. This example illustrates the importance of radiologists maintaining a high-level of suspicion for incidental findings noted on PET imaging, as early detection of the virus can lead to improved clinical outcomes, especially in those highly susceptible to severe complications[41].

In addition to aiding in early detection, 18F-FDG PET has also shown promise in predicting the severity of a lesion and the length of time it will take to heal by correlating 18F-FDG uptake with erythrocyte sedimentation rates[42]. Furthermore, the use of PET imaging may be beneficial in further understanding the neurological complications initiated by infection with SARS-CoV-2. For example, it may aid in identifying which brain regions are affected, which cells in the brain are involved, and also could aid in selecting patients at risk of developing neurological complications [43]. Nevertheless, the cost, exposure to excess radiation, prolonged acquisition time, and involvement of multiple lines of medical staff and consumption of an unnecessary amount of PPE argue against the use of PET imaging for diagnostic purposes[44]. Further research is warranted to examine the utility of PET imaging in assessing functionality of lesions and predicting disease severity.

MRI

MRI of the chest does not provide additional findings in patients with COVID-19 when compared with CT in terms of pulmonary manifestations. It is less widely available, more expensive, and has an increased imaging acquisition time[23,45,46]. The primary indications for the use of MRI in patients with COVID-19 are in the evaluation of complications involving the neurological and cardiac systems, such as acute necrotizing encephalopathy or myocarditis[1]. Furthermore, for patient groups in whom exposure to ionizing radiation should be avoided (*i.e.*, young children, pregnant patients), MRI may be a viable option[47].

COVID-19 imaging severity scoring systems

Being able to quantitatively capture the severity of disease in COVID-19 patients *via* imaging provides clinicians with a method of identifying and managing patients with severe disease in situations where rapid triage is a necessity. The application of pre-COVID-19 severity scores has been utilized and novel scoring systems have also been developed specifically for patients with COVID-19[48]. The details of various scoring systems developed in both CXR and Chest CT are outlined below. Although it is unclear as to which scoring method is the most optimal, it is imperative that radiological departments around the world adopt a system and consistently use it, while also ensuring their results can be consistently reproduced[48].

As previously stated, CXR has a low sensitivity early in the COVID-19 disease course, but in the emergency setting and for patients in the ICU, it can be used to monitor rapid progression of lung involvement in later stages of the disease[48]. The severe acute respiratory infection chest radiography severity scoring system was developed in 2015 with the original intent for it to be used by the non-radiologist clinicians to examine patients with acute respiratory processes[49]. Yoon *et al*[50] reported the use of this scoring system in the assessment of pulmonary involvement in COVID-19 patients[48]. The Radiographic Assessment of Lung Edema classification system was developed in March of 2020 by Wong *et al* [15], but it was adapted based on a similar score created by Warren *et al* in 2018. The only score to date created solely for patients with COVID-19 were proposed by Borghesi in March of 2020[51]. The median score of patients from the original study was 6.5 and the CXR score in patients who died was significantly higher than those discharged from the hospital[51]. A summary of the various features of each chest radiographic scoring system is detailed in Table 1.

The use of CT imaging is highly effective at detecting COVID-19 early on in the disease course, with a sensitivity of up to 95%[15]. Thus, early on in the pandemic, clinicians pursued a severity scoring system for patients with COVID-19 based on CT findings[48]. The chest computed tomography severity score was developed by Yang *et al*[52] in March of 2020 as an adaptation from a previously used method during the SARS epidemic of 2005, and was used to rapidly identify those patients in need of hospital admission on initial presentation. The total severity score (TSS), also developed in March of 2020 by Li *et al*[53], was designed to examine the relationship between imaging findings and clinical presentation in patients with COVID-19. The chest computed tomography score was published by Li *et al*[54] in March of 2020 and is similar to the TSS. A summary of the various features of each chest CT scoring

Table 1 Three main chest radiographic scoring systems use for coronavirus disease-2019 and their characteristic features

	Chest Radiography Scoring Systems for COVID-19		
Characteristics of Chest Radiography Scoring Systems	Severe Acute Respiratory Infection[48]	Radiographic Assessment of Lung Edema[49]	Chest X-ray Score[51]
Division of Lungs	None	2 lungs	6 zones (3 zones each lung)
Methodology of Score Calculation	Entire lungs scored as one	Each lung scored and totaled	Each zone scored and totaled
Characteristics Scored	Various radiographic findings	[1]GGOs or consolidation	Various radiographic findings
Scoring Scale	1 = normal; 2 = patchy/hyperinflation/bronchial wall thickening; 3 = focal consolidation; 4 = multifocal consolidation; 5 = diffuse alveolar change	1 ≤ 25%; 2 = 25%-50%; 3 = 50%-75%; 4 ≥ 75%	0 = no abnormalities; 1 = interstitial infiltrates; 2 = interstitial (predominant) & alveolar infiltrates; 3 = interstitial & alveolar (predominant) infiltrates
Designed Specifically for COVID-19 Disease	No	No	Yes

[1]Ground glass opacities. Modified based on study from Wasilewski *et al*[47]. COVID-19: Coronavirus disease-2019; GGO: Ground-glass opacities.

system is detailed in Table 2.

CHALLENGES

Differential diagnosis

One of the main challenges in COVID-19 imaging lies in its differential diagnosis on chest CT. This is due to the fact many of the findings on CT can be observed in other categories of disease, which include the following: inspiration/motion artifacts, trauma, other alveolar infectious etiologies (both viral and non-viral), as well as various interstitial and vascular pathologies[55]. While it is not possible to arrive at a diagnosis for COVID-19 based on imaging features alone, it is crucial to understand its features and their overlap with other infectious and non-infectious causes. Furthermore, it is also critical to always consider the epidemiological history of the patient and their symptoms in addition the objective laboratory and imaging findings prior to making a diagnosis[33]. Nonetheless, the various infectious/non-infectious mimickers of COVID-19 pneumonia follow hereafter.

GGOs may be one of the most common manifestations on CT of COVID-19 pneumonia; however, shallow inspiration, motion artifact from cardiac pulsation, and fibrotic bands/sub segmental atelectasis may present as a GGO-like appearance[56]. Traumatic lung findings, such as pulmonary contusion, can lead to the appearance of nodular opacities or large areas of consolidation based on the degree of trauma. Although these findings are present in COVID-19 pneumonia, appropriate clinical assessment of the patient will help to differentiate a trauma related finding from COVID-19 pneumonia[57]. Furthermore, pulmonary edema may present as diffuse or patchy GGOS, but with a central predominance and will change with positioning because of the gravitational predominance. Additionally, pulmonary edema is often accompanied by pleural effusions, an uncommon finding in COVID-19 pneumonia.

Viral causes of pneumonia that can present similarly to COVID-19 pneumonia include influenza virus, parainfluenza virus, adenovirus virus, respiratory syncytial virus, and other coronaviruses[33,58]. The typical findings for these viral infections include those involving the interstitium and non-unique findings such as GGOs, peribronchovascular thickening, centrilobular opacities, "tree-in-bud" pattern, and patchy consolidations[58]. However, some findings that more often support COVID-19 pneumonia specifically include the presence of GGOs in a peripheral and sub-pleural distribution, a reverse halo sign, and vascular enlargement[59]. It is important to note that while these findings may be typical in COVID-19 infection, they are not completely unique to the disease. For example, the reverse halo sign has been described in tuberculosis and various fungal infections, and the sub-pleural distribution of opacities and crazy-paving pattern can also be observed in other coronaviruses such as SARS and Middle East respiratory syndrome virus[60].

Table 2 Three main chest computed tomography scoring systems use for coronavirus disease-2019 and their characteristic features

	Chest CT Scoring Systems for COVID-19		
Characteristics of Chest CT Scoring Systems	Chest Computed Tomography Severity Score[52]	Total Severity Score [53]	Chest Computed Tomography Score [54]
Division of Lungs	20 regions for each lung	5 lobes	5 lobes
Methodology of Score Calculation	Each region scored & amount totaled	Each lobe scored and amount totaled	Each lobe scored and amount totaled
Characteristics Scored	Amount of opacification	% of disease in each lobe ([1]GGOs, mixed GGOs, consolidation)	% of disease in each lobe (no specific features)
Scoring Scale	0 = 0%; 1 = 1%-50%; 2 = 51%-100%	0 = 0%; 1 = 1%-25%; 2 = 26%-50%; 3 = 51%-75%; 4 = 76%-100%	0 = 0%; 1 ≤ 5%; 2 = 5%-25%; 3 = 26%-49%; 4 = 50%-75%; 5 ≥ 75%
Sensitivity & Specificity	83% & 94%	83% & 100%	80% & 82%
Lowest Score for Severe COVID-19 Cases	19.5	7.5	7
Designed Specifically for COVID-19 Disease	Yes	Yes	Yes

[1]Ground glass opacities. Modified based on study from Wasilewski *et al*[47]. CT: Computed tomography; COVID-19: Coronavirus disease-2019; GGO: Ground-glass opacities.

Bacterial pneumonias can also be included on the differential diagnosis when examining a chest CT for COVID-19; however, bacterial pneumonia commonly causes a lobar/bronchopneumonia and pleural effusions, both of which are atypical findings in COVID-19 pneumonia[61]. Pneumocystis jiroveci pneumonia commonly presents as GGOs with a crazy-paving pattern in the immunosuppressed host. However, these can typically be observed in the upper lobes and in a central distribution, helping to distinguish it from COVID-19 pneumonia[62]. Other fungal infections such as candidiasis, cryptococcosis, and coccidiomycosis tend to cause lymphadenopathy and cavitation, both uncommon findings in patients with COVID[63].

Neoplasms may also be included in the differential of a suspected COVID-19 patient since the presence of focal GGOs and/or rounded opacities may be features of both [64]. For completeness, additional pathologies to be included in the differential diagnosis include organizing pneumonia, pulmonary alveolar proteinosis, sarcoidosis, pulmonary infarction, various interstitial lung diseases, vasculitides, and aspiration pneumonia[33,55,58,65].

Operational challenges and preparedness

It is important to consider the logistical challenges that radiological imaging has faced throughout the COVID-19 pandemic and understand how those challenges have been dealt with systematically. Because COVID-19 is spread through person-to-person contact and/or respiratory droplets, and one of the most effective methods to prevent spread of the virus is through social distancing, radiology departments around the world were required to come up with efficient and safe protocols to keep staff and patients safe while imaging patients with suspected COVID-19[66]. In general, for radiology departments to continue to safely operate during the COVID-19 pandemic, constant communication concerning the number of positive cases in the department, the available amount of PPE, the currently quarantined staff, as well as scheduling for previously cancelled non-urgent imaging and a daily analysis of labor costs vs. staffing and the available work shift slots are all vital tasks[67]. Many of the specific examples of adjustments made with in departments in response to operational challenges prompted by virus are detailed below.

One of the initial steps taken by many departments to provide safety for those working in the radiology department has been to limit the number of onsite radiologists and ensure a reserve of radiologists at home with less potential exposure to COVID-19. Additionally, any in-person meetings that could be held on a virtual platform were transitioned appropriately[68]. Furthermore, radiologist workstations have been spread out amongst areas in the hospital with extra availability, and the option of remote interpretation has become more widely employed[68]. Finally, many non-urgent imaging examinations such as low-dose CT for lung cancer screening and screening mammography were postponed at one point or another to decrease the

volume of patients in and out of the radiology imaging rooms[69]. This latter adjustment led to a significant decrease in outpatient imaging (*i.e.*, In July 2020, an 87% reduction overall in outpatient imaging was observed, with a 93% reduction in mammography specifically)[70].

Patients with suspected or confirmed COVID-19 are now often dedicated to isolated imaging rooms for both chest radiography and CT, and dedicated pathways to these rooms through the hospital have been created to limit contact with unnecessary staff and other patients[71,72]. Moreover, non-essential items within these dedicated COVID-19 imaging rooms are removed to ensure more effective and efficient sanitization sessions[71]. To ensure staff safety during imaging acquisition of patients with suspected or confirmed COVID-19, protocols have been developed for each type of imaging. In chest radiographs, one method reported used two separate radiographers; one that managed the workstation and one that positioned the patient appropriately. A similar two person staffing procedure can be applied when using CT [67,72]. Patients and staff should always be wearing a surgical mask throughout the examination and during transport and all equipment used should be properly sanitized after use, and an N95 mask is to be worn by staff if an aerosolizing procedure is being performed[73]. These extra safety measures lead to an increased turnover time between imaging and thus less availability of imaging throughout the hospital. For example, after decontamination of a CT scanner, the room must be closed for 1 h to allow for appropriate ventilation and circulation[74]. Furthermore, requiring a higher staff to patient ratio leaves departments with less available employees available for other work-related tasks at a given time[75].

Interventional radiology (IR) also has faced several unique challenges throughout the COVID-19 pandemic. At the most basic level, IR suites were forced to redesign their layouts to provide maximal containment of disease before, during, and after patient transmission, as well as minimal transmission through fomite exposure[76,77]. Furthermore, adjustments in case prioritization often *via* a tier-based system became a necessity to balance both risk of infection with appropriately timed delivery of care to non-COVID-19 patients[78]. The volume of cases in IR was also impacted by the COVID-19 pandemic. For example, according to a survey administered to IR departments in Canada in May of 2020, 50% of respondents reported a decreased demand for acute IR services, which correlated with a simultaneous decrease in emergency department admissions[79,80]. Elective IR procedures were also noted to be reduced as a necessary measure to ensure maximum risk reduction in terms of viral spread[81]. While the overall volume of cases within IR declined as a result of the pandemic and many procedures within IR were documented to decrease in volume, venous IR procedures actually increased in volume[82]. It is possible that this rise could be attributed in part to the association of COVID-19 with venous thromboembolism, as well as the predominantly sedentary lifestyle of the general public in the face of stay-at-home orders and social distancing policies[83].

OPPORTUNITIES

While SARS-CoV-2 primarily causes respiratory related illness, it has also been demonstrated to manifest pathologically in the cardiac, neurologic, gastrointestinal, genitourinary, vascular, and dermatological systems[38,84]. It is hypothesized that the complex pathophysiology the virus induces, which involves a heightened immune response, coagulation system dysfunction, and severe hypoxia, contribute to its induction of multiorgan system disease processes[84]. Additionally, its mechanism of cell entry *via* the angiotensin-cell converting enzyme II receptor, which is distributed widely throughout human tissues, may also explain these multisystem manifestations. Briefly, each organ system impacted by COVID-19 and the associated pathologies and the relevant imaging used to assess these pathologies will be described. The reader may reference Table 3 for a comparison of the various imaging modalities used in COVID-19 disease and their associated findings/features characterized by organ system (both pulmonary and extrapulmonary).

Extrapulmonary manifestations

In terms of cardiac dysfunction, COVID-19 disease has been reported to induce myocardial injury, arrythmias (*i.e.*, atrial fibrillation), arterial/venous thromboemboli, cardiomyopathies, myocarditis, and cardiogenic shock[85,86]. Cardiac MRI is the ideal imaging modality to detect cardiac abnormalities in COVID-19 patients and the use of CT angiography is also important in surveying for coagulation related pathologies

Table 3 Four most common imaging modalities used in the diagnosis and management of coronavirus disease-2019 and their unique features/findings characterized by organ system

	Characteristic Features of COVID-19 by Imaging Modality			
Organ Systems Impacted by COVID-19	[1]CT	Ultrasound	Magnetic resonance imaging	Chest radiography
Pulmonary	[2]GGOs and reticular opacities; consolidations; [3]crazy paving pattern; multifocal and bilateral in a peripheral, sub-pleural, and posterior distribution	[4]B-line artifacts; irregularly thickened pleura; sub-pleural consolidations	Similar to CT	Interstitial reticular and reticulonodular patterns; alveolar hazy pulmonary opacities (equivalent to GGOs on CT); consolidations; multifocal & bilateral in a peripheral, sub-pleural, and posterior distribution
Cardiac	Cardiac thromboembolism	Pericardial effusion	Myocarditis; pericardial effusion	
Neurological	Stroke (ischemic/thromboembolic)	Venous sinus thrombosis	Stroke (ischemic/thromboembolic); venous sinus thrombosis, hyper-intensities	
Gastrointestinal	Wall thickening; edema; fluid filled intestinal lumen; mucosal hyper-enhancement; mesenteric vascular thrombi/ischemia	Portal vein thrombosis		
Genitourinary	Perinephric fat stranding	Renal vein/artery thrombosis		

Both pulmonary and extrapulmonary manifestations of coronavirus disease-2019 disease are detailed. Items are listed from the most common to the least common for each imaging modality and its associated organ system.

[1]Computed Tomography: refers to both computed tomography (CT) and CT angiography.

[2]Ground-glass opacities (GGOs): ground glass opacities.

[3]Crazy paving pattern: GGOs with superimposed intralobular lines and interlobular septal thickening.

[4]B-line artifacts: vertically oriented hyperechoic artifacts that originate from the pleura or from areas of consolidation. CT: Computed tomography; COVID-19: Coronavirus disease-2019; GGO: Ground-glass opacities.

such as cardiac thrombosis[87,88]. Neurologically, COVID-19 has been reported to be associated with acute stroke, encephalopathy, epilepsy, altered mental status, hypogeusia, hyposmia, and anosmia[89,90]. The use of non-contrast CT and/or non-enhanced MRI can be used to detect areas of infarct or venous sinus thrombosis related to COVID-19[91]. Furthermore, T2-weighted fluid-attenuated-inversion recovery imaging can detect areas of hyper-intensity, one of the most common locations being unilaterally in the mesial temporal lobe[92,93].

Disturbance of the permeability of the small and large intestine caused by SARS-CoV-2 is thought to be one of the mechanisms for gastrointestinal symptoms in COVID-19 patients[94]. In fact, up to 40% of COVID-19 patients present with abdominal symptoms such as acute abdominal pain, nausea/vomiting, and diarrhea, although these symptoms may be a result of referred pain due to the basilar distribution of COVID-19 infection[83,95]. If these symptoms construct the primary chief complaint of the patient, an abdominopelvic CT is indicated; clinicians should include COVID-19 on the differential diagnosis if bilateral ground glass opacities are observed at the lung bases[95]. CT findings of the gastrointestinal tract in COVID-19 patients include wall thickening, edema, fluid filled intestinal lumen, and mucosal hyper-enhancement[96]. Furthermore, the use of CT angiography is beneficial for assessing for mesenteric arterial or venous thrombi and ischemia, a common finding in the COVID-19 patients given the pathophysiology of the disease involves coagulation system dysfunction[97]. Doppler ultrasound may also be employed in situations where portal vein thrombosis is suspected[97].

Other abdominal symptoms are a result of infection of the liver, which is the second most common organ to be involved in COVID-19 infection behind the lungs, and can be adequately assessed with CT, MRI, or ultrasound[98]. It is thought that the virus infects the cholangiocytes of the liver and not the hepatocytes themselves, and thus abnormality in liver function tests or gall bladder enzymes (found in 53% of COVID-19 patients) should prompt the use of these imaging modalities to assess the hepato-biliary system[38].

The genitourinary system, and in particular, the kidneys, are commonly injured among critically ill COVID-19 patients (20%-40%) as a result of infarction and inflammation[99]. The use of ultrasound is first line for evaluating suspected renal vascular involvement as allergies to contrast and renal insufficiency preclude the use of CT with contrast[100]. Other notable extrapulmonary manifestations of COVID-19 that don't necessarily maintain a role for imaging but are included here for completeness sake include dermatologic pathologies such as COVID toes (frostbite-like toes or "pseudochilbain") and maculopapular eruptions[101]. These are the result of microvascular thrombosis and often appear in more severe cases[102].

Complications

A number of complications from COVID-19 infection can arise and the use of imaging in the detection and monitoring of each may improve patient outcomes and overall survival[103]. The presence of pleural effusions, multiple lung nodules, tree-in-bud opacities, and lymphadenopathy–all uncommon findings in isolated COVID-19 pneumonia–on imaging should raise a suspicion for a bacterial superinfection, a complication reported in 14% of patients in the ICU[104,105]. ARDS, a severe complication in COVID-19 patients more common in patients in critical condition, presents clinically as marked arterial de-oxygenation and respiratory failure and can be confirmed by CT imaging that shows diffuse bilateral areas of GGOs[106]. Pulmonary emboli have been reported to arise in 13% of COVID-19 patients, with the majority of cases also occurring in critically ill patients[103]. Clinical suspicion of this complication should prompt the use of CT-angiography for confirmation and determination of the clinical treatment course[107]. Interestingly, because COVID-19 can lead to both macro- and micro-vascular complications, it is possible that those in the recovery phase of COVID-19 may develop chronic thromboembolic disease (CTED) or chronic thromboembolic pulmonary hypertension (CTEPH)[108]. The work-up of suspected CTED and CTEPH should be pursued with ventilation/perfusion scintigraphy over CT as it more sensitive in detection[109].

Because of the wide variety of disease COVID-19 can cause, it is critical for radiologists to understand the pathophysiology that leads to multiorgan system dysfunction so that complications are recognized more regularly and the detection of one complication prompts a thorough search for others[38]. As more research is pursued and our understanding of the pathophysiology and manifestations of COVID-19 disease evolve, so too will the role of imaging in the detection, diagnosis, and monitoring of disease progression in the extrapulmonary manifestations and complications in COVID-19 patients[38,110].

Teleradiology & virtual care

Teleradiology is a subset of telemedicine that involves the interpretation of diagnostic imaging at a site that is remote from where that image was acquired[111]. It can be categorized as intramural–the radiologist interpreting the imaging works for the institution where the image was taken–or extramural–the radiologist interpreting the imaging works for a group or practice that is not a part of the institution where the image was acquired[112]. Teleradiology was originally used in the 1990s to provide intramural emergency radiology access from remote sites[113]. However, advances in technology and demand from market forces quickly propelled its growth and utility in a variety of aspects of diagnostic imaging[114]. In fact, the global teleradiology market is projected to reach $ 8.2 billion in size by the year 2024[113,115]. During the COVID-19 pandemic, teleradiology has unsurprisingly become an important asset for the field of radiology. It allows for isolation of radiologists from suspected or confirmed COVID-19 patients in the clinical setting and a reduction in the number of staff in the hospital[75]. Additionally, a teleradiology infrastructure that is properly organized and staffed can allow for enhanced preparedness in surges in imaging as a result of COVID-19 patient influxes[78]. With these benefits in mind, it is important to consider the challenges facing teleradiology in aspects such as licensing and credentialing, technology and systems along with their integration, and staffing models[115]. Addressing these will allow for a more robust integration of teleradiology into everyday clinical practice and will improve the response and handling of the COVID-19 pandemic and future pandemics alike.

The use of teleradiology in strengthening our response to surges in imaging, as well as reducing the risk of viral spread *via* providing the opportunity to socially distance, are not the only aspects of virtual care in the field of radiology that has played a role in the COVID-19 pandemic. IR clinics, for example, have made an effort to transition to virtual appointments to reduce the spread of COVID-19. A recent survey of 122 patients from an Interventional Neuroradiology clinic demonstrated additional

benefits in having a virtual clinic beyond social distancing[116]. The study found that virtual clinics are not only more efficient, but also are preferred among patients and physicians in the non-urgent setting[116]. This illustrates an important shift in the delivery of care for patients that not only reduces the transmission of COVID-19, but also delivers more efficient and preferred care[116-118].

EVOLVING TRENDS AND FUTURE DIRECTIONS

Standardized reporting

A standardized reporting system known as the COVID-19 Reporting and Data System was developed by the Dutch Radiological Society in April of 2020[119]. This task was pursued to promote a form of standardized communication in regard to COVID-19 CT imaging disease findings and improve communication between radiologists and referring physicians[59,119,120]. The Radiological Society of North America also developed a consensus on standardized reporting for COVID-19 imaging findings [121]. A comparison of the two systems can be found in Table 4.

Structured reporting aids in the radiologists' recognition of certain disease patterns, decreases the variability in radiological reporting, and provides more certainty for findings that are likely a result of COVID-19 disease. Furthermore, standardized reporting systems such as these lead to improved educational and research-oriented projects, improve selection of cutoff points that clinicians utilize for clinical management, and enhance the specificity of CT imaging for COVID-19[122]. These systems and future systems alike will continue to improve and their adoption, implementation and utilization among radiologists around the world will be vital for optimal patient care and future clinician education.

Point of care diagnostics

Aside from RT-PCR, one of the main point of care diagnostic imaging tools that is showing promise for COVID-19 patients is POCUS. POCUS has begun to gain traction in the medical community for the diagnosis and subsequent management of COVID-19 patients as it offers many benefits. For example, it is quick, affordable, requires no ionizing radiation, can be done at the bedside, and it addresses many of the same clinical questions that chest radiography and CT scans address[123]. In fact, lung ultrasound has been shown to be more sensitive than traditional chest radiography in the detection of infections involving the lower respiratory tract[124,125]. POCUS can not only be useful in the initial diagnosis of COVID-19, but it is also useful in following disease progression and monitoring for many of the associated complications[34]. These include evaluating for ARDS, cardiogenic pulmonary edema, pericardial and pleural effusions, determining ventricular function, assessing for a pneumothorax, screening for deep vein thromboses, assessing adequate lung recruitment during mechanical ventilation, predicting the efficacy of prone positioning, aiding in weaning of patients on mechanical ventilation[126-130].

A recent study from Italy proposed a standardized acquisition protocol and scoring system for lung ultrasound in COVID-19 patients[36]. The acquisition protocol requires scanning of 14 areas (3 posterior, 2 lateral and 2 anterior) for 10 s. The scoring procedure is as follows: 0 = the pleural line is continuous and horizontal artifacts (A-lines) are present; 1 = the pleural line is indented, and vertical areas of white are visible; 2 = the pleural line is broken and below the breaking point are darker areas with corresponding white areas beneath, indicating areas of consolidation; 3 = the pleural line is broken, and the scanned area shows dense and diffuse white lung with or without darker areas of consolidation[36]. Additionally, a United States study developed a 6-zone protocol that emphasizes provider safety, image time acquisition, and focuses mostly on the posterior and lateral fields[131].

It is important to consider the logistical adjustments that need to be made when using POCUS in COVID-19 patients. For example, acquiring video loops instead of static images decreases image acquisition time and thus exposure time. Additionally, POCUS examinations should be performed in pairs with one healthcare provider coming in contact with the patient as to minimize transmission[132]. Furthermore, properly disinfecting machines and the associated equipment and materials involved per manufacturer specific guidelines is critical to ensuring safe use of POCUS in the management of patients with COVID-19[22,133-135].

There are many limitations to the use of POCUS in COVID-19 patients and the evidence supporting its use to date. For example, many of the studies conducted thus far were during a period of high prevalence of disease, which likely influences the

Table 4 Two main standardized reporting systems used for coronavirus disease-2019 compared by their characteristic features

	Standardized CT Imaging Reporting Systems for COVID-19	
Characteristics of the Reporting System	Coronavirus Disease 2019 Reporting and Data System[118]-Dutch Radiological Society	Consensus Statement on Reporting Chest CT Findings for COVID-19-Radiological Society of North America[120]
Type of Reporting System	Quantitative	Qualitative
Components & Relationship Between Both Reporting Systems	0 = inadequate or suboptimal imaging	No equivalent
	1 = very low suspicion for COVID-19 with findings of non-infectious etiology	Negative for pneumonia = no CT features to suggest pneumonia
	2 = low suspicion of COVID-19 with infectious findings not typical for COVID-19	Atypical appearance = absence of typical or indeterminate features & the presence of lobar or segmental consolidation, but no GGOs or centrilobular nodules
	3 = equivocal scan with common findings of COVID-19	No equivalent
	4 = high suspicion of COVID-19 with typical features that overlap with other viral pneumonias	Indeterminate appearance = absence of typical features and the presence of multifocal, diffuse, or unilateral GGOs with or without consolidation in a non-specific distribution
	5 = very high suspicion of COVID-19 with typical findings of disease in typical locations	Typical appearance = peripheral and bilateral GGOs with or without consolidations/crazy paving pattern
	6 = RT-PCR positive COVID-19	No equivalent
Inter-observer agreement	Absolute agreement between 68.2% of observers; > 80% observer agreement on COVID-19 being low to very low or high to very high	No data

CT: Computed tomography; COVID-19: Coronavirus disease-2019; GGO: Ground-glass opacities; RT-PCR: Real time-polymerase chain reaction.

diagnostic accuracy of POCUS[136]. Furthermore, inter-operator reproducibility of POCUS on COVID-19 patients is not known. This is especially valuable information as ultrasound is heavily operator dependent and inexperienced providers may not achieve optimal images[137]. However, in general, while there are limited studies and none that are prospective in nature in regard to POCUS in COVID-19, POCUS has many features that offer clinicians valuable data while managing COVID-19 patients [138,139]. More research is needed to better understand the role it plays in managing COVID-19 patients.

Artificial intelligence

Another exciting avenue of research in COVID-19 imaging involves the use of artificial intelligence (AI). One manner through which AI can be utilized in the field of radiology is to help gather and integrate large data sets from disconnected sources that can then be used to create models that aid in predicting diagnosis of disease[140]. Using AI to do this, for example, with imaging findings related to COVID-19, is the most effective method to ensure an expeditious development of these models[19]. These data sets should include not only imaging data, but also the radiology reports and the clinical information such as symptoms and laboratory data[141]. It is also important to note that the widespread use of standardized reporting of COVID-19 imaging findings is necessary for the development of deep learning networks following data set acquisition, which can eventually assist in the detection of COVID-19 based on imaging features and other clinically relevant data[20].

One of the main uses of AI in imaging for the detection of COVID-19 applies to CXR and CT[142]. Several studies have demonstrated the use of AI models that accurately differentiate COVID-19 from community-acquired-pneumonia on based on the differences in their associated imaging features on both CXR and CT[143-145]. Aside from detection and differentiation of disease from other similar presentations, AI models have been developed to assess severity of infection and predict clinical outcomes based on the amount of opacities present, vascular changes, and other pertinent imaging findings[146]. Despite these promising advances, there remains much more room for improvement in the homogeneity of COVID-19 imaging sets and also in the detection and prediction of complications from COVID-19, which contribute significantly to mortality in COVID-19 patients[142,147].

CONCLUSION

The role of radiology and the radiologist have evolved throughout the COVID-19 pandemic, but both have always remained important in the diagnosis and subsequent management of patients with COVID-19 disease. Many challenges at the operational level have been overcome within the field of radiology and the current rising trend in teleradiology offers an opportunity for better preparedness during the remaining duration of the COVID-19 pandemic and future pandemics alike. Opportunities to better utilize of imaging for detection of extrapulmonary manifestations and complications of COVID-19 disease will arise as a more detailed understanding of the pathophysiology of the virus continues to be uncovered and identification of predisposing risk factors for complication development continue to be better understood. Furthermore, unidentified advancements in areas such as standardized imaging reporting, POCUS and AI offer exciting discovery pathways that will inevitably lead to improved care for patients with COVID-19.

REFERENCES

1 **Meirelles GSP**. COVID-19: a brief update for radiologists. *Radiol Bras* 2020; **53**: 320-328 [PMID: 33071376 DOI: 10.1590/0100-3984.2020.0074]

2 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

3 **Johns Hopkins University**. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). 2020. [cited 7 Feb 2021]. Available from: https://publichealthupdate.com/jhu/

4 **Woolf SH**, Chapman DA, Lee JH. COVID-19 as the Leading Cause of Death in the United States. *JAMA* 2021; **325**: 123-124 [PMID: 33331845 DOI: 10.1001/jama.2020.24865]

5 **Tan BS**, Dunnick NR, Gangi A, Goergen S, Jin ZY, Neri E, Nomura CH, Pitcher RD, Yee J, Mahmood U. RSNA International Trends: A Global Perspective on the COVID-19 Pandemic and Radiology in Late 2020. *Radiology* 2021; **299**: E193-E203 [PMID: 33289616 DOI: 10.1148/radiol.2020204267]

6 **Jiang MD**, Zu ZY, Schoepf UJ, Savage RH, Zhang XL, Lu GM, Zhang LJ. Current Status of Etiology, Epidemiology, Clinical Manifestations and Imagings for COVID-19. *Korean J Radiol* 2020; **21**: 1138-1149 [PMID: 32767867 DOI: 10.3348/kjr.2020.0526]

7 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin J, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest* 2020; **158**: 106-116 [PMID: 32275978 DOI: 10.1016/j.chest.2020.04.003]

8 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

9 **Bernheim A**, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020; **295**: 200463 [PMID: 32077789 DOI: 10.1148/radiol.2020200463]

10 **Kwee TC**, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. *Radiographics* 2020; **40**: 1848-1865 [PMID: 33095680 DOI: 10.1148/rg.2020200159]

11 **Roshkovan L**, Chatterjee N, Galperin-Aizenberg M, Gupta N, Shah R, Barbosa EM Jr, Simpson S, Cook T, Nachiappan A, Knollmann F, Litt H, Desjardins B, Jha S, Panebianco N, Baston C, Thompson JC, Katz SI. The Role of Imaging in the Management of Suspected or Known COVID-19 Pneumonia. A Multidisciplinary Perspective. *Ann Am Thorac Soc* 2020; **17**: 1358-1365 [PMID: 33124905 DOI: 10.1513/AnnalsATS.202006-600FR]

12 **Floridi C**, Fogante M, Agostini A, Borgheresi A, Cellina M, Natella R, Bruno F, Cozzi D, Maggialetti N, Palumbo P, Miele V, Carotti M, Giovagnoni A. Radiological diagnosis of Coronavirus Disease 2019 (COVID-19): a Practical Guide. *Acta Biomed* 2020; **91**: 51-59 [PMID: 32945279 DOI: 10.23750/abm.v91i8-S.9973]

13 **Gravell RJ**, Theodoreson MD, Buonsenso D, Curtis J. Radiological manifestations of COVID-19: key points for the physician. *Br J Hosp Med (Lond)* 2020; **81**: 1-11 [PMID: 32589534 DOI: 10.12968/hmed.2020.0231]

14 **Wong MD**, Thai T, Li Y, Liu H. The role of chest computed tomography in the management of COVID-19: A review of results and recommendations. *Exp Biol Med (Maywood)* 2020; **245**: 1096-1103 [PMID: 32588660 DOI: 10.1177/1535370220938315]

15 **Kim H**, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse Transcriptase Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. *Radiology* 2020; **296**: E145-E155 [PMID: 32301646 DOI: 10.1148/radiol.2020201343]

16 **Kovács A**, Palásti P, Veréb D, Bozsik B, Palkó A, Kincses ZT. The sensitivity and specificity of chest CT in the diagnosis of COVID-19. *Eur Radiol* 2021; **31**: 2819-2824 [PMID: 33051732 DOI: 10.1007/s00330-020-07347-x]

17 **Laghi A**, Grassi R. Italian Radiology's Response to the COVID-19 Outbreak. *J Am Coll Radiol* 2020; **17**: 699-700 [PMID: 32348740 DOI: 10.1016/j.jacr.2020.04.012]

18 **Li M**. Chest CT features and their role in COVID-19. *Radiol Infect Dis* 2020; **7**: 51-54 [PMID: 32309528 DOI: 10.1016/j.jrid.2020.04.001]

19 **Kaufman AE**, Naidu S, Ramachandran S, Kaufman DS, Fayad ZA, Mani V. Review of radiographic findings in COVID-19. *World J Radiol* 2020; **12**: 142-155 [PMID: 32913561 DOI: 10.4329/wjr.v12.i8.142]

20 **Salehi S**, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19) imaging reporting and data system (COVID-RADS) and common lexicon: a proposal based on the imaging data of 37 studies. *Eur Radiol* 2020; **30**: 4930-4942 [PMID: 32346790 DOI: 10.1007/s00330-020-06863-0]

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

22 **Gandhi D**, Ahuja K, Grover H, Sharma P, Solanki S, Gupta N, Patel L. Review of X-ray and computed tomography scan findings with a promising role of point of care ultrasound in COVID-19 pandemic. *World J Radiol* 2020; **12**: 195-203 [PMID: 33033574 DOI: 10.4329/wjr.v12.i9.195]

23 **Fields BKK**, Demirjian NL, Dadgar H, Gholamrezanezhad A. Imaging of COVID-19: CT, MRI, and PET. *Semin Nucl Med* 2021; **51**: 312-320 [PMID: 33288215 DOI: 10.1053/j.semnuclmed.2020.11.003]

24 **Hani C**, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, Revel MP. COVID-19 pneumonia: A review of typical CT findings and differential diagnosis. *Diagn Interv Imaging* 2020; **101**: 263-268 [PMID: 32291197 DOI: 10.1016/j.diii.2020.03.014]

25 **Pontone G**, Scafuri S, Mancini ME, Agalbato C, Guglielmo M, Baggiano A, Muscogiuri G, Fusini L, Andreini D, Mushtaq S, Conte E, Annoni A, Formenti A, Gennari AG, Guaricci AI, Rabbat MR, Pompilio G, Pepi M, Rossi A. Role of computed tomography in COVID-19. *J Cardiovasc Comput Tomogr* 2021; **15**: 27-36 [PMID: 32952101 DOI: 10.1016/j.jcct.2020.08.013]

26 **Shi H**, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]

27 **Bao C**, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. *J Am Coll Radiol* 2020; **17**: 701-709 [PMID: 32283052 DOI: 10.1016/j.jacr.2020.03.006]

28 **Nagpal P**, Narayanasamy S, Vidholia A, Guo J, Shin KM, Lee CH, Hoffman EA. Imaging of COVID-19 pneumonia: Patterns, pathogenesis, and advances. *Br J Radiol* 2020; **93**: 20200538 [PMID: 32758014 DOI: 10.1259/bjr.20200538]

29 **Song F**, Shi N, Shan F, Zhang Z, Shen J, Lu H, Ling Y, Jiang Y, Shi Y. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology* 2020; **297**: E346 [PMID: 33196374 DOI: 10.1148/radiol.2020209021]

30 **McLaren TA**, Gruden JF, Green DB. The bullseye sign: A variant of the reverse halo sign in COVID-19 pneumonia. *Clin Imaging* 2020; **68**: 191-196 [PMID: 32853842 DOI: 10.1016/j.clinimag.2020.07.024]

31 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]

32 **Wang Y**, Dong C, Hu Y, Li C, Ren Q, Zhang X, Shi H, Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296**: E55-E64 [PMID: 32191587 DOI: 10.1148/radiol.2020200843]

33 **Fan L**, Li D, Xue H, Zhang L, Liu Z, Zhang B, Yang W, Xie B, Duan X, Hu X, Cheng K, Peng L, Yu N, Song L, Chen H, Sui X, Zheng N, Liu S, Jin Z. Progress and prospect on imaging diagnosis of COVID-19. *Chin J Acad Radiol* 2020; 1-10 [PMID: 32292880 DOI: 10.1007/s42058-020-00031-5]

34 **Kulkarni S**, Down B, Jha S. Point-of-care lung ultrasound in intensive care during the COVID-19 pandemic. *Clin Radiol* 2020; **75**: 710.e1-710.e4 [PMID: 32405081 DOI: 10.1016/j.crad.2020.05.001]

35 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? *J Ultrasound Med* 2020; **39**: 1459-1462 [PMID: 32198775 DOI: 10.1002/jum.15284]

36 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for International Standardization of

the Use of Lung Ultrasound for Patients With COVID-19: A Simple, Quantitative, Reproducible Method. *J Ultrasound Med* 2020; **39**: 1413-1419 [PMID: 32227492 DOI: 10.1002/jum.15285]

37 **Revzin MV**, Raza S, Warshawsky R, D'Agostino C, Srivastava NC, Bader AS, Malhotra A, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 1: Viral Pathogenesis and Pulmonary and Vascular System Complications. *Radiographics* 2020; **40**: 1574-1599 [PMID: 33001783 DOI: 10.1148/rg.2020200149]

38 **Revzin MV**, Raza S, Srivastava NC, Warshawsky R, D'Agostino C, Malhotra A, Bader AS, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 2: From Cardiac Complications to Pediatric Manifestations. *Radiographics* 2020; **40**: 1866-1892 [PMID: 33136488 DOI: 10.1148/rg.2020200195]

39 **Ghosh S**, Deshwal H, Saeedan MB, Khanna VK, Raoof S, Mehta AC. Imaging algorithm for COVID-19: A practical approach. *Clin Imaging* 2021; **72**: 22-30 [PMID: 33197713 DOI: 10.1016/j.clinimag.2020.11.022]

40 **Maurea S**, Mainolfi CG, Bombace C, Annunziata A, Attanasio L, Petretta M, Del Vecchio S, Cuocolo A. FDG-PET/CT imaging during the Covid-19 emergency: a southern Italian perspective. *Eur J Nucl Med Mol Imaging* 2020; **47**: 2691-2697 [PMID: 32572561 DOI: 10.1007/s00259-020-04931-7]

41 **Polverari G**, Arena V, Ceci F, Pelosi E, Ianniello A, Poli E, Sandri A, Penna D. ^{18}F-Fluorodeoxyglucose Uptake in Patient With Asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus Disease 2019) Referred to Positron Emission Tomography/Computed Tomography for NSCLC Restaging. *J Thorac Oncol* 2020; **15**: 1078-1080 [PMID: 32243920 DOI: 10.1016/j.jtho.2020.03.022]

42 **Qin C**, Liu F, Yen TC, Lan X. ^{18}F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1281-1286 [PMID: 32088847 DOI: 10.1007/s00259-020-04734-w]

43 **Fontana IC**, Bongarzone S, Gee A, Souza DO, Zimmer ER. PET Imaging as a Tool for Assessing COVID-19 Brain Changes. *Trends Neurosci* 2020; **43**: 935-938 [PMID: 33131922 DOI: 10.1016/j.tins.2020.10.010]

44 **Guedj E**, Million M, Dudouet P, Tissot-Dupont H, Bregeon F, Cammilleri S, Raoult D. ^{18}F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? *Eur J Nucl Med Mol Imaging* 2021; **48**: 592-595 [PMID: 32728799 DOI: 10.1007/s00259-020-04973-x]

45 **Ates OF**, Taydas O, Dheir H. Thorax Magnetic Resonance Imaging Findings in Patients with Coronavirus Disease (COVID-19). *Acad Radiol* 2020; **27**: 1373-1378 [PMID: 32830031 DOI: 10.1016/j.acra.2020.08.009]

46 **Yang S**, Zhang Y, Shen J, Dai Y, Ling Y, Lu H, Zhang R, Ding X, Qi H, Shi Y, Zhang Z, Shan F. Clinical Potential of UTE-MRI for Assessing COVID-19: Patient- and Lesion-Based Comparative Analysis. *J Magn Reson Imaging* 2020; **52**: 397-406 [PMID: 32491257 DOI: 10.1002/jmri.27208]

47 **Torkian P**, Rajebi H, Zamani T, Ramezani N, Kiani P, Akhlaghpoor S. Magnetic resonance imaging features of coronavirus disease 2019 (COVID-19) pneumonia: The first preliminary case series. *Clin Imaging* 2021; **69**: 261-265 [PMID: 33002753 DOI: 10.1016/j.clinimag.2020.09.002]

48 **Wasilewski PG**, Mruk B, Mazur S, Półtorak-Szymczak G, Sklinda K, Walecki J. COVID-19 severity scoring systems in radiological imaging - a review. *Pol J Radiol* 2020; **85**: e361-e368 [PMID: 32817769 DOI: 10.5114/pjr.2020.98009]

49 **Taylor E**, Haven K, Reed P, Bissielo A, Harvey D, McArthur C, Bringans C, Freundlich S, Ingram RJ, Perry D, Wilson F, Milne D, Modahl L, Huang QS, Gross D, Widdowson MA, Grant CC; SHIVERS Investigation Team. A chest radiograph scoring system in patients with severe acute respiratory infection: a validation study. *BMC Med Imaging* 2015; **15**: 61 [PMID: 26714630 DOI: 10.1186/s12880-015-0103-y]

50 **Yoon SH**, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, Park CM, Kim YH. Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea. *Korean J Radiol* 2020; **21**: 494-500 [PMID: 32100485 DOI: 10.3348/kjr.2020.0132]

51 **Borghesi A**, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. *Radiol Med* 2020; **125**: 509-513 [PMID: 32358689 DOI: 10.1007/s11547-020-01200-3]

52 **Yang W**, Sirajuddin A, Zhang X, Liu G, Teng Z, Zhao S, Lu M. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). *Eur Radiol* 2020; **30**: 4874-4882 [PMID: 32296940 DOI: 10.1007/s00330-020-06827-4]

53 **Li K**, Fang Y, Li W, Pan C, Qin P, Zhong Y, Liu X, Huang M, Liao Y, Li S. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur Radiol* 2020; **30**: 4407-4416 [PMID: 32215691 DOI: 10.1007/s00330-020-06817-6]

54 **Li K**, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. *Invest Radiol* 2020; **55**: 327-331 [PMID: 32118615 DOI: 10.1097/RLI.0000000000000672]

55 **Bakhshayeshkaram M**, Haseli S, Iranpour P. Radiological Mimickers of COVID-19 Pneumonia: A Pictorial Review. *Tanaffos* 2020; **19**: 100-107 [PMID: 33262796]

56 **Lynch DA**. Ground glass attenuation on CT in patients with idiopathic pulmonary fibrosis. *Chest* 1996; **110**: 312-313 [PMID: 8697823 DOI: 10.1378/chest.110.2.312]

57 **Thoongsuwan N**, Kanne JP, Stern EJ. Spectrum of blunt chest injuries. *J Thorac Imaging* 2005; **20**:

89-97 [PMID: 15818207 DOI: 10.1097/01.rti.0000148210.89718.f5]
58 **Duzgun SA**, Durhan G, Demirkazik FB, Akpinar MG, Ariyurek OM. COVID-19 pneumonia: the great radiological mimicker. *Insights Imaging* 2020; **11**: 118 [PMID: 33226521 DOI: 10.1186/s13244-020-00933-z]
59 **Bai HX**, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, Pan I, Shi LB, Wang DC, Mei J, Jiang XL, Zeng QH, Egglin TK, Hu PF, Agarwal S, Xie FF, Li S, Healey T, Atalay MK, Liao WH. Performance of Radiologists in Differentiating COVID-19 from Non-COVID-19 Viral Pneumonia at Chest CT. *Radiology* 2020; **296**: E46-E54 [PMID: 32155105 DOI: 10.1148/radiol.2020200823]
60 **Marchiori E**, Zanetti G, Escuissato DL, Souza AS Jr, de Souza Portes Meirelles G, Fagundes J, Souza CA, Hochhegger B, Marom EM, Godoy MCB. Reversed halo sign: high-resolution CT scan findings in 79 patients. *Chest* 2012; **141**: 1260-1266 [PMID: 22016487 DOI: 10.1378/chest.11-1050]
61 **Miller WT Jr**, Mickus TJ, Barbosa E Jr, Mullin C, Van Deerlin VM, Shiley KT. CT of viral lower respiratory tract infections in adults: comparison among viral organisms and between viral and bacterial infections. *AJR Am J Roentgenol* 2011; **197**: 1088-1095 [PMID: 22021500 DOI: 10.2214/AJR.11.6501]
62 **Fujii T**, Nakamura T, Iwamoto A. Pneumocystis pneumonia in patients with HIV infection: clinical manifestations, laboratory findings, and radiological features. *J Infect Chemother* 2007; **13**: 1-7 [PMID: 17334722 DOI: 10.1007/s10156-006-0484-5]
63 **Orlowski HLP**, McWilliams S, Mellnick VM, Bhalla S, Lubner MG, Pickhardt PJ, Menias CO. Imaging Spectrum of Invasive Fungal and Fungal-like Infections. *Radiographics* 2017; **37**: 1119-1134 [PMID: 28622118 DOI: 10.1148/rg.2017160110]
64 **Chung M**, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A, Li K, Li S, Shan H. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020; **295**: 202-207 [PMID: 32017661 DOI: 10.1148/radiol.2020200230]
65 **McStay R**, Johnstone A, Hare SS, Jacob J, Nair A, Rodrigues JCL, Edey A, Robinson G. COVID-19: looking beyond the peak. Challenges and tips for radiologists in follow-up of a novel patient cohort. *Clin Radiol* 2021; **76**: 74.e1-74.e14 [PMID: 33109350 DOI: 10.1016/j.crad.2020.09.025]
66 **Fallucchi F**, Faravelli M, Quercia S. Fair allocation of scarce medical resources in the time of COVID-19: what do people think? *J Med Ethics* 2021; **47**: 3-6 [PMID: 33046588 DOI: 10.1136/medethics-2020-106524]
67 **Seghers VJ**, Desai NK, Masand PM, Nasir S, Foster TL, Indiero DA, Johnson TD, Huisman TAGM. After the initial COVID-19 surge: a phased radiology departmental re-opening plan. *Pediatr Radiol* 2020; **50**: 1551-1559 [PMID: 32827259 DOI: 10.1007/s00247-020-04792-0]
68 **Prabhakar AM**, Glover M 4th, Schaefer PW, Brink JA. Academic Radiology Departmental Operational Strategy Related to the Coronavirus Disease 2019 (COVID-19) Pandemic. *J Am Coll Radiol* 2020; **17**: 730-733 [PMID: 32315599 DOI: 10.1016/j.jacr.2020.04.004]
69 **Rosen MP**, Norbash A, Kruskal J, Meltzer CC, Yee J, Thrall J. Impact of Coronavirus Disease 2019 (COVID-19) on the Practice of Clinical Radiology. *J Am Coll Radiol* 2020; **17**: 1096-1100 [PMID: 32721410 DOI: 10.1016/j.jacr.2020.07.002]
70 **Naidich JJ**, Boltyenkov A, Wang JJ, Chusid J, Hughes D, Sanelli PC. Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Imaging Case Volumes. *J Am Coll Radiol* 2020; **17**: 865-872 [PMID: 32425710 DOI: 10.1016/j.jacr.2020.05.004]
71 **Wan YL**, Schoepf UJ, Wu CC, Giovagnoli DP, Wu MT, Hsu HH, Chang YC, Yang CT, Cherng WJ. Preparedness and Best Practice in Radiology Department for COVID-19 and Other Future Pandemics of Severe Acute Respiratory Infection. *J Thorac Imaging* 2020; **35**: 239-245 [PMID: 32384412 DOI: 10.1097/RTI.0000000000000529]
72 **Zanardo M**, Martini C, Monti CB, Cattaneo F, Ciaralli C, Cornacchione P, Durante S. Management of patients with suspected or confirmed COVID-19, in the radiology department. *Radiography (Lond)* 2020; **26**: 264-268 [PMID: 32340912 DOI: 10.1016/j.radi.2020.04.010]
73 **Kooraki S**, Hosseiny M, Raman SS, Myers L, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19) Precautions: What the MRI Suite Should Know. *J Am Coll Radiol* 2020; **17**: 830 [PMID: 32473107 DOI: 10.1016/j.jacr.2020.05.018]
74 **Stogiannos N**, Fotopoulos D, Woznitza N, Malamateniou C. COVID-19 in the radiology department: What radiographers need to know. *Radiography (Lond)* 2020; **26**: 254-263 [PMID: 32532596 DOI: 10.1016/j.radi.2020.05.012]
75 **Mossa-Basha M**, Medverd J, Linnau KF, Lynch JB, Wener MH, Kicska G, Staiger T, Sahani DV. Policies and Guidelines for COVID-19 Preparedness: Experiences from the University of Washington. *Radiology* 2020; **296**: E26-E31 [PMID: 32687455 DOI: 10.1148/radiol.2019201326]
76 **H'ng MW**, Tan BP, Punamiya S. Setting Up an Interventional Radiology Suite in an Infectious Diseases Centre: Lessons from the Novel Coronavirus (COVID-19) Outbreak. *Ann Acad Med Singap* 2020; **49**: 684-689 [PMID: 33241258]
77 **Lamparello NA**, Choi S, Charalel R, Lee KS, Kesselman A, Scherer K, Harnain CM, Browne WF, Shiffman M, Holzwanger DJ, Pua BB. Transforming Positive Pressure IR Suites to Treat COVID-19 Patients. *J Vasc Interv Radiol* 2020; **31**: 1496-1499 [PMID: 32747141 DOI: 10.1016/j.jvir.2020.06.019]
78 **Orsi MA**, Oliva AG, Cellina M. Radiology Department Preparedness for COVID-19: Facing an Unexpected Outbreak of the Disease. *Radiology* 2020; **295**: E8 [PMID: 32228364 DOI: 10.1148/radiol.2020201214]
79 **Lazzerini M**, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision

of care in Italy resulting from fear of COVID-19. *Lancet Child Adolesc Health* 2020; **4**: e10-e11 [PMID: 32278365 DOI: 10.1016/S2352-4642(20)30108-5]

80 **Patel NR**, El-Karim GA, Mujoomdar A, Mafeld S, Jaberi A, Kachura JR, Tan KT, Oreopoulos GD. Overall Impact of the COVID-19 Pandemic on Interventional Radiology Services: A Canadian Perspective. *Can Assoc Radiol J* 2020; 846537120951960 [PMID: 32864995 DOI: 10.1177/0846537120951960]

81 **Mujoomdar A**, Graham T, Baerlocher MO, Soulez G. The Canadian Association for Interventional Radiology (CAIR) and Canadian Association of Radiologists (CAR) Guidelines for Interventional Radiology Procedures for Patients With Suspected or Confirmed COVID-19. *Can Assoc Radiol J* 2020; **71**: 514-517 [PMID: 32380846 DOI: 10.1177/0846537120924310]

82 **Marone EM**, Rinaldi LF. Upsurge of deep venous thrombosis in patients affected by COVID-19: Preliminary data and possible explanations. *J Vasc Surg Venous Lymphat Disord* 2020; **8**: 694-695 [PMID: 32305586 DOI: 10.1016/j.jvsv.2020.04.004]

83 **Zhang L**, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation* 2020; **142**: 114-128 [PMID: 32421381 DOI: 10.1161/CIRCULATIONAHA.120.046702]

84 **Behzad S**, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview. *Clin Imaging* 2020; **66**: 35-41 [PMID: 32425338 DOI: 10.1016/j.clinimag.2020.05.013]

85 **Kang Y**, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, Chen Y, Han Y. Cardiovascular manifestations and treatment considerations in COVID-19. *Heart* 2020; **106**: 1132-1141 [PMID: 32354800 DOI: 10.1136/heartjnl-2020-317056]

86 **Rojulpote C**, Gonuguntla K, Patil S, Bhattaru A, Bravo PE. COVID-19 and the Heart. *Colomb Med (Cali)* 2020; **51**: e4320 [PMID: 33012891 DOI: 10.25100/cm.v51i2.4320]

87 **Citro R**, Pontone G, Bellino M, Silverio A, Iuliano G, Baggiano A, Manka R, Iesu S, Vecchione C, Asch FM, Ghadri JR, Templin C. Role of multimodality imaging in evaluation of cardiovascular involvement in COVID-19. *Trends Cardiovasc Med* 2021; **31**: 8-16 [PMID: 33065315 DOI: 10.1016/j.tcm.2020.10.001]

88 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]

89 **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683-690 [PMID: 32275288 DOI: 10.1001/jamaneurol.2020.1127]

90 **Wu Y**, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun* 2020; **87**: 18-22 [PMID: 32240762 DOI: 10.1016/j.bbi.2020.03.031]

91 **Egbert AR**, Cankurtaran S, Karpiak S. Brain abnormalities in COVID-19 acute/subacute phase: A rapid systematic review. *Brain Behav Immun* 2020; **89**: 543-554 [PMID: 32682993 DOI: 10.1016/j.bbi.2020.07.014]

92 **Conklin J**, Frosch MP, Mukerji S, Rapalino O, Maher M, Schaefer PW, Lev MH, Gonzalez RG, Das S, Champion SN, Magdamo C, Sen P, Harrold GK, Alabsi H, Normandin E, Shaw B, Lemieux J, Sabeti P, Branda JA, Brown EN, Westover MB, Huang SY, Edlow BL. Cerebral Microvascular Injury in Severe COVID-19. *medRxiv* 2020 [PMID: 32743599 DOI: 10.1101/2020.07.21.20159376]

93 **Kremer S**, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, Collange O, Bonneville F, Adam G, Martin-Blondel G, Rafiq M, Geeraerts T, Delamarre L, Grand S, Krainik A, Caillard S, Constans JM, Metanbou S, Heintz A, Helms J, Schenck M, Lefèbvre N, Boutet C, Fabre X, Forestier G, de Beaurepaire I, Bornet G, Lacalm A, Oesterlé H, Bolognini F, Messié J, Hmeydia G, Benzakoun J, Oppenheim C, Bapst B, Megdiche I, Henry Feugeas MC, Khalil A, Gaudemer A, Jager L, Nesser P, Talla Mba Y, Hemmert C, Feuerstein P, Sebag N, Carré S, Alleg M, Lecocq C, Schmitt E, Anxionnat R, Zhu F, Comby PO, Ricolfi F, Thouant P, Desal H, Boulouis G, Berge J, Kazémi A, Pyatigorskaya N, Lecler A, Saleme S, Edjlali-Goujon M, Kerleroux B, Zorn PE, Matthieu M, Baloglu S, Ardellier FD, Willaume T, Brisset JC, Boulay C, Mutschler V, Hansmann Y, Mertes PM, Schneider F, Fafi-Kremer S, Ohana M, Meziani F, David JS, Meyer N, Anheim M, Cotton F. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. *Radiology* 2020; **297**: E242-E251 [PMID: 32544034 DOI: 10.1148/radiol.2020202222]

94 **Gu J**, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. *Gastroenterology* 2020; **158**: 1518-1519 [PMID: 32142785 DOI: 10.1053/j.gastro.2020.02.054]

95 **Dane B**, Brusca-Augello G, Kim D, Katz DS. Unexpected Findings of Coronavirus Disease (COVID-19) at the Lung Bases on Abdominopelvic CT. *AJR Am J Roentgenol* 2020; **215**: 603-606 [PMID: 32319792 DOI: 10.2214/AJR.20.23240]

96 **Bhayana R**, Som A, Li MD, Carey DE, Anderson MA, Blake MA, Catalano O, Gee MS, Hahn PF, Harisinghani M, Kilcoyne A, Lee SI, Mojtahed A, Pandharipande PV, Pierce TT, Rosman DA, Saini

S, Samir AE, Simeone JF, Gervais DA, Velmahos G, Misdraji J, Kambadakone A. Abdominal Imaging Findings in COVID-19: Preliminary Observations. *Radiology* 2020; **297**: E207-E215 [PMID: 32391742 DOI: 10.1148/radiol.2020201908]

97 **Parry AH**, Wani AH, Yaseen M. Acute Mesenteric Ischemia in Severe Coronavirus-19 (COVID-19): Possible Mechanisms and Diagnostic Pathway. *Acad Radiol* 2020; **27**: 1190 [PMID: 32475635 DOI: 10.1016/j.acra.2020.05.016]

98 **Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: 32170806 DOI: 10.1111/liv.14435]

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

100 **Fabrizi F**, Alfieri CM, Cerutti R, Lunghi G, Messa P. COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. *Pathogens* 2020; **9** [PMID: 33334023 DOI: 10.3390/pathogens9121052]

101 **Galván Casas C**, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, Navarro Fernández I, Ruiz-Villaverde R, Falkenhain-López D, Llamas Velasco M, García-Gavín J, Baniandrés O, González-Cruz C, Morillas-Lahuerta V, Cubiró X, Figueras Nart I, Selda-Enriquez G, Romaní J, Fustà-Novell X, Melian-Olivera A, Roncero Riesco M, Burgos-Blasco P, Sola Ortigosa J, Feito Rodriguez M, García-Doval I. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol* 2020; **183**: 71-77 [PMID: 32348545 DOI: 10.1111/bjd.19163]

102 **Manalo IF**, Smith MK, Cheeley J, Jacobs R. A dermatologic manifestation of COVID-19: Transient livedo reticularis. *J Am Acad Dermatol* 2020; **83**: 700 [PMID: 32283229 DOI: 10.1016/j.jaad.2020.04.018]

103 **Monpara JD**, Sodha SJ, Gupta PK. COVID-19 associated complications and potential therapeutic targets. *Eur J Pharmacol* 2020; **886**: 173548 [PMID: 32926918 DOI: 10.1016/j.ejphar.2020.173548]

104 **Bassetti M**, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. *Intensive Care Med* 2020; **46**: 2071-2074 [PMID: 32902729 DOI: 10.1007/s00134-020-06219-8]

105 **Jajodia A**, Ebner L, Heidinger B, Chaturvedi A, Prosch H. Imaging in corona virus disease 2019 (COVID-19)-A Scoping review. *Eur J Radiol Open* 2020; **7**: 100237 [PMID: 32395567 DOI: 10.1016/j.ejro.2020.100237]

106 **Tang X**, Du RH, Wang R, Cao TZ, Guan LL, Yang CQ, Zhu Q, Hu M, Li XY, Li Y, Liang LR, Tong ZH, Sun B, Peng P, Shi HZ. Comparison of Hospitalized Patients With ARDS Caused by COVID-19 and H1N1. *Chest* 2020; **158**: 195-205 [PMID: 32224074 DOI: 10.1016/j.chest.2020.03.032]

107 **Malas MB**, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine* 2020; **29**: 100639 [PMID: 33251499 DOI: 10.1016/j.eclinm.2020.100639]

108 **Gall H**, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev* 2017; **26** [PMID: 28356407 DOI: 10.1183/16000617.0121-2016]

109 **Gopalan D**, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017; **26** [PMID: 28298387 DOI: 10.1183/16000617.0108-2016]

110 **Azer SA**. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New Microbes New Infect* 2020; **37**: 100738 [PMID: 32834902 DOI: 10.1016/j.nmni.2020.100738]

111 **Bashshur RL**, Krupinski EA, Thrall JH, Bashshur N. The Empirical Foundations of Teleradiology and Related Applications: A Review of the Evidence. *Telemed J E Health* 2016; **22**: 868-898 [PMID: 27585301 DOI: 10.1089/tmj.2016.0149]

112 **European Society of Radiology (ESR)**. ESR white paper on teleradiology: an update from the teleradiology subgroup. *Insights Imaging* 2014; **5**: 1-8 [PMID: 24443129 DOI: 10.1007/s13244-013-0307-z]

113 **Thrall JH**. Teleradiology. Part I. History and clinical applications. *Radiology* 2007; **243**: 613-617 [PMID: 17517922 DOI: 10.1148/radiol.2433070350]

114 **Boland GW**. Teleradiology coming of age: winners and losers. *AJR Am J Roentgenol* 2008; **190**: 1161-1162 [PMID: 18430825 DOI: 10.2214/AJR.07.3114]

115 **Hanna TN**, Steenburg SD, Rosenkrantz AB, Pyatt RS Jr, Duszak R Jr, Friedberg EB. Emerging Challenges and Opportunities in the Evolution of Teleradiology. *AJR Am J Roentgenol* 2020; **215**: 1411-1416 [PMID: 33052736 DOI: 10.2214/AJR.20.23007]

116 **Lun R**, Walker G, Daham Z, Ramsay T, Portela de Oliveira E, Kassab M, Fahed R, Quateen A, Lesiuk H, P Dos Santos M, Drake B. Transition to virtual appointments for interventional neuroradiology due to the COVID-19 pandemic: a survey of satisfaction. *J Neurointerv Surg* 2020; **12**: 1153-1156 [PMID: 33028673 DOI: 10.1136/neurintsurg-2020-016805]

117 **Lam PW**, Sehgal P, Andany N, Mubareka S, Simor AE, Ozaldin O, Leis JA, Daneman N, Chan AK. A virtual care program for outpatients diagnosed with COVID-19: a feasibility study. *CMAJ Open* 2020; **8**: E407-E413 [PMID: 32447283 DOI: 10.9778/cmajo.20200069]

118 **Robb JF**, Hyland MH, Goodman AD. Comparison of telemedicine versus in-person visits for

persons with multiple sclerosis: A randomized crossover study of feasibility, cost, and satisfaction. *Mult Scler Relat Disord* 2019; **36**: 101258 [PMID: 31472419 DOI: 10.1016/j.msard.2019.05.001]

119 **Prokop M**, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**: E97-E104 [PMID: 32339082 DOI: 10.1148/radiol.2020201473]

120 **Vermani S**, Kaushal A, Kaushal J. COVID-19 and the Radiology Department: What We Know So Far. *SN Compr Clin Med* 2020; 1-7 [PMID: 33024936 DOI: 10.1007/s42399-020-00554-z]

121 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]

122 **Figliozzi S**, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, Stamatelopoulos K, Dimopoulos MA, Caforio ALP, Georgiopoulos G. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. *Eur J Clin Invest* 2020; **50**: e13362 [PMID: 32726868 DOI: 10.1111/eci.13362]

123 **Kumar S**, Kumar A, Goel P, Vyas S, Baitha U, Wig N. Use of ultrasonography in COVID-19: Probing for success. *J Family Med Prim Care* 2020; **9**: 3863-3866 [PMID: 33110780 DOI: 10.4103/jfmpc.jfmpc_764_20]

124 **Bitar ZI**, Maadarani OS, El-Shably AM, Al-Ajmi MJ. Diagnostic accuracy of chest ultrasound in patients with pneumonia in the intensive care unit: A single-hospital study. *Health Sci Rep* 2019; **2**: e102 [PMID: 30697596 DOI: 10.1002/hsr2.102]

125 **Testa A**, Soldati G, Copetti R, Giannuzzi R, Portale G, Gentiloni-Silveri N. Early recognition of the 2009 pandemic influenza A (H1N1) pneumonia by chest ultrasound. *Crit Care* 2012; **16**: R30 [PMID: 22340202 DOI: 10.1186/cc11201]

126 **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]

127 **Copetti R**, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. *Cardiovasc Ultrasound* 2008; **6**: 16 [PMID: 18442425 DOI: 10.1186/1476-7120-6-16]

128 **Tusman G**, Acosta CM, Costantini M. Ultrasonography for the assessment of lung recruitment maneuvers. *Crit Ultrasound J* 2016; **8**: 8 [PMID: 27496127 DOI: 10.1186/s13089-016-0045-9]

129 **Qian Z**, Yang M, Li L, Chen Y. Ultrasound assessment of diaphragmatic dysfunction as a predictor of weaning outcome from mechanical ventilation: a systematic review and meta-analysis. *BMJ Open* 2018; **8**: e021189 [PMID: 30287605 DOI: 10.1136/bmjopen-2017-021189]

130 **Wang XT**, Ding X, Zhang HM, Chen H, Su LX, Liu DW; Chinese Critical Ultrasound Study Group (CCUSG). Lung ultrasound can be used to predict the potential of prone positioning and assess prognosis in patients with acute respiratory distress syndrome. *Crit Care* 2016; **20**: 385 [PMID: 27899151 DOI: 10.1186/s13054-016-1558-0]

131 **Duggan NM**, Shokoohi H, Liteplo AS, Huang C, Goldsmith AJ. Best Practice Recommendations for Point-of-Care Lung Ultrasound in Patients with Suspected COVID-19. *J Emerg Med* 2020; **59**: 515-520 [PMID: 32713618 DOI: 10.1016/j.jemermed.2020.06.033]

132 **Antúnez-Montes OY**, Buonsenso D. Routine use of Point-of-Care lung ultrasound during the COVID-19 pandemic. *Med Intensiva (Engl Ed)* 2020 [PMID: 32386997 DOI: 10.1016/j.medin.2020.04.010]

133 **World Federation for Ultrasound in Medicine and Biology Safety Committee (Jacques S Abramowicz**, Iwaki Akiyama, David Evans, J Brian Fowlkes, Karel Marsal, Yusef Sayeed and Gail ter Haar), Abramowicz JS, Basseal JM. World Federation for Ultrasound in Medicine and Biology Position Statement: How to Perform a Safe Ultrasound Examination and Clean Equipment in the Context of COVID-19. *Ultrasound Med Biol*. 2020; **46**: 1821-1826 [PMID: 32327199 DOI: 10.1016/j.ultrasmedbio.2020.03.033]

134 **Moore S**, Gardiner E. Point of care and intensive care lung ultrasound: A reference guide for practitioners during COVID-19. *Radiography (Lond)* 2020; **26**: e297-e302 [PMID: 32327383 DOI: 10.1016/j.radi.2020.04.005]

135 **Sheth S**, Fetzer D, Frates M, Needleman L, Middleton W, Jones J, Podrasky A, Mankowski Gettle L. Guidelines for Ultrasound in the Radiology Department During the COVID-19 Pandemic. *Ultrasound Q* 2020; **36**: 200-205 [PMID: 32890322 DOI: 10.1097/RUQ.0000000000000526]

136 **Piscaglia F**, Stefanini F, Cantisani V, Sidhu PS, Barr R, Berzigotti A, Chammas MC, Correas JM,

Dietrich CF, Feinstein S, Huang P, Jenssen C, Kono Y, Kudo M, Liang P, Lyshchik A, Nolsøe C, Xie X, Tovoli F. Benefits, Open questions and Challenges of the use of Ultrasound in the COVID-19 pandemic era. The views of a panel of worldwide international experts. *Ultraschall Med* 2020; **41**: 228-236 [PMID: 32294795 DOI: 10.1055/a-1149-9872]

137 **Vetrugno L**, Bove T, Orso D, Barbariol F, Bassi F, Boero E, Ferrari G, Kong R. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. *Echocardiography* 2020; **37**: 625-627 [PMID: 32239532 DOI: 10.1111/echo.14664]

138 **Jackson K**, Butler R, Aujayeb A. Lung ultrasound in the COVID-19 pandemic. *Postgrad Med J* 2021; **97**: 34-39 [PMID: 32895294 DOI: 10.1136/postgradmedj-2020-138137]

139 **Yau O**, Gin K, Luong C, Jue J, Abolmaesumi P, Tsang M, Nair P, Tsang TSM. Point-of-care ultrasound in the COVID-19 era: A scoping review. *Echocardiography* 2021; **38**: 329-342 [PMID: 33332638 DOI: 10.1111/echo.14951]

140 **Long JB**, Ehrenfeld JM. The Role of Augmented Intelligence (AI) in Detecting and Preventing the Spread of Novel Coronavirus. *J Med Syst* 2020; **44**: 59 [PMID: 32020374 DOI: 10.1007/s10916-020-1536-6]

141 **Li L**, Qin L, Xu Z, Yin Y, Wang X, Kong B, Bai J, Lu Y, Fang Z, Song Q, Cao K, Liu D, Wang G, Xu Q, Fang X, Zhang S, Xia J. Using Artificial Intelligence to Detect COVID-19 and Community-acquired Pneumonia Based on Pulmonary CT: Evaluation of the Diagnostic Accuracy. *Radiology* 2020; **296**: E65-E71 [PMID: 32191588 DOI: 10.1148/radiol.2020200905]

142 **Shaikh F**, Andersen MB, Sohail MR, Mulero F, Awan O, Dupont-Roettger D, Kubassova O, Dehmeshki J, Bisdas S. Current Landscape of Imaging and the Potential Role for Artificial Intelligence in the Management of COVID-19. *Curr Probl Diagn Radiol* 2021; **50**: 430-435 [PMID: 32703538 DOI: 10.1067/j.cpradiol.2020.06.009]

143 **Apostolopoulos ID**, Mpesiana TA. Covid-19: automatic detection from X-ray images utilizing transfer learning with convolutional neural networks. *Phys Eng Sci Med* 2020; **43**: 635-640 [PMID: 32524445 DOI: 10.1007/s13246-020-00865-4]

144 **Shi F**, Wang J, Shi J, Wu Z, Wang Q, Tang Z, He K, Shi Y, Shen D. Review of Artificial Intelligence Techniques in Imaging Data Acquisition, Segmentation, and Diagnosis for COVID-19. *IEEE Rev Biomed Eng* 2021; **14**: 4-15 [PMID: 32305937 DOI: 10.1109/RBME.2020.2987975]

145 **Wang L**, Lin ZQ, Wong A. COVID-Net: a tailored deep convolutional neural network design for detection of COVID-19 cases from chest X-ray images. *Sci Rep* 2020; **10**: 19549 [PMID: 33177550 DOI: 10.1038/s41598-020-76550-z]

146 **Tang Z**, Zhao W, Xie X, Zhong Z, Shi F, Ma T, Liu J, Shen D. Severity assessment of COVID-19 using CT image features and laboratory indices. *Phys Med Biol* 2021; **66**: 035015 [PMID: 33032267 DOI: 10.1088/1361-6560/abbf9e]

147 **Helms J**, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, Meziani F. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020; **382**: 2268-2270 [PMID: 32294339 DOI: 10.1056/NEJMc2008597]

World Journal of Radiology

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

World J Radiol 2021 June 28; 13(6): 192-222

DOI: 10.4329/wjr.v13.i6.192

ISSN 1949-8470 (online)

REVIEW

Imaging in the COVID-19 era: Lessons learned during a pandemic

Georgios Antonios Sideris, Melina Nikolakea, Aikaterini-Eleftheria Karanikola, Sofia Konstantinopoulou, Dimitrios Giannis, Lucy Modahl

ORCID number: Georgios Antonios Sideris 0000-0001-7927-3690; Melina Nikolakea 0000-0001-9095-0007; Aikaterini-Eleftheria Karanikola 0000-0002-9153-5697; Sofia Konstantinopoulou 0000-0001-7459-9923; Dimitrios Giannis 0000-0001-9246-976X; Lucy Modahl 0000-0001-7428-5035.

Author contributions: Sideris GA conceived the topic and designed the structure of the manuscript; Sideris GA, Nikolakea M, Karanikola AE, Konstantinopoulou S and Giannis D wrote the manuscript; Modahl L critically revised the manuscript; Sideris GA and Modahl L selected the images; Sideris GA, Nikolakea M, Karanikola AE, Konstantinopoulou S, Giannis D and Modahl L provided final approval.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the

Georgios Antonios Sideris, Lucy Modahl, Department of Radiology, University of Massachusetts Medical School, Baystate Medical Center, Springfield, MA 01199, United States

Georgios Antonios Sideris, Melina Nikolakea, Aikaterini-Eleftheria Karanikola, Radiology Working Group, Society of Junior Doctors, Athens 11527, Greece

Sofia Konstantinopoulou, Division of Pulmonary Medicine, Department of Pediatrics, Sheikh Khalifa Medical City, Abu Dhabi W13-01, United Arab Emirates

Dimitrios Giannis, Institute of Health Innovations and Outcomes Research, The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY 11030, United States

Corresponding author: Georgios Antonios Sideris, MD, Doctor, Department of Radiology, University of Massachusetts Medical School, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199, United States. siderismd@gmail.com

Abstract

The first year of the coronavirus disease 2019 (COVID-19) pandemic has been a year of unprecedented changes, scientific breakthroughs, and controversies. The radiology community has not been spared from the challenges imposed on global healthcare systems. Radiology has played a crucial part in tackling this pandemic, either by demonstrating the manifestations of the virus and guiding patient management, or by safely handling the patients and mitigating transmission within the hospital. Major modifications involving all aspects of daily radiology practice have occurred as a result of the pandemic, including workflow alterations, volume reductions, and strict infection control strategies. Despite the ongoing challenges, considerable knowledge has been gained that will guide future innovations. The aim of this review is to provide the latest evidence on the role of imaging in the diagnosis of the multifaceted manifestations of COVID-19, and to discuss the implications of the pandemic on radiology departments globally, including infection control strategies and delays in cancer screening. Lastly, the promising contribution of artificial intelligence in the COVID-19 pandemic is explored.

Key Words: COVID-19; Infectious diseases; Diagnostic imaging; Radiography; Computed tomography; Artificial intelligence

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: February 8, 2021
Peer-review started: February 8, 2021
First decision: March 17, 2021
Revised: April 2, 2021
Accepted: June 15, 2021
Article in press: June 15, 2021
Published online: June 28, 2021

P-Reviewer: Liu Y
S-Editor: Gao CC
L-Editor: A
P-Editor: Wang LYT

Core Tip: The coronavirus disease 2019 pandemic has had dramatic implications for radiology practices worldwide. In this review, the evidence-based role of various imaging modalities in the diagnosis and management of the multisystemic manifestations of severe acute respiratory syndrome coronavirus 2 infection is summarized. In addition, the infection control strategies, the impact of delayed cancer screening and the future role of artificial intelligence are explored.

Citation: Sideris GA, Nikolakea M, Karanikola AE, Konstantinopoulou S, Giannis D, Modahl L. Imaging in the COVID-19 era: Lessons learned during a pandemic. *World J Radiol* 2021; 13(6): 192-222
URL: https://www.wjgnet.com/1949-8470/full/v13/i6/192.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i6.192

INTRODUCTION

The year 2020 has been marked by the worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel SARS-CoV-2 that emerged in Wuhan, China in December 2019 belongs to the same genus as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS), which caused epidemics with high mortality rates in 2002 and 2012 respectively[1]. Despite the similarities in genomic identity, SARS-CoV-2 has a higher infectivity rate and a lower case-fatality rate, contributing to its much wider spread[2]. Since the first official SARS-CoV-2 case was documented, the virus has resulted in 173.4 million infections and 3.7 million deaths worldwide as of June 4, 2021[3].

SARS-CoV-2 causes multiorgan damage by attaching to the angiotensin-converting enzyme 2 receptors expressed by epithelial cells and microvascular pericytes. It primarily targets the lung parenchyma, resulting in acute respiratory distress syndrome (ARDS). Multiorgan dysfunction can occur either by direct viral-mediated damage, or indirectly *via* the systemic inflammatory response syndrome and the hypercoagulable state induced by the virus[4]. The constellation of end-organ injuries stemming from SARS-CoV-2 infection has been referred to as coronavirus disease 2019 (COVID-19). Around 80% of infected individuals develop mild-moderate disease, whereas 14% have severe symptoms and 5% patients become critically ill[5]. Factors associated with worse outcomes and higher mortality include hypertension, diabetes mellitus, coronary artery disease, older age and severe obesity[6-8].

Similar to previous pandemics, imaging has played a pivotal role in the management of patients with acute respiratory illness. In 1918, just 23 years after the discovery of X-rays, the deadly H1N1 influenza A pandemic was the first ever large-scale application of radiology. Although plain radiography could not provide a specific diagnosis, it was the only available modality that could visualize the presence, the extent and complications of a pulmonary infection[9]. Nearly a century later, advanced imaging technologies, including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) have dramatically increased the value of imaging in patient care.

The radiology community has faced numerous challenges as a result of the new global public health emergency. The initially unknown imaging manifestations of the novel virus were described and made available to the scientific community soon after the onset of the pandemic, although studies reporting on radiologic-pathologic correlation were not released till later[10,11]. Unlike previous pandemics, COVID-19 has been the subject of an extraordinary number of publications, the majority of which were commentaries and opinion papers[12]. Many medical journals initiated a rapid peer-review process for COVID-19- related submissions in order to make the latest advances quickly available to the scientific community[13]. However, the lack of meticulous review has led to the publication of biased studies, some of which were later retracted even from top medical journals. This so-called "infodemic" contributes to confusion and dilutes the pool of legitimate original research investigations[12,14].

Radiology departments worldwide implemented drastic policies to minimize transmission of the virus between patients and staff. Some of the strategies that were enforced include efficient triaging of patients, designation of imaging rooms specifically for suspected cases, meticulous disinfection, enforcement of personal

protective equipment (PPE) and shortening of scanning protocols whenever possible. Elective imaging studies were postponed during the first surge of the pandemic, which caused a significant drop in case volumes and a delay in cancer detection[15,16].

The aim of this review is to summarize the current knowledge of the multi-organ imaging manifestations of COVID-19 and to describe the infection control strategies that were enforced in radiology departments. Moreover, the repercussions of delayed screening studies and the promise of artificial intelligence (AI) are explored.

PULMONARY MANIFESTATIONS

CT

Diagnostic value: The gold standard for the diagnosis of SARS-CoV-2 is the real-time reverse transcriptase polymerase chain reaction (RT-PCR) using nasopharyngeal samples[17]. Although it has excellent specificity, sensitivity may vary between 42%-83%[18,19]. This wide range in reported sensitivities can be attributed to inadequate or improper tissue sampling, early timing of sampling (when the viral load is low), or laboratory errors[20]. High false-negative rates can have a crucial impact, as patients who are misdiagnosed as negative can continue transmitting the virus within the hospital or the community. Moreover, the initial RT-PCR test kits had long processing times and were not readily available in certain regions due to high demand.

Given the need for rapid triaging of patients and prevention of transmission, chest CT was proposed as a rapid, reproducible and widely available screening tool[21-23]. However, many methodologic concerns and shortcomings are present in studies reporting on the performance of chest CT as a diagnostic tool[24]. The majority of published studies based their findings on populations with high disease prevalence or with only symptomatic patients, introducing a selection bias[25]. Furthermore, some studies used CT as a binary test with a low threshold for determining a positive examination, which may also overestimate sensitivity and compromise specificity[26,27]. Several meta-analyses have attempted to generate an estimated sensitivity; however, many of them did not assess the risk of bias in the included studies[28].

As a result of these discrepancies, there is great variability in the reported sensitivities (60%-98%) and specificities (25%-53%) of chest CT in the detection of COVID-19 pneumonia [19]. A Cochrane meta-analysis including data from 31 studies with low risk of bias and 8014 participants, 53% of which were COVID-19 positive, showed that chest CT has 89.9% sensitivity and 61.1% specificity[29]. The use of CT as a screening tool has multiple limitations, including high cost, radiation exposure, and transmission risk within the radiology department due to clustering of patients[30]. It has poor specificity due to overlap with other pulmonary diseases (*i.e.*, viral pneumonias, pulmonary edema, interstitial lung disease), and therefore cannot be used as a confirmatory test[31]. Moreover, with a reported negative predictive value of 42%, CT chest can lead to false negative results in patients early in the course of the disease. In view of these limitations, the World Health Organization (WHO), the American College of Radiology (ACR) and other societies have released statements urging against the use of chest CT as a screening tool[32,33].

Indications: Chest CT is a valuable imaging modality that can provide an accurate assessment of the severity and extent of disease, detect complications, evaluate treatment efficacy and rule out alternative diagnoses[34].

Based on the guidelines released by the Fleischner Society, chest imaging is indicated in patients with worsening clinical status and for rapid triage of patients with moderate-severe respiratory symptoms in a setting of high pre-test probability and low RT-PCR availability[35]. Additionally, the WHO recommends chest imaging when RT-PCR is negative but clinical suspicion for COVID-19 remains high, and to help guide admission to the medical floor *vs* intensive care unit (ICU) in patients with moderate-severe illness[32]. Although imaging is not indicated in suspected cases with mild symptoms based on the Fleischner Society guidelines, the WHO recommends chest imaging in suspected or confirmed mild cases to help decide on hospital admission *vs* discharge, especially in patients at high risk of disease progression. Neither of the aforementioned guidelines clarify which chest imaging modality needs to be used on each clinical scenario or provide guidance on follow-up imaging intervals and scanning protocols.

Imaging findings: COVID-19 pneumonia causes a wide spectrum of acute lung injury ranging from mild inflammation to diffuse alveolar damage[36]. Ground-glass opacities (GGOs) are the most common imaging manifestation, seen in 65% of patients

[37]. GGOs are bilateral in 88%, although they may remain unilateral throughout the course of the disease in 17% of cases[38,39]. They typically have a peripheral/subpleural distribution with a predilection for the posterior segments of the lower lobes, but may be diffuse in 29% of cases[39]. GGOs may be pure (more commonly) or be accompanied by consolidations (mixed pattern). Intralobular and interlobular septal thickening, likely a combination of interstitial inflammation and fluid, is seen in 27% of cases. Superimposed GGOs giving a crazy-paving pattern is seen in 12% and may be a sign of more severe lung injury and disease progression[37]. Consolidations, seen in up to 32% of cases, have a subpleural or peribronchovascular distribution and may or may not have air-bronchograms[37,40]. They are associated with more severe disease requiring management in the ICU[41]. Cavitations are not typically seen.

Subsegmental vascular enlargement (greater than 3 mm) within parenchymal abnormalities has been described in up to 64%-89% of patients[42,43]. Although the exact pathogenesis is uncertain, it is thought to be related to hyperemia or thrombotic microangiopathy[43,44]. Pulmonary nodules are considered atypical, as they are seen in only 9% of cases. The halo sign (consolidation surrounded by GGO) and the reverse halo sign (GGO surrounded by a rim of consolidation) have been described late in the disease course of COVID-19 pneumonia but are considered non-specific[4]. Pleural thickening has been described more commonly than pleural effusions (1.6%). Mediastinal adenopathy is rarely seen in COVID-19 pneumonia (0.7%) and when seen it should point to another process such as concurrent chronic congestive heart failure or even bacterial superinfection. The presence of pericardial effusion should raise concern for COVID-19 related cardiac injury.

Differential diagnosis: GGOs are a non-specific finding that may occur in numerous other entities. However, the distribution and pattern of GGOs as well as accompanying features can aid in the differential diagnosis. Pulmonary edema can manifest with GGOs in a central distribution and peripheral sparing, along with smooth interlobular septal thickening, peribronchial cuffing, cardiomegaly, dilated pulmonary veins, and pleural effusions. Diffuse alveolar hemorrhage is characterized by diffuse peribronchovascular GGOs but no subpleural predominance. Drug-induced pneumonitis can present as non-specific interstitial pneumonia with subpleural sparing. E-cigarette vaping induce lung injury (EVALI) can present with peribronchovascular GGOs with subpleural sparing. Bronchiolitis is characterized by centrilobular opacities, as well as bronchial wall thickening, bronchiectasis and air-trapping[45,46].

Pulmonary manifestations of SARS-CoV-2 on CT overlap with other viral infections. In SARS-CoV-1 and MERS infection, GGOs are typically unifocal and less extensive, and the halo and reverse halo signs are atypical[47,48]. Influenza can also manifest as bilateral GGOs, with or without consolidations, with a lower lobe predilection; bronchiectasis and pleural effusions are, however, more common[49]. In parainfluenza, centrilobular nodules and bronchial wall thickening are typical. Respiratory syncytial virus infection is characterized by centrilobular nodules (tree-in-bud) and asymmetric consolidations. In adenovirus infection, bilateral multifocal GGOs and consolidations are seen in a lobar or segmental distribution, frequently with pleural effusion[46,50].

Lobar bacterial pneumonia (primarily caused by *Streptococcus pneumoniae*, *Legionella pneumophila*, *Mycoplasma*) manifests as lobar or multilobar consolidations, typically with regional adenopathy and pleural effusions. Bronchopneumonia (*Staphylococus aureus*, *Pseudomonas*, *Klebsiella*, *Haemophilus influenzae*) manifests as confluent peribronchial consolidations, GGOs, centrilobular nodules, bronchial wall thickening, and mucoid impaction. Lymphadenopathy, pleural effusions and cavitations are common with some of these organisms. Interstitial pneumonia (caused by *Mycoplasma* and other atypical agents) presents with patchy GGOs, consolidations and centrilobular nodules [46].

Structured reporting: The Fleischner society recommends RT-PCR in patients with CT findings suggestive of COVID-19[35]. The Radiological Society of North America (RSNA) suggested the use of a structured reporting system to decrease reporting variability among radiologists and to reduce uncertainty about the findings that should raise concern for COVID-19[19]. It has been validated by several studies and appears to be useful in clinical decision making[18,51]. According to this system, findings on CT are categorized in 4 categories: typical, indeterminate, atypical and negative for COVID-19 pneumonia.

Typical findings are the bilateral multifocal peripheral GGOs, which may or may not be accompanied by consolidations and thickened interlobular septa. Additionally, typical findings include signs of organizing pneumonia (OP), such as the reverse halo sign. When applied to chest CTs of 211 patients positive for SARS-CoV-2 and 249 negative patients in Italy, the "typical" pattern had a 71.6% sensitivity, 91.6% specificity and 87.8% PPV for COVID-19 infection, although the PPV varied by disease prevalence. In negative patients with a typical pattern (8.4%), the final diagnosis was viral pneumonia other than COVID-19 (81.0%), bacterial infection (9.5%) and drug toxicity (9.5%)[51].

The "indeterminate" category includes findings with a lower specificity for COVID-19 pneumonia. These include GGOs that are non-peripheral, multifocal, diffuse, perihilar, unilateral, with or without consolidations. The "indeterminate" category imposes a diagnostic challenge as there is marked overlap with other infectious and non-infectious diagnoses, such as acute hypersensitivity pneumonitis, Pneumocystis infection and diffuse alveolar hemorrhage.

Atypical findings include lobar or segmental consolidations without GGOs, cavitations, small discrete centrilobular nodules, smooth interlobar septal thickening and pleural effusions. These findings are uncommonly reported in association with COVID-19 pneumonia, and are associated with bacterial pneumonia, necrotizing pneumonia, or aspiration, among others. The "negative" category includes cases with no evidence of pneumonia on CT. The atypical and negative patterns were more frequently observed in SARS-CoV-19 - negative patients[51].

Similar to other reporting and data systems widely used primarily for cancer reporting, the COVID-19 Reporting and Data System (CO-RADS) was designed by the Dutch Radiological Society to provide a standardized assessment of the level of suspicion for COVID-19 on chest CT. Seven categories were created, with a considerable overlap with the RSNA reporting system: CO-RADS 0 (technical limitations, uninterpretable), CO-RADS 1 (negative or very low suspicion), CO-RADS 2 (low suspicion), CO-RADS 3 (equivocal), CO-RADS 4 (high suspicion), CO-RADS 5 (very high suspicion) and CO-RADS 6 (confirmed by RT-PCR)[52]. The pilot study that assessed the performance of CO-RADS included 105 suspected COVID-19 cases, 51% of which were confirmed by a positive RT-PCR. Highest interobserver agreement was seen with the CO-RADS 1 and 5 categories. Performance, however, was tested in a setting of high prevalence of SARS-CoV-2 and low prevalence of other viral pneumonias, which may overestimate the positive predictive value[52]. Further studies have investigated the utility of CO-RADS in larger samples. A study included 859 suspected cases (42% of which were positive by RT-PCR), as well as 1138 controls who presented to the emergency room for other reasons within the same time period (5% of which were incidentally found to be COVID-19 positive). In the symptomatic cohort, when CO-RADS 4 was used as a threshold, sensitivity and specificity were 85% and 85% respectively, whereas for CO-RADS 5 rates were 78% and 93%, respectively. In asymptomatic patients, a threshold of CO-RADS 3 had a very poor sensitivity (45%) but high specificity (89%), suggesting that incidental CO-RADS 3 findings should prompt RT-PCR testing[53]. The high sensitivity of CO-RADS 4 and 5 suggests that patients who belong to these categories and have a negative initial RT-PCR need to remain in isolation until a repeat RT-PCR is negative, quarantine has lapsed or an alternate diagnosis is made[29,54].

Various severity scoring systems have been created in order to provide a quantified assessment of pulmonary involvement on chest CT. They usually divide each lung into segments and assign a score for the extent of involvement and nature of opacities. A final score is created by summing the scores for each individual segment. Higher CT severity scores are seen in patients with critical disease compared to those with milder disease[34] and have been associated with worse long-term outcomes[55]. No association has been found between the extent of CT findings and infectivity[56].

Disease phases: The findings on chest CT follow the temporal changes of COVID-19 pneumonia. Chest CT has a limited value during the first 48 h from symptom onset, as up to 56% of patients have no lung abnormalities[54,57]. Within 4 d, pure GGOs develop, which may have rounded margins or may outline adjacent secondary pulmonary lobules[37]. In the progressive phase of the disease (5-14 d), the GGOs become more extensive and may coalesce into multifocal consolidations. Septal thickening and crazy-paving are more frequent. Findings reach their peak at day 9-13 after symptom onset[38,58]. In the late or absorption phase (after day 14), there is a gradual clearance of GGOs and consolidations. Signs of fibrosis and parenchymal remodeling may develop, which can manifest as parenchymal bands, subpleural lines, interlobular septal distortion and traction bronchiectasis[39,59].

OP has been described as a pattern of response to acute lung injury caused by SARS-CoV-2, similar to other viral infections such as SARS-CoV-1, MERS and influenza[60,61]. It is histologically characterized by fibrous plugs within the alveoli and respiratory bronchioles. The transformation of GGOs into linear consolidations is typical for OP (Figure 1). Consolidations can be single or diffuse in a peripheral or peribronchial distribution. A reverse halo sign and spontaneous migration of infiltrates are commonly seen[62]. Treatment with corticosteroids shows dramatic improvement, as evidenced by the decreased mortality rates in COVID-19 patients on oxygen or mechanical ventilation (MV) receiving corticosteroids for 10 d in the RECOVERY trial[63]. However, this treatment duration may be insufficient, as longer duration and higher doses are typically needed for OP[64].

ARDS occurs in 31% of hospitalized patients with COVID-19 pneumonia and is the third most common complication following sepsis and respiratory failure[6]. Unlike typical ARDS which occurs within 1 wk based on the Berlin definition, ARDS in COVID-19 pneumonia develops within 8-15 d of disease onset[6,65]. ARDS is a clinical diagnosis encompassing features of non-cardiogenic pulmonary edema, and stems from the disordered vasoregulation in the setting of an acute systemic inflammatory response. Autopsies of COVID-19 patients revealed diffuse alveolar damage, as well as microvascular thrombosis[66]. Although ARDS is a clinical diagnosis, imaging can play a supportive role in diagnosis and monitoring of treatment response. In the early exudative phase, diffuse ground glass opacities and consolidations develop primarily in a posterior/basal distribution (Figure 1B and Figure 2B). Perfusion abnormalities may be seen on dual-energy CT as a result of ventilation/perfusion mismatches. In the late phase, 2 wk following the symptom onset, fibrotic changes may occur[4].

Patients with critical disease are at increased risk for complications[10]. Secondary bacterial or fungal infection occurs in up to 15% of inpatients with COVID-19 pneumonia and is a major cause of mortality[6]. Moreover, an increased incidence of barotrauma events (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema) has been observed in COVID-19 patients on MV, particularly in younger age groups (Figure 2). A study showed that 15% ventilated patients with COVID-19 experienced one or more barotrauma events and that the rate was significantly higher compared to ventilated non-COVID-19 patients. Barotrauma was associated with higher mortality rates and longer hospital stay[67].

Both OP and ARDS have the potential to progress into pulmonary fibrosis (Figures 3 and 4). However, there is a paucity of data with regards to the long-term pulmonary sequela of COVID-19 pneumonia. A study prospectively followed 114 patients who were admitted for severe COVID-19 pneumonia. Follow-up CT scans after 6 mo showed fibrotic changes in 35% of patients. Factors associated with a higher risk of fibrosis were older age (> 50 years), longer hospital stay (> 17 d), ARDS, non-invasive ventilation, tachycardia on admission and high CT severity scores on the initial CT scans[68]. Another study prospectively followed a cohort of 83 patients with no pulmonary or cardiovascular comorbidities, who were admitted for severe COVID-19 pneumonia that was managed without the use of MV. Although there was a temporal improvement in pulmonary function tests and imaging findings in most patients, 33% had impaired diffusing capacity of the lungs for carbon monoxide (DLCO) and 24% had residual lung findings on high-resolution CT 12 mo after discharge, including GGOs in 23%, interlobular septal thickening in 5% and reticular opacities in 4% of patients. Patients with a longer hospital stay, higher peak CT severity scores and those who required high-flow oxygen therapy or non-invasive ventilation were more likely to have residual lung abnormalities on follow-up CT[55]. Studies reporting on long-term outcomes are limited by small sample sizes and lack of histologic correlation. Ongoing trials with larger samples and longer follow-up intervals will help elucidate the long-term outcomes of COVID-19 pneumonia (NCT04483752, NCT04376840, NCT04376840).

Pulmonary embolism: SARS-CoV-2 causes prothrombotic endothelial injury leading to thromboembolic phenomena, which are further propagated by hypoxia[10,69]. Pulmonary embolism (PE) is seen in 22%-30% of COVID-19 patients who undergo a CT pulmonary angiogram (CTPA) (Figure 5), a rate that is markedly higher than critically-ill patients without COVID-19[70-72]. In a multicenter study of 1042 COVID-19 patients, PE was found in 5.6%. PE was diagnosed on the day of admission in 47%, and was proximal in 46%, segmental in 41%, and sub-segmental in 14%. Of patients with PE, 42% required ICU management and MV, while 20% of PE patients died. Patients on MV were at higher risk for developing PE, irrespective of the extent of lung abnormalities on chest CT[72]. Other risk factors include severe obesity and African-American decent [71].

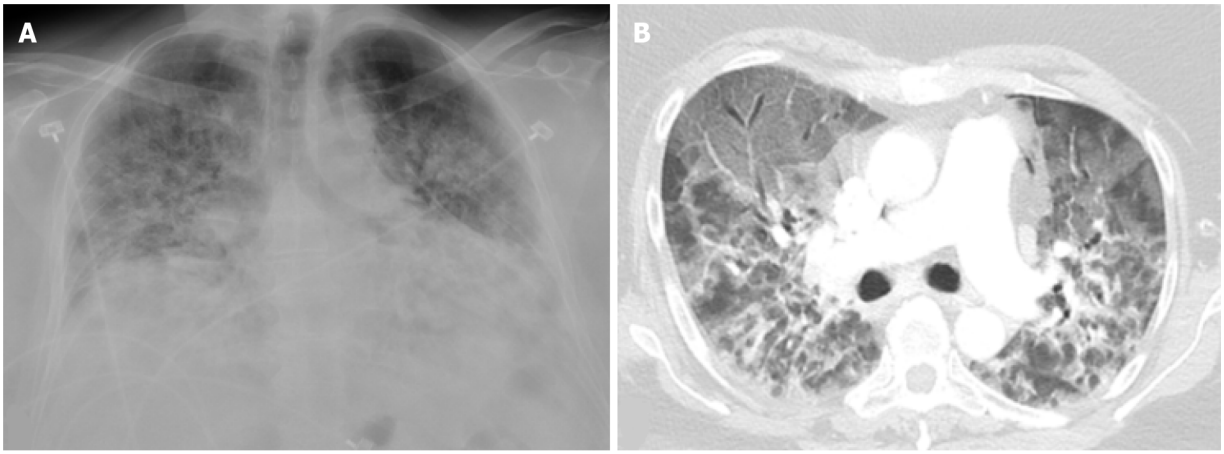


Figure 1 Severe coronavirus disease 2019 pneumonia. Portable chest X-ray and axial image from a computed tomography of the chest in a 52-yr-old female with a history of morbid obesity who was admitted for acute hypoxic respiratory failure secondary to severe acute respiratory syndrome coronavirus 2. A: Chest X-ray shows low lung volumes with diffuse bilateral alveolar and interstitial opacities; B: Chest computed tomography shows diffuse ground glass opacities anteriorly, typical of acute lung injury. The peribronchial and perilobular opacities posteriorly are typical of acute lung injury that has entered a healing phase. The patient subsequently expired.

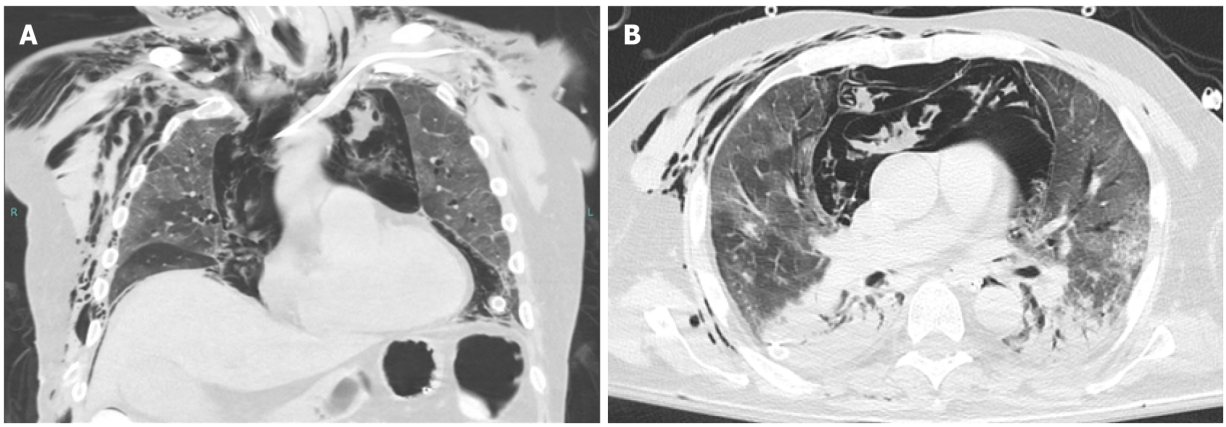


Figure 2 Barotrauma. A and B: Coronal (A) and axial (B) images from an unenhanced computed tomography of the chest of a 75-yr-old male with no significant past medical history, who was intubated for acute hypoxic respiratory failure secondary to coronavirus disease 2019 pneumonia. There are ground glass opacities anteriorly, as well as consolidations with air bronchograms posteriorly, a pattern typical for acute respiratory distress syndrome. There is a massive amount of air within the mediastinum resulting from alveolar rupture (Macklin effect). The arrow on image (A) points to interstitial emphysema, surrounding a pulmonary vein. The arrow on image (B) points to nonanatomic air within a pulmonary lobule, which may represent the initial barotrauma event. There is extensive soft tissue emphysema in the lower neck and lateral chest wall, as well as in the extraperitoneal space of the abdominal cavity. Bilateral thoracostomy tubes and a peripherally-inserted central catheter are in place. The patient could not be weaned from ventilation and subsequently expired.

Patients with COVID-19 may have elevated D-dimer levels even in the absence of PE, due to the prothrombotic state induced by the virus. Higher D-dimers are associated with more severe disease[73]. However, COVID-19 patients with PE have significantly higher CRP and D-dimer levels compared to those without PE[71]. A D-dimer value of 2600 ng/mL has been suggested by some studies as the threshold to prompt suspicion for PE[70,72]. The Dutch National institute of Public Health recommends routine D-dimer testing on admission and serial testing during hospital stay. If initial D-dimers are < 1000 μg/L and a significant increase to > 2000-4000 occurs, imaging for deep venous thrombosis or PE should be pursued[43].

Apart from the D-dimer trend, other clinical factors that should prompt a CTPA are: worsening hypoxia not explained by the extent of lung involvement, hemoptysis, tachycardia, deep venous thrombosis, and acute deterioration upon mobilization[56]. Presence of kidney disease should not preclude investigation with CTPA, as no significant increase in the risk for acute kidney injury (AKI) has been shown in patients receiving iodinated contrast compared to controls[74]. Dual-energy CT is useful in visualizing perfusion abnormalities, even in the absence of PE. It can demonstrate perfusion defects within lung opacities, and halos of increased perfusion surrounding consolidations[75], although the significance of these findings has not

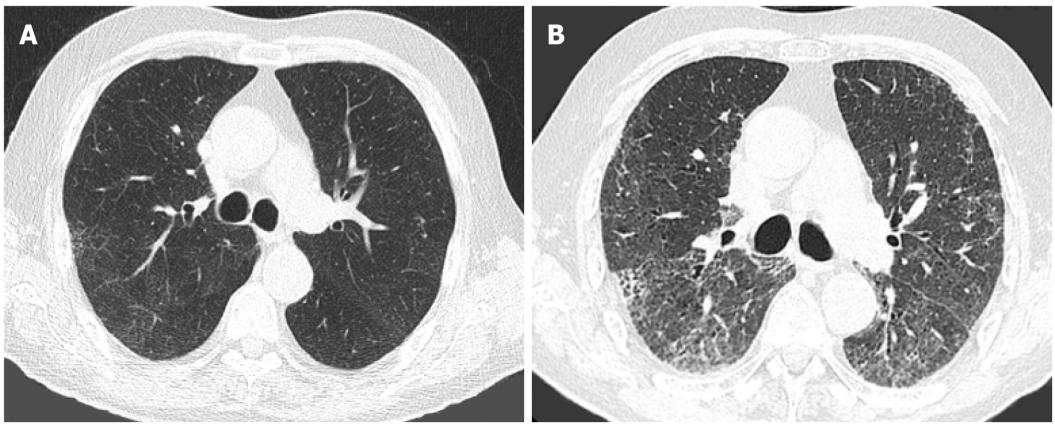


Figure 3 Pulmonary fibrosis. Axial images from computed tomographies of the chest performed 2 yr apart in an 83-yr-old male with a history of silicosis. A: In June 2018, there was mild lung hyperaeration with mild reticulation; B: In August 2020, 4 mo after recovering from coronavirus disease 2019 pneumonia, there is extensive fibrosis, with areas of honeycombing, traction bronchiectasis/bronchiolectasis and architectural distortion.

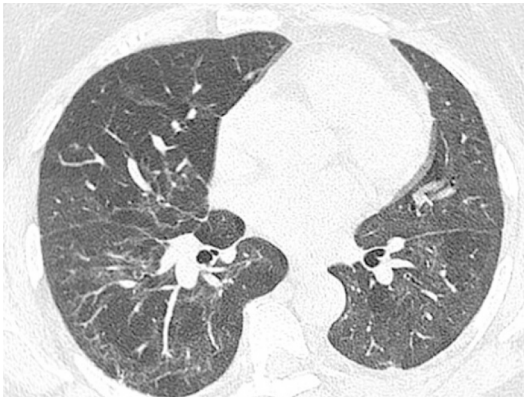


Figure 4 Non-specific interstitial pneumonia. Axial image from a computed tomography of the chest in a 59-yr-old female 6 mo after recovering from acute hypoxic respiratory failure secondary to coronavirus disease 2019. Mild fibrosis in a peribronchial distribution and subpleural sparing in the right lower lobe is in keeping with mild fibrotic non-specific interstitial pneumonia. There is also a mosaic pattern caused by obstructive small airways disease (confirmed on expiration views, not shown), with altered perfusion in the lungs.

been determined. The use of pulmonary scintigraphy has been discouraged[76]. Due to the risk of aerosolization with the ventilation component of a V/Q scan, perfusion-only scans have been performed when clinically mandated since the onset of this pandemic, which may lack specificity. Combining Q- SPECT with a low-dose CT has been shown to increase the diagnostic performance of the perfusion scan, achieving higher accuracy than planar V/Q[77,78]. Optical coherence tomography may provide a novel means of assessing for microvascular thrombosis in patients with elevated D-dimer levels and a negative CTPA (NCT04410549).

CT scanning protocols: There is a paucity of guidance regarding the optimal CT techniques and protocols for patients with suspected or proven COVID-19 pneumonia. The Fleischner Society guidelines do not provide recommendations regarding scanning protocols and the need for dose-reduction.

A single-phase, unenhanced chest CT performed with volumetric acquisitions in deep inspiration and a < 3 mm thickness is preferred[79]. Expiratory phase is not considered of value as air trapping has not been associated with the acute phase of COVID-19 pneumonia[10]. Motion artifacts may be present in patients who are short of breath or have cough. Faster scanning by means of faster gantry rotation time and higher pitch can prevent suboptimal imaging[80]. High-resolution CT is not required unless there is concern for interstitial lung disease; it may, however, play a role on follow up to characterize fibrosis.

There is no value in obtaining post-contrast images as the findings of uncomplicated COVID-19 are confined to the lung parenchyma. Contrast-enhanced CT is justified when assessing for complications (*e.g.*, abscess, necrotizing infection) or other diagnoses (such as PE or aortic dissection). If contrast-enhanced imaging is needed,

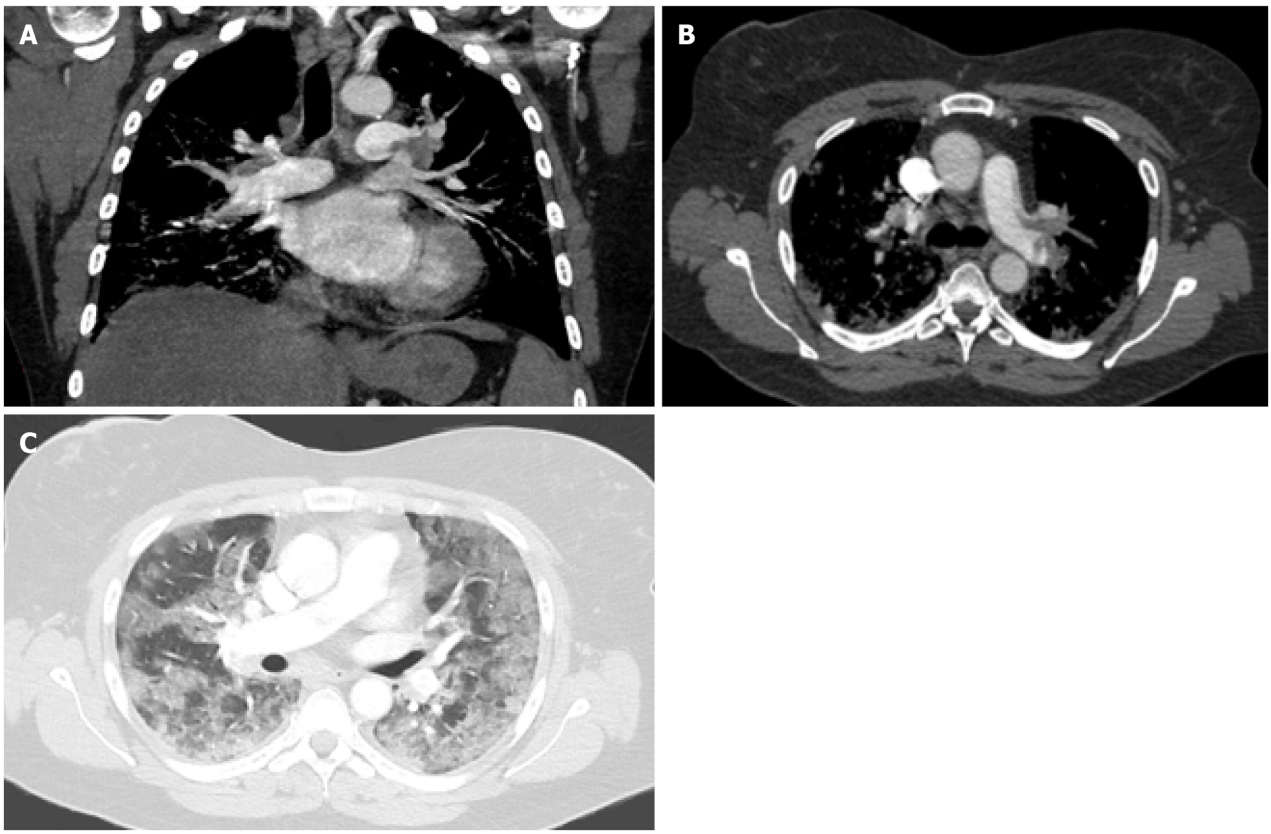


Figure 5 Pulmonary embolism. A-C: Coronal (A) and axial (B and C) images from a computed tomography angiography of the chest in a 53-year-old female with a history of chronic lymphocytic leukemia and asthma who was admitted for acute hypoxic respiratory failure secondary to coronavirus disease 2019 pneumonia, complicated by pulmonary emboli. A large filling defect is seen in the left pulmonary artery extending into lobar and segmental branches (A and B). Diffuse ground glass opacities are noted on the lungs bilaterally (C).

there is no need for pre-contrast imaging[81].

A study collected data of CT acquisition protocols and dosimetry across 54 healthcare centers worldwide. It demonstrated wide variations in the median volumetric CT Dose index (CTDIvol) and in the median dose length product[82]. It also showed that 30% of COVID-19 patients underwent 2-8 chest CT examinations within one month[82]. Even though the majority of patients affected by COVID-19 pneumonia are adults and the risk for radiation-induced cancer in this demographic is low, there is a tendency to reduce the overall radiation burden. Low-dose protocols have been recommended for COVID-19 patients by very few studies, with a diagnostic quality comparable to that of standard protocols. A dose reduction of up to 90% has been reported, without significant reduction in the signal-to-noise or contrast-to-noise ratios[83,84]. Spectral shaping with a tin filter has been applied to reduce radiation dose[84]. Low tube voltage (≤ 100 kV) and low tube current are desired for low-dose scanning. Automatic tube current modulation technique is preferred as it accounts for body habitus. Iterative reconstruction can further reduce radiation dose. A target of CTDIvol less than 3 mGy should be selected. A multicenter study revealed that only 1 out of 28 countries reported a median CTDIvol of less than 3 mGy, indicating that low-dose imaging has not been broadly adopted yet[82]. Whether the use of low-dose CT should be a standard for baseline imaging or for follow-up of COVID-19 cases has yet to be determined.

Chest radiography

Chest X-ray (CXR) is the most widely used imaging modality in the workup of patients presenting with respiratory symptoms. It is a cost-effective, widely available examination that is easy to repeat sequentially to monitor disease progression or to evaluate for alternate diagnoses. Portable CXR has been favored as it can be performed on the bedside in isolation rooms, minimizing the risk for transmission[32]. However, routine daily CXR are not recommended in stable intubated patients according to Fleischner Society guidelines[35].

Chest radiography has low sensitivity in the early stages of the disease, as initial imaging can be normal[85]. Diagnostic accuracy increases 6 d after symptom onset [85]. Sensitivity and specificity of CXR in detecting COVID-19 pneumonia vary greatly in the literature, ranging between 57%-89% and 11%-89% respectively and, therefore, its real diagnostic performance is unknown[29].

Similar to CT, findings on CXR reflect the various stages of COVID-19 pneumonia. The typical findings are multifocal, usually bilateral, GGOs and/or consolidations in a peripheral distribution. Lung opacities may coalesce creating a diffuse pattern, peaking at 6-12 d from symptom onset. Reticular opacities may be seen accompanying the GGO. Pleural effusions, cavitations and pneumothorax are considered atypical for COVID-19 pneumonia[4,86,87].

Structured reporting, similar to CO-RADS for CT, has been proposed for chest radiography as well[56]. In a mixed cohort of 582 suspected COVID-19 cases, patients with "characteristic" or "highly suspicious" features on CXR had an 88% probability of having a positive RT-PCR. "Characteristic" pattern included bilateral subpleural opacities, relatively symmetrical, involving > 20% of the lung, predominantly in the outer 1/3 of the lung parenchyma. Highly suspicious findings included unilateral subpleural opacities involving > 20% of the lung, or bilateral large-volume patchy or ill-defined opacities[88].

Severity scores quantifying lung opacities on CXR have been used to predict patient outcomes and track disease progression. The most widely used scoring system is the radiographic assessment of lung edema (RALE) score, whereby each lung is divided in upper and lower parts, and each part is graded based on the extent (0 = no involvement, 1 ≤ 25%, 2 = 25%-50%, 3 = 50%-75%, 4 ≥ 75%) and density (1 = hazy, 2 = moderate, 3 = dense) of opacities. The 2 scores for each segment are multiplied and the final scores of all segments are added[89]. A modified version of the RALE score assigns a score to each lung as a whole instead of dividing the lung in two segments [90]. Higher RALE scores in patients with COVID-19 pneumonia have been associated with higher probability of ICU admission, MV, and death[85].

US

US of the chest is a widely used modality in the emergency department, ICU or wards as it can be performed in a portable manner at the patient's bedside, limiting the need for patient transport. US is used to assess the extent and severity of lung disease, and to monitor disease progression and treatment response[91]. Given the predilection of COVID-19 pneumonia for the lung periphery, findings are often within the US beam's reach. Deeper lesions, however, cannot be identified as the aerated lung parenchyma impedes acoustic waves. Performance of US is also limited in obese patients. A convex or linear probe with a bandwidth of 2-6 MHz with the depth set at 15cm and a single focal point on the pleural line is used to scan all intercostal areas[92,93]. Pocket-sized handheld US probes have also been utilized due to their easier handling, with similar results[94].

The reported sensitivity and specificity of lung US in COVID-19 pneumonia ranges between 89%-97% and 59%-62%, respectively[95,96]. Studies, however, often exclude patients with known heart failure or interstitial lung disease and, therefore, values are likely overestimated[93]. Diagnostic performance of US is higher in severe disease[97]. It is considered superior to CXR in detecting lung lesions and has a good correlation with findings on CT[56,91,98]. The lack of non-ionizing radiation makes lung US a favorable imaging modality in pregnant or pediatric patients[32,93]. Its diagnostic performance and prognostic value are topics of ongoing research (NCT04353141, NCT04513210, NCT04338568).

Specificity of lung US is poor due to overlap with other pathologies. A commonly encountered US manifestation are the B-lines, which are vertical echogenic comet-tail artifacts originating from the pleura and extending to the bottom of the screen. They represent thickened subpleural interlobular septa (*e.g.*, interstitial pneumonia, fibrosis) or fluid-filled alveoli (*e.g.*, cardiogenic or non-cardiogenic pulmonary edema)[99]. In early mild-moderate disease, discrete scattered B-lines are observed, along with small (< 1 cm) consolidations. Consolidations appear as subpleural hypoechoic areas with an irregular border (shred sign) and a "white lung" pattern posteriorly. As the disease progresses, the B-lines coalesce and become more confluent and multifocal. The consolidations increase in size, and the pleural lines becomes irregular and thickened [93,100]. In critical disease consolidations may assume a tissue-like pattern. During recovery, consolidations and B-lines gradually disappear, while normal horizontal reverberation artefacts (A-lines) become prominent. Absence of lung sliding indicates pneumothorax. Pleural effusions are usually absent. Various scoring systems have been suggested to quantitate the severity of findings[91].

MRI

Though not a first-line modality, MRI of the chest may be considered when exposure to ionizing radiation should be avoided, such as in pregnant or pediatric patients, or in patients with an increased overall radiation burden due to frequent serial imaging [101]. T2 sequences that have been used in published studies include: HASTE (half-fourier acquisition single-shot turbo spin echo), TSE (turbo spin echo), FISP (fast imaging with steady-state precession), TIRM (turbo inversion recovery magnitude) [102]. Lung infiltrates are characterized by increased proton density and therefore demonstrate high signal intensity. There is a high concordance with CT in the assessment of the typical lung findings (GGOs, consolidations, reticulations)[102]. However, due to the lower tissue resolution, more detailed findings such as air-bronchograms and crazy-paving cannot be readily demonstrated[103]. Chest MRI has a limited practical role due to its considerably higher cost and due to various artifacts that may limit the diagnostic quality (*e.g.*, cardiac and respiratory motion artifacts, low proton density of lung parenchyma, susceptibility artifacts, fast T2* decay)[104]. Ultrashort echo-time (UTE) and respiratory-gating have been shown to curb some of the limitations[103]. The value of chest MRI will be further elucidated by several ongoing trials. (NCT04424355, NCT04369807, NCT04510025).

Positron emission tomography/CT

Positron emission tomography/CT (PET/CT) is a highly sensitive modality that can demonstrate metabolically active end-organ damages caused by SARS-CoV-2. It also offers a quantifiable assessment of disease progression and treatment response[48]. Due to its low specificity, PET/CT has a limited added benefit in the diagnostic process and may impose the nuclear medicine personnel at risk of infection due to the prolonged acquisition times[104]. Increased activity of pulmonary lesions has been shown with multiple radiopharmaceuticals, including ^{18}F-FDG (fluorodeoxyglucose), ^{18}F-chlorine, ^{68}Ga-PSMA (prostate-specific membrane antigen). The incidental detection of hypermetabolic areas in the lungs of asymptomatic SARS-CoV-2-positive patients shows the potential of FDG-PET to detect early parenchymal changes and prevent disease spread[104]. A systematic review reported a mean SUV of 4.9 ± 2.3 in pulmonary lesions on ^{18}F-FDG PET[105]. Increased ^{18}F-FDG uptake in mediastinal and hilar lymph nodes has been observed, in the absence of enlargement by CT size criteria [105]. PET/CT using ^{18}F selectively binding to the αvβ6 integrin binding protein will be used in future studies to determine the degree of fibrosis in patients with active or resolved COVID-19 pneumonia (NCT04376593, NCT03183570).

EXTRAPULMONARY MANIFESTATIONS

Cardiac manifestations

The vulnerability of cardiac tissue to SARS-CoV-2 has been alarming given the potentially dire consequences. SARS-CoV-2 can cause acute cardiac injury *via* multiple mechanisms: direct ACE-2 mediated myocardial cell damage, hypoxic vasoconstriction-mediated myocardial ischemia and microvascular damage[106]. Cardiac complications are seen in 20%-30% of hospitalized patients with COVID-19 and are associated with high mortality rates reaching 37%[107,108]. Patients with more extensive lung opacities, cardiovascular comorbidities and older age are more prone to myocardial injury[107]. Cardiac complications (including myocarditis, arrhythmia, cardiomyopathy, cardiogenic shock, and cardiac arrest) account for 7% of deaths in COVID-19 patients[109]. Patients who died of COVID-19 had significantly elevated levels of high-sensitivity Troponin I[6]. Troponin elevations have been associated with elevated C-reactive and pro- B-type natriuretic peptide levels, suggesting an interplay between myocardial injury and systemic inflammation[108,110].

Imaging plays a significant role in the early diagnosis of cardiac abnormalities and their potential complications. Echocardiography is a first-line modality in the work-up of patients with suspected cardiac injury. It is an invaluable bedside tool that can reveal structural and functional damage, such as wall-motion abnormalities, chamber dilation, valvular disease, pericardial effusion, decreased ejection fraction and cardiac thrombi. Right ventricular systolic dysfunction may indicate PE or pulmonary hypertension. Transesophageal echocardiography is considered an aerosol-generating procedure and therefore should be avoided during the pandemic, unless there is an absolute indication such as suspected endocarditis[111].

Myocarditis is a potentially threatening complication that can present in a wide spectrum of ways, ranging from mild disease to fulminant heart failure and cardiogenic shock[112]. Although invasive, endomyocardial biopsy is the gold standard for the diagnosis of myocarditis and should not be delayed in suspected cases. Cardiac MRI (cMRI) is the most sensitive imaging modality in detecting myocardial injury. Late gadolinium enhancement (LGE) has high sensitivity in detecting areas of myocardial fibrosis or necrosis and can also have prognostic value as it is associated with worse outcomes[113]. A typical cMRI protocol includes a short-axis CINE sequence for size and functional assessment, T1/T2 mapping for edema assessment, a delayed post-contrast scan for scar assessment and a T2 sequence. Certain modifications have been proposed to abbreviate the CMR protocol and decrease acquisition times[114].

Imaging manifestations of myocarditis on cMRI include diffuse myocardial edema, pseudo- wall hypertrophy, non-ischemic pattern of LGE, and increased signal on STIR, T1 mapping and T2 mapping. Regional or global wall-motion abnormalities may be present. cMRI aids in the differentiation from alternate diagnoses, such as myocardial infarction (regional wall-motion abnormalities, LGE in sub-endocardial or transmural distribution), Takotsubo cardiomyopathy (diffuse wall edema without arterial territory distribution, transient apical dyskinesias/akinesis, mild LGE only in areas of wall-motion abnormalities) and myocardial infarction with non-obstructive coronary arteries (MINOCA) (edema in non-coronary pattern). cMRI is applied by several ongoing trials for the evaluation of long-term myocardial damage 1-2 years after recovery from COVID-19 (NCT04375748, NCT04625075, NCT04636320, NCT04661657).

Contrast-enhanced cardiac CT (CCT) with electrocardiographic gating is a valuable alternative when cMRI is not feasible, with the advantage of shorter scanning times [115]. Unenhanced, early and delayed post-contrast scans, as well as extracellular volume mapping, are required for the diagnosis of myocarditis. CCT can rule out coronary artery disease in patients with acute chest pain without ST-elevation, and can assess for possible myocarditis, pericarditis, cardiomyopathy or left atrial thrombus [114].

CXR has low sensitivity and specificity in detecting cardiac injury. It may reveal pulmonary edema superimposed on lung opacities, cardiomegaly in the setting of cardiomyopathy, and pericardial effusion.

Abdominal manifestations

The abundance of ACE-2 receptors in epithelial cells along the gastrointestinal (GI) tract, in cholangiocytes and in the intraabdominal vasculature explains the multifaceted abdominal implications of SARS-CoV-2[116,117]. The pooled prevalence of symptoms from the GI tract is 15%-18%[118,119]. Most common complaints are vague abdominal pain, nausea, vomiting, diarrhea and appetite loss. Abdominal complaints may be present even in the absence of pulmonary symptoms and may be the sole complaint in 16% of COVID-19 patients[119-121]. The prevalence of GI symptoms was 12% in patients with non-severe COVID-19 and 17% in patients with severe disease, a difference that was not statistically significant[118]. No increase in mortality has been observed in patients with abdominal manifestations[119].

In a study of 1057 patients with COVID-19 and GI complaints, abdominal CTs were warranted in just 4%, the majority of which (63%) showed no acute abnormality[120]. Bowel wall abnormalities have been observed in 3% of hospitalized patients with COVID-19[122]. On contrast-enhanced CT, enterocolitis can manifest as small or large bowel wall thickening with mucosal enhancement, fluid-filled bowel lumen and mesenteric inflammation[106]. The presence of non-enhancing bowel wall, pneumatosis intestinalis or portal venous gas is suggestive of ischemia and bowel infarction. Discontinuity of bowel wall and pneumoperitoneum indicate bowel perforation[106, 123]. The etiology of acute mesenteric ischemia is multifactorial. It may occur as a result of hypercoagulability, direct viral-mediated damage on the bowel, and hemodynamic compromise due to shock[123]. Patients may present with abdominal pain, nausea, vomiting, diarrhea, or more severe symptoms suggestive of sepsis. CT angiography is the imaging of choice as it can readily detect filing defects in the mesenteric vasculature. However, non-occlusive ischemia may occur secondary to systemic vasodilation and intestinal hypoperfusion in the setting of sepsis (Figure 6).

Hepatobiliary manifestations are more common in patients with severe disease [119]. Liver function tests may be abnormal in 37% of hospitalized patients and are associated with a longer hospital stay[124]. Cholestasis has been observed in up to 54% of hospitalized patients with COVID-19[122]. It may manifest as a sludge-filled gallbladder and intra- and extrahepatic biliary ductal dilation in the absence of an obstructing gallstone or mass. Biliary stasis can predispose to acute cholecystitis. As a

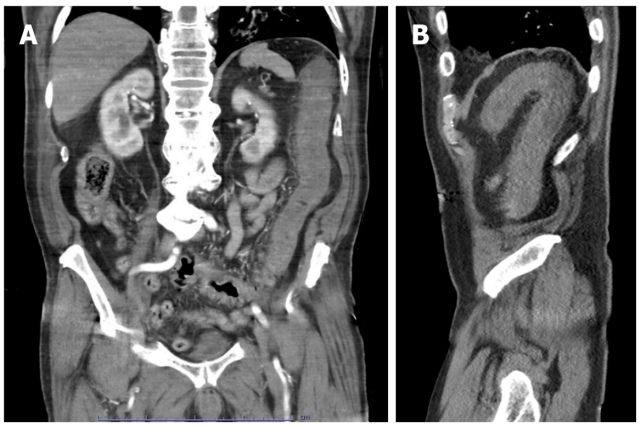


Figure 6 Acute ischemic colitis. A and B: Coronal (A) and sagittal (B) reconstructed images from a computed tomography angiogram of the abdomen and pelvis in an 80-yr-old male admitted for sepsis and lactic acidosis. There is bowel wall thickening and hypoenhancement involving the descending colon, with surrounding inflammatory changes. There is no evidence of pneumatosis coli, pneumoperitoneum or proximal vessel occlusion. Bilateral ground-glass opacities were visualized at the lung bases (not shown). The patient was positive for severe acute respiratory syndrome coronavirus 2.

result of the prothrombotic state induced by SARS-CoV-2, hepatic or portal venous thrombosis may occur, which can manifest as absent flow on color Doppler or as filling defects on contrast-enhanced CT. Pancreatic inflammation has been described in patients with COVID-19 and is thought to occur secondary to direct cytotoxicity of the virus or systemic inflammatory response[125]. US has low sensitivity for pancreatitis; it may, however, demonstrate an enlarged pancreas with decreased echogenicity and blurred margins. On CT, the pancreatic parenchyma has an edematous and hypoattenuating appearance, with associated peripancreatic fat stranding[106]. Necrotizing pancreatitis in the setting of COVID-19 is uncommon[125].

Renal damage occurs *via* various mechanisms including direct endothelial and podocyte injury, glomerular injury by immune complexes, capillary obstruction by aggregated erythrocytes, and disruption of the renin-angiotensin-aldosterone system [126]. AKI is a frequent complication of COVID-19 occurring in up to 37% of hospitalized patients[127]. Electrolyte imbalances (primarily hyperkalemia and alkalosis), hematuria and proteinuria can be observed even in patients without AKI[116]. On US, AKI may manifest as cortical echogenicity and loss of corticomedullary differentiation. Focal areas of decreased vascularity on color Doppler indicate renal infarcts. Contrast-enhanced CT may demonstrate infarcts as wedge-shaped areas of hypoenhancement involving both the cortex and medulla as well as renal vascular thrombosis[106]. Infarcts, either single or multifocal, can also occur in the spleen secondary to microangiopathy, hypercoagulopathy or thromboembolism[128]. The extent to which contrast-enhanced US can demonstrate microvascular perfusion deficits in patients with COVID-19 is under investigation (NCT04640038).

Central nervous system manifestations

The neurotropism of SARS-CoV-2 accounts for some of its potentially fatal sequela, as evidenced by the presence of viral RNA in brain tissues of deceased patients[129]. SARS-CoV-2 enters the central nervous system (CNS) *via* the hematogenous or the transneuronal route, causing neurological damage *via* multiple mechanisms. Endothelial cell injury can cause disruption of the blood-brain barrier, facilitating the penetration of the virus into the CNS as well as the crossing of immune cells and cytokines. The direct micro- and macrovascular injury, combined with the prothrombotic state, can lead to ischemic phenomena. Moreover, prolonged hypoxia and acidosis associated with ARDS can promote cerebral vasodilation and edema[130, 131].

Up to 12% of hospitalized patients with COVID-19 undergo neuroimaging[132]. The most common neurological symptoms are: anosmia, ageusia, altered mental status, headache, dizziness and focal neurological deficits[116]. Patients with severe disease are more likely to develop neurological abnormalities[133]. Among critically-ill patients with COVID-19, neurological symptoms were observed upon admission to the ICU in 14% and upon weaning from sedation in 67%[134]. Patients with altered mentation were more likely to be hypotensive, hypoxic, and have elevated creatinine, D-dimers and inflammatory markers, suggesting an interplay between neurological damage and multi-system failure[132]. Neuroimaging may be revealing in up to 23%

of patients; however, none of the reported abnormalities is specific for COVID-19[135].

Three non-specific imaging patterns of leukoencephalopathy have been observed in patients with severe COVID-19[136]. A commonly reported finding pertains to signal abnormalities in the mesial temporal lobe seen in up to 43%[136]. These are characterized by hyperintensity on fluid-attenuated inversion-recovery (FLAIR) and diffusion-weighted imaging (DWI), which may also be seen in infectious (*e.g.*, herpes simplex virus) or autoimmune encephalitis (Figure 7). Another pattern involves multifocal supratentorial white matter lesions that are hyperintense on FLAIR and DWI and may be seen in 30% of critically ill patients. These may be related to post-infectious demyelination secondary to the hypoxic-ischemic damage of oligodendrocytes. Other potential causes include delayed post-hypoxic leukoencephalopathy, metabolic or toxic encephalopathy, and posterior reversible encephalopathy syndrome [135]. White matter lesions may be associated with microhemorrhages, resembling acute disseminated encephalomyelitis or acute hemorrhagic leukoencephalitis[137, 138]. Isolated, yet extensive, microhemorrhages in the subcortical and deep white matter may also be seen in 24% of patients, in a pattern similar to diffuse intravascular coagulation. This finding has been attributed to hypoxia or small-vessel vasculitis [137]. The splenium of the corpus callosum is one of the predominantly affected areas [135]. There are rare reports of acute necrotizing encephalopathy which presents as rim-enhancing lesions in the thalami, temporal lobes and subinsular regions[137]. Leptomeningeal enhancement suggestive of meningoencephalitis is frequently seen [138].

Acute ischemic infarcts have been reported in 9% of patients with neurological symptoms and in 1% of all hospitalized patients with COVID-19, even in the absence of underlying risk factors. Among ICU patients undergoing neuroimaging, acute infarcts were identified in 23%[134]. The occurrence of a stroke in COVID-19 patients has been associated with a higher mortality rate [132]. An unenhanced CT of the head is usually the first-line imaging modality, as it can identify acute infarcts (ischemic, embolic or venous), large vessel occlusion, hemorrhagic transformation, and venous sinus thrombosis[106]. Abbreviated MRI protocols with DWI, apparent diffusion coefficient mapping and T2/FLAIR have been recommended for the definitive assessment of infarcts in order to decrease acquisition times[106].

Long-term neurologic morbidity after recovery from SARS-CoV-2 has yet to be determined. Several ongoing trials will examine the presence of structural and cognitive impairment in patients who suffered from acute neurological damage related to COVID-19 infection (NCT04564287, NCT04476589).

Peripheral nervous system and ocular manifestations

Rare cases of acute polyneuropathy in the spectrum of Guillain-Barré syndrome (GBS) have been reported as a result of SARS-CoV-2 infection. Symptoms reportedly occur within 8-24 d after the onset of respiratory symptoms[139]. The most frequently reported manifestation is the classic form of GBS (acute inflammatory demyelinating polyradiculoneuropathy) which is characterized by ascending sensorimotor deficits, with varying degrees of facial nerve involvement, dysphagia and dysautonomia. Other less common variants include the Miller Fisher syndrome (characterized by opthalmoplegia, ataxia, areflexia), pure motor or pure sensory variants, bilateral facial palsies, the pharyngeal-cervical-brachial motor variant, and others[140]. MRI can reveal thickening of the affected nerve roots and avid contrast enhancement of the conus medullaris and cauda equina, with preferential enhancement of the ventral nerve roots[141]. The fact that viral RNA has not been identified on cerebrospinal fluid analysis in affected patients suggests that injury occurs *via* an immune-mediated mechanism, such as molecular mimicry or antibody precipitation, rather than by direct viral insult[142]. A similar mechanism has been proposed for rare cases of new-onset myasthenia gravis developing in the setting of COVID-19[143].

Patients with severe disease and a prolonged stay in the ICU are at risk for critical illness polyradiculopathy and myopathy, which is characterized by degeneration of sensory and motor axons. The pathophysiology for this disease has not been elucidated yet, but it is thought to involve microvascular alterations, metabolic abnormalities, ion-channel dysfunction[144]. It may lead to ventilator dependence and chronic disability, which are associated with high morbidity rates[145]. Positioning maneuvers in the ICU may also affect the peripheral nerves by causing compression or entrapment[140].

Cranial nerves can also be affected by the immune dysregulation propagated by the viral infection. Anosmia and ageusia occur in up to 88% of patients, even in the absence of upper or lower respiratory symptoms[146]. SARS-CoV-2 causes a direct viral insult to the nasoepithelial cells by directly attaching to olfactory and gustatory

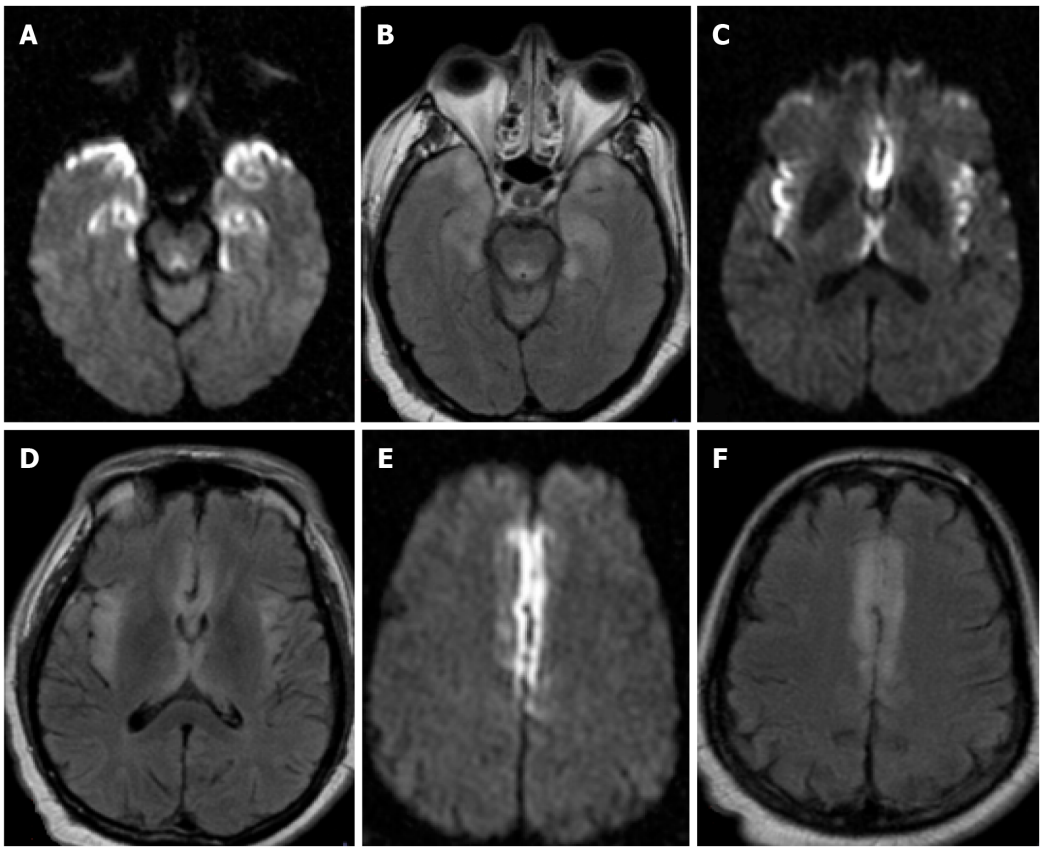


Figure 7 Encephalopathy. A-F: Axial DWI (A, C and E) and FLAIR (B, D and F) sequences from a brain MRI in a 49-year-old - male who was admitted for acute hypoxic respiratory failure secondary to severe acute respiratory syndrome coronavirus 2. A brain MRI was ordered 3d after presentation for progressive lethargy. There were multifocal symmetric areas of restricted diffusion and T2/FLAIR prolongation in bilateral mesial temporal lobes (A and B), insular cortex (C and D), and cingulate cortex (E and F). Cerebrospinal fluid analysis was negative. The patient's mental status gradually returned to baseline after medical management. Findings were attributed to COVID-19 – related encephalopathy.

receptors, potentially creating a route for retrograde entry into the CNS. Olfactory cleft widening and FLAIR hyperintensities in bilateral olfactory bulbs have been observed, which resolved after recovery of the acute illness[147,148]. Other cranial neuropathies, either single or multiple, have also been reported, which manifest on MRI with signal hyperintensity on T2 and enhancement on post-contrast images[140,149].

As a mucosal surface, the conjunctiva can be exposed to respiratory droplets and act as a potential port of entry for SARS-CoV-2. Ocular manifestations occur in up to 7% of COVID-19 patients, with conjunctivitis being the most prevalent[150]. Less frequently, retinal abnormalities may occur as a result of the microangiopathic damage caused by the virus, which can lead to ischemia[151]. Conditions related to ICU stay (including sedation, MV, neuromuscular blockade and prone positioning) may potentiate keratopathy, acute angle-closure, ischemic optic neuropathy and retinal vascular occlusion[152,153]. A study revealed the incidental presence of nodules on the posterior pole of the globes in patients with severe COVID-19 undergoing brain MRI for altered mental status. The nodules were located in bilateral macular regions, were T2/FLAIR hyperintense, non-enhancing and showed no susceptibility artifacts. No correlate was identified on fundoscopy or optical coherence tomography. The nature of these nodules remains unclear[154].

Musculoskeletal and cutaneous manifestations

Myalgia is a fairly common constitutional symptom that is present in up to 44% of SARS-CoV-2-infected patients upon presentation[155]. It stems from intramuscular inflammation and is typically self-limiting. More severe viral myositis manifesting with pain, tenderness, weakness and elevated creatine kinase may occur in a small percentage of patients. Rhabdomyolysis is a potentially life-threatening complication caused by the breakdown of muscular tissue, which may lead to AKI, compartment syndrome or superimposed infection[141].

Damaged muscles appear enlarged and hypoattenuating on CT. Rim-enhancement may be seen, although intravenous contrast is avoided. Intramuscular calcifications may be seen in the subacute and chronic phase. MRI is the preferred imaging modality as it can distinguish two different types of rhabdomyolysis based on the presence or absence of myonecrosis. In type 1, there is homogeneously increased signal intensity on T2/STIR representing edema, as well as homogeneous hyperenhancement. Increased T1 signal indicates the presence of methemoglobin. In chronic rhabdomyolysis, focal T1 hyperintensity or blooming artifact on susceptibility weighted imaging may be present indicating hemosiderin deposition. In type 2, there is heterogeneously increased signal intensity on T2/STIR, as well as non-enhancing necrotic areas. Rim enhancement may be present in subacute myonecrosis and should not be mistaken for an abscess[106,141,156].

Viral arthritis presents with acute arthralgia that is self-limiting and responds to non-steroidal anti-inflammatory medications. Other causes of arthritis, such as reactive or crystalline arthritis, should be considered in the differential as they may present with similar symptoms. Rare cases of acute exacerbations of chronic rheumatologic diseases (such as systemic lupus erythematosus and rheumatoid arthritis) have been reported. MRI may demonstrate thickened and hyperenhancing synovium, as well as features specific for the underlying autoimmune process[141].

Skin involvement has been reported in up to 8% of patients with SARS-CoV-2[157]. Microthrombi, small-vessel vasculitis, immune response and drug reaction (secondary to remdesivir, toclizumab, hydroxychloroquine, *etc*.) are some of the suspected mechanisms of injury[116]. The most common manifestation is an acrocutaneous lesion similar to chilblain or frostbite. Other possible phenotypes include: uriticarial rash, maculopapular rash, papulovesicular rash, livedo reticularis and purpuric rash [158]. Dry gangrene has been reported in severe cases, likely exacerbated by pressors and coagulopathy in vulnerable patients with diabetes mellitus or peripheral arterial disease. Imaging may reveal skin ulcerations, high signal intensity on T2 and lack of enhancement[106]. Acute soft tissue hematomas may develop secondary to disordered coagulation. They appear as heterogeneous hypoechoic collections on US, and, if large, they may cause compartment syndrome and compressive neuropathy[141].

PEDIATRIC MANIFESTATIONS

There is evidence that children of all ages are susceptible to SARS-CoV-2[159]. Pediatric patients are more likely to have a milder disease course or to be asymptomatic carriers compared to adults, likely due to immature immune response and ACE-2 receptors[5,160,161]. Fever and cough are the most common complaints in symptomatic children[162].

There is no indication for routine chest imaging in children with suspected COVID-19 infection, due to the high rate of false negative examinations[162]. If imaging is clinically warranted, chest radiography is the first-line modality. CT should be reserved for more complex cases, suspected complications or to rule out alternative diagnoses, particularly in children with underlying medical conditions[163]. No imaging differences have been demonstrated among age groups[161]. Bilateral GGOs, pure or mixed with consolidations, in a peripheral/subpleural distribution are the predominant findings on chest imaging in the pediatric population[164,165]. Crazy-paving pattern and halo signs are also observed indicating a common response to acute lung injury[166]. Airway inflammation, as evidenced by peribronchial thickening has been very frequently observed in pediatric patients[164]. Pleural effusion and lymphadenopathy are atypical. PE is significantly less prevalent than in the adult population. Lung US is being increasingly applied due to the lack of ionizing radiation and higher sensitivity compared to CXR[167,168].

Although the risk of severe illness is significantly lower than in adults, critical cases have been observed in the pediatric population, particularly in patients with underlying medical conditions[160,169]. The multisystem inflammatory syndrome in children (MIS-C) is a worrisome late complication that presents with multiorgan damage in children previously exposed to COVID-19. Its distinction from Kawasaki disease and toxic shock syndrome can be challenging. MIS-C is diagnosed based on clinical and laboratory criteria, such as those established by the WHO. These include: fever, rash, conjunctivitis, shock, end-organ damage (*e.g*., respiratory, cardiac, renal, neurological or GI), coagulopathy, elevated inflammatory markers, laboratory evidence of recent SARS-CoV-2 infection or contact with a known case, and absence of an alternative diagnosis[170]. Patients typically present with fever, rash, conjunctivitis,

vomiting, diarrhea, abdominal pain mimicking appendicitis. Shock may be present on admission in 60% of patients[171]. Although 71% of children may require management in the ICU, mortality rates are relatively low (1.7%)[172].

In patients with MIS-C, chest imaging may reveal bilateral airspace opacities, peribronchial thickening, interstitial thickening, cardiomegaly, pulmonary edema and pleural effusions. 46% of patients may have normal CXRs. CCT may demonstrate myocarditis, pericarditis and coronary aneurysms. Bowel wall thickening involving the terminal ileum or the cecum accompanied by mesenteric inflammation is present in 23% of patients (Figure 8). These findings most likely represent bowel ischemia secondary to small vessel vasculitis or shock. Other findings on abdominal imaging include small-volume ascites, lymphadenopathy, periportal and pericholecystic edema and a normal appendix[171,173]. Although most patients recover after the acute phase with medical management, the long-term morbidity remains unclear. Future studies will attempt to identify the potential long-term complications by prospectively following patients for 2-5 yearsafter recovery from MIS-C (NCT04455347, NCT-04757831).

INFECTION CONTROL IN RADIOLOGY DEPARTMENTS

Since the onset of the pandemic, drastic measures have been implemented by radiology departments in order to curb the transmission of SARS-CoV-2 within the hospital. As an initial step, the radiology staff underwent training by a team of infection control specialists regarding the safe handling of patients, use of PPE and disinfection of imaging devices[174]. The dramatic drop in case load as a result of the suspension of all non-urgent imaging examinations in the initial surge of the pandemic allowed for radiology departments to function with limited staff capacities. Division of staff into groups alternating between 2 wk of self-quarantine and 2 wk of on-site work was widely implemented. Remote working of radiologists was also encouraged[175].

Given the long processing times of RT-PCR, triaging of patients in the emergency department based on typical clinical symptoms and known exposure to SARS-CoV-2 was essential in order to provide timely isolation and implement appropriate protective measures. Temperature measurement was not a reliable triaging method as patients may be afebrile in the early phase of the disease[174]. Patients were classified into 3 categories: confirmed and highly suspected cases, suspected cases, and confirmed negative cases. Dedicated imaging rooms, waiting areas and routes of transportation were designated for suspected or confirmed cases. Different levels of PPE and disinfection were applied after interaction with each patient category[176]. The use of portable imaging equipment (for radiography or US) has been preferred as it can be brought to the patient's bedside and can be more easily disinfected[177]. Scanning protocols were abbreviated so that the clinical question can be addressed while limiting the duration of the scan and the contact between staff and patients.

CANCER SCREENING DELAYS

Soon after the onset of the pandemic, multiple medical societies (including the American Cancer Society, the American Society of Breast Surgeons, the ACR and the American College of Chest Physicians) released statements suggesting the suspension of all non-urgent cancer screening studies in order to mitigate the spread of SARS-CoV-2[178-180].

Between March and May 2020, a 39%-85% decrease in mammograms and a 52% decline in novel breast cancer diagnoses were observed in the United States compared to the previous year[16,181]. Similar rates were reported in other countries[182,183]. Given that breast cancer screening can reduce mortality by 40% in females aged 50-69, cancer upstaging due to missed screening appointments could be a serious threat [184]. It is estimated that deaths from breast cancer could increase by up to 10% within the next 5 years[185]. Low-dose CT examinations for lung cancer screening dropped by 72%-78% between March and May 2020[186]. The mortality rate of lung malignancies is projected to increase by up to 5% in the next 5 years[185]. Hepatocellular carcinoma (HCC) surveillance in at-risk individuals by abdominal US, CT or MRI scans demonstrated a declining trend across two centers in the United States and Singapore[187]. Guidelines that were published during the early phase of the pandemic recommended that HCC screening should be limited to high-risk patients [188]. A marked drop was also observed in colorectal cancer screening tests[189]. It

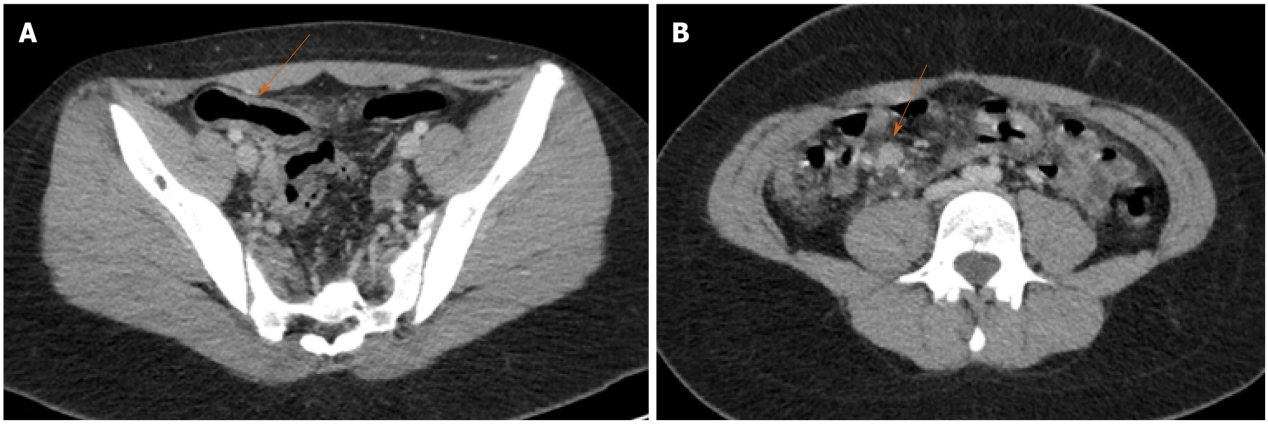


Figure 8 Terminal ileitis in the setting of multisystem inflammatory syndrome in a child. Axial images of a contrast-enhanced computed tomography of the abdomen and pelvis in a 13-yr-old female who presented with a 4d history of abdominal pain. A: There is wall thickening in the terminal ileum with adjacent fat stranding; B: Multiple reactive lymph nodes are seen in the right lower quadrant. Clinical and laboratory findings met criteria for multisystem inflammatory syndrome in children. Of note, the patient had tested positive for severe acute respiratory syndrome coronavirus-2 4 wk prior to presentation. The patient recovered after medical treatment including intravenous immunoglobulin, prednisone and dopamine.

was suggested that CT colonography could be a substitute for colonoscopy during the early phase of the pandemic due to its shorter in-hospital stay, limited patient contact and lower risk of complications[190].

As a result of the universal cancer screening interruptions, a large backlog of cancelled appointments emerged. As the first pandemic wave subsided, healthcare institutions implemented a phased reopening, prioritizing patients with acute complaints suspicious for disease progression, those with newly diagnosed cancer and those undergoing treatment[191]. Despite the fact that hospitals returned to their pre-pandemic capacity, patients were reluctant to reschedule their appointments due to fear of exposure within the hospital or due to lack of health insurance and unemployment[192]. Outreach programs have made significant efforts to address patients' concerns and to facilitate their access to screening facilities, aspiring to limit the long-term repercussions of these unprecedented screening delays[193].

The emergency authorization of vaccines against SARS-CoV-2 in late 2020 initiated a widescale vaccination program, prioritizing the vulnerable populations and the healthcare workers. As of June 4, 2021, 447.9 million people have fully vaccinated and 424 million people have been partially vaccinated globally[194]. Vaccine-induced axillary lymphadenopathy following COVID-19 vaccination has been reported by multiple studies and is thought to occur at a higher rate compared to other vaccines such as the influenza vaccine[195]. The presence of post-vaccine axillary lymphadenopathy on imaging studies may lead to false-positive results and may provoke unnecessary anxiety especially in patients undergoing cancer screening or surveillance [196,197].

To address the issue, radiological societies have released statements regarding cancer screening. The Radiology scientific expert panel recommends that routine screening imaging studies be scheduled at least 6 wk after the final dose of the vaccine. In patients with cancer history, the vaccine should be administered on the contralateral side of the primary or suspected cancer or in the thigh[198]. If axillary adenopathy is present on a low-dose CT for lung cancer screening, the "S" modifier should be added on the Lung-RADS reporting system and no further imaging should be pursued[199]. Based on the Society of Breast Imaging, the presence of unilateral axillary lymphadenopathy should warrant a BI-RADS 0 and prompt further assessment and documentation of the patient's vaccination history. In women with a recent (4-wk) history of vaccination, short-term follow-up 4-12 wk after their final vaccine dose is recommended (BI-RADS 3). Persistence of adenopathy is considered suspicious (BI-RADS 4) and should warrant a biopsy[200]. A less conservative approach has also been proposed, whereby the isolated presence of axillary adenopathy on mammography or breast MRI in the setting of recent ipsilateral COVID-19 vaccination is considered benign (BI-RADS 2) and warrants clinical follow-up. If concern persists 6 wk after the final vaccination dose, an axillary ultrasound is recommended[201].

THE PROMISE OF AI

AI using deep learning technology has shown great promise in radiology in the recent years. By extracting pixel-based information from medical images, deep convolutional neural networks (CNNs) can aid in diagnosis and provide valuable prognostic estimations. Undoubtedly, the global outbreak of SARS-CoV-2 has created new opportunities for AI both in radiology and patient management. The non-specific clinical presentation and imaging findings of COVID-19 infection and the long processing times of RT-PCR may cause delays in diagnosis, isolation and treatment. The use of deep learning models has the potential to facilitate patient triaging, aid in decision-making, and improve outcomes.

The creation of a CNN-based model has various phases, including an initial training phase where it is exposed to a large pool of images for each specific category that it will learn to differentiate. Its performance is subsequently validated on test sets with randomly assigned images. CV19-Net is a CNN designed to perform a binary diagnosis (COVID-19 pneumonia *vs* non-COVID-19 pneumonia) on CXRs. The algorithm achieved an area under the curve (AUC) of 0.94, which was significantly higher than the AUC of 0.85 achieved by radiologists[202]. Similarly, DeepCOVID-XR presented an 82% accuracy in distinguishing positive from negative patients for COVID-19 pneumonia on CXRs[203]. Another binary model (DensNet201) was able to differentiate COVID-19 pneumonia from normal with 97% accuracy[204]. CNNs that provide a three-scale classification have also been created. COVID-Net was designed to differentiate COVID-19 pneumonia from both normal and non-COVID-19 pneumonia on CXRs, achieving a 93% accuracy and 91% sensitivity in COVID-19 diagnosis[205]. Another deep learning model trained at performing three-scale classifications of chest CTs accomplished high sensitivity and specificity for COVID-19 pneumonia with an AUC of 0.96[206]. Models may also enhance the performance of radiologists. When radiologists were provided with an AI-based prediction while reviewing images, their accuracy was significantly higher than in the absence of the AI-derived information[207].

With the help of radiomics, imaging features can evolve into quantifiable biomarkers that can provide a measurement of the disease severity and predict its progression[208]. A model performing automated volumetric quantification of lung opacities while integrating clinical and laboratory data, showed potential in stratifying patients based on disease severity and distinguishing those that may require MV[209]. In a study comparing radiomic features to clinical markers in terms of their predictive value, CT radiomic features showed a greater accuracy in predicting the progression of lung opacities in COVID-19 pneumonia. The value of radiomic data was enhanced when combined with clinical features and laboratory markers[210]. Fusion models that involve both imaging and clinical features can play a crucial role in patient management and prognostication. However, their application has not been widespread so far. Multiple ongoing trials will attempt to identify CT biomarkers that can predict the clinical course of patients with COVID-19 (NCT04377685, NCT04481620, NCT04418245). The free online database of thoracic CT images of COVID-19 positive patients from international sites made available by RSNA provides a platform for further studies to develop more generalizable and valuable algorithms[211].

Despite the promising role of AI, there are certain limitations that need to be considered. The extraordinary interest of the scientific community in COVID-19 has led to the rapid development of numerous AI-based models that were created and validated in a setting of high disease prevalence with data from a small number of institutions, introducing a selection bias and limiting the model's generalizability [212]. Moreover, the performance of CNNs has been shown to degrade over time and, therefore, retraining is essential to maintain their diagnostic performance in the long-term. Although certain institutions have already applied AI-assisted technologies in daily clinical practice, the field remains largely unregulated and, therefore, several serious concerns persist. Transferring and analyzing large volumes of data poses a threat to patient privacy in the event of a data breach[213,214]. In malpractice cases where AI-technologies are involved, it not clear which party bears the responsibility and to what extent[215,216]. Finally, making medical decisions solely based on deep learning algorithms without human consultation may lead to ethical pitfalls and accentuate healthcare disparities among various ethnic groups and minorities[213, 216].

CONCLUSION

Over the past year, our knowledge regarding COVID-19 has dramatically increased. There is now much better understanding of the mechanisms of injury, imaging manifestations, and best available treatments. Future studies with larger samples and longer follow-up intervals are needed to elucidate the long-term complications of SARS-CoV-2 infection. Whether deep learning algorithms can replace traditional diagnostic pathways or can generate useful prognostic information remains under investigation. Although most radiology departments have already been functioning at their pre-pandemic capacity since the first surge of the pandemic subsided, preparedness for future waves of this pandemic and for future pandemics is essential.

REFERENCES

1 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

2 **Zhang B**, Wang X, Tian X, Zhao X, Liu B, Wu X, Du Y, Huang G, Zhang Q. Differences and prediction of imaging characteristics of COVID-19 and non-COVID-19 viral pneumonia: A multicenter study. *Medicine (Baltimore)* 2020; **99**: e22747 [PMID: 33080737 DOI: 10.1097/MD.0000000000022747]

3 **Johns Hopkins University and Medicine**. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). [cited 15 December 2020]. In: Johns Hopkins University and Medicine [Internet]. Available from: https://coronavirus.jhu.edu/map.html

4 **Revzin MV**, Raza S, Warshawsky R, D'Agostino C, Srivastava NC, Bader AS, Malhotra A, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 1: Viral Pathogenesis and Pulmonary and Vascular System Complications. *Radiographics* 2020; **40**: 1574-1599 [PMID: 33001783 DOI: 10.1148/rg.2020200149]

5 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

6 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

7 **Mehraeen E**, Karimi A, Barzegary A, Vahedi F, Afsahi AM, Dadras O, Moradmand-Badie B, Seyed Alinaghi SA, Jahanfar S. Predictors of mortality in patients with COVID-19-a systematic review. *Eur J Integr Med* 2020; **40**: 101226 [PMID: 33101547 DOI: 10.1016/j.eujim.2020.101226]

8 **Palaiodimos L**, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, Southern WN, Mantzoros CS. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism* 2020; **108**: 154262 [PMID: 32422233 DOI: 10.1016/j.metabol.2020.154262]

9 **Mollura DJ**, Morens DM, Taubenberger JK, Bray M. The role of radiology in influenza: novel H1N1 and lessons learned from the 1918 pandemic. *J Am Coll Radiol* 2010; **7**: 690-697 [PMID: 20816630 DOI: 10.1016/j.jacr.2010.01.007]

10 **Kwee TC**, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. *Radiographics* 2020; **40**: 1848-1865 [PMID: 33095680 DOI: 10.1148/rg.2020200159]

11 **Henkel M**, Weikert T, Marston K, Schwab N, Sommer G, Haslbauer J, Franzeck F, Anastasopoulos C, Stieltjes B, Michel A, Bremerich J, Menter T, Mertz KD, Tzankov A, Sauter AW. Lethal COVID-19: Radiologic-Pathologic Correlation of the Lungs. *Radiol Cardiothorac Imaging* 2020; **2**: e200406 [PMID: 33778642 DOI: 10.1148/ryct.2020200406]

12 **Gazendam A**, Ekhtiari S, Wong E, Madden K, Naji L, Phillips M, Mundi R, Bhandari M. The "Infodemic" of Journal Publication Associated with the Novel Coronavirus Disease. *J Bone Joint Surg Am* 2020; **102**: e64 [PMID: 32618912 DOI: 10.2106/JBJS.20.00610]

13 **Moy L**, Bluemke D; Radiology Editorial Board. The *Radiology* Scientific Expert Panel. *Radiology* 2020; **296**: E105 [PMID: 32105563 DOI: 10.1148/radiol.2020204005]

14 **Naeem SB**, Bhatti R. The Covid-19 'infodemic': a new front for information professionals. *Health Info Libr J* 2020; **37**: 233-239 [PMID: 32533803 DOI: 10.1111/hir.12311]

15 **Carlon T**, Finkelstein M, Maron SZ, Goldman D, Kihira S, Marinelli B, Dayan E, Sullivan N, Hart J, Doshi AH, Delman BN, Lookstein R, Drayer BP. Sources of Revenue Loss and Recovery in Radiology Practices During the Coronavirus Disease 2019 (COVID-19) Pandemic. *Acad Radiol* 2021; **28**: 447-456 [PMID: 33495075 DOI: 10.1016/j.acra.2021.01.015]

16 **Kaufman HW**, Chen Z, Niles J, Fesko Y. Changes in the Number of US Patients With Newly Identified Cancer Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic. *JAMA Netw Open* 2020; **3**: e2017267 [PMID: 32749465 DOI: 10.1001/jamanetworkopen.2020.17267]

17 **World Health Organization**. Laboratory testing of 2019 novel coronavirus (2019-nCoV) in suspected human cases: interim guidance. [cited 25 January 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/i/item/Laboratory-testing-of-2019-novel-coronavirus-(-2019-ncov)-in-suspected-human-cases-interim-guidance-17-january-2020

18 **Byrne D**, Neill SBO, Müller NL, Müller CIS, Walsh JP, Jalal S, Parker W, Bilawich AM, Nicolaou S. RSNA Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19: Interobserver Agreement Between Chest Radiologists. *Can Assoc Radiol J* 2021; **72**: 159-166 [PMID: 32615802 DOI: 10.1177/0846537120938328]

19 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]

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

21 **Li Y**, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. *AJR Am J Roentgenol* 2020; **214**: 1280-1286 [PMID: 32130038 DOI: 10.2214/AJR.20.22954]

22 **Fang Y**, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296**: E115-E117 [PMID: 32073353 DOI: 10.1148/radiol.2020200432]

23 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

24 **Waller JV**, Allen IE, Lin KK, Diaz MJ, Henry TS, Hope MD. The Limited Sensitivity of Chest Computed Tomography Relative to Reverse Transcription Polymerase Chain Reaction for Severe Acute Respiratory Syndrome Coronavirus-2 Infection: A Systematic Review on COVID-19 Diagnostics. *Invest Radiol* 2020; **55**: 754-761 [PMID: 32554983 DOI: 10.1097/RLI.0000000000000700]

25 **Raptis CA**, Hammer MM, Short RG, Shah A, Bhalla S, Bierhals AJ, Filev PD, Hope MD, Jeudy J, Kligerman SJ, Henry TS. Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date. *AJR Am J Roentgenol* 2020; **215**: 839-842 [PMID: 32298149 DOI: 10.2214/AJR.20.23202]

26 **Adams HJA**, Kwee TC, Kwee RM. Coronavirus Disease 2019 and Chest CT: Do Not Put the Sensitivity Value in the Isolation Room and Look Beyond the Numbers. *Radiology* 2020; **297**: E236-E237 [PMID: 32339083 DOI: 10.1148/radiol.2020201709]

27 **Bai HX**, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, Pan I, Shi LB, Wang DC, Mei J, Jiang XL, Zeng QH, Egglin TK, Hu PF, Agarwal S, Xie FF, Li S, Healey T, Atalay MK, Liao WH. Performance of Radiologists in Differentiating COVID-19 from Non-COVID-19 Viral Pneumonia at Chest CT. *Radiology* 2020; **296**: E46-E54 [PMID: 32155105 DOI: 10.1148/radiol.2020200823]

28 **Kim H**, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse Transcriptase Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. *Radiology* 2020; **296**: E145-E155 [PMID: 32301646 DOI: 10.1148/radiol.2020201343]

29 **Islam N**, Salameh JP, Leeflang MM, Hooft L, McGrath TA, van der Pol CB, Frank RA, Kazi S, Prager R, Hare SS, Dennie C, Spijker R, Deeks JJ, Dinnes J, Jenniskens K, Korevaar DA, Cohen JF, Van den Bruel A, Takwoingi Y, van de Wijgert J, Wang J, McInnes MD; Cochrane COVID-19 Diagnostic Test Accuracy Group. Thoracic imaging tests for the diagnosis of COVID-19. *Cochrane Database Syst Rev* 2020; **11**: CD013639 [PMID: 33242342 DOI: 10.1002/14651858.CD013639.pub3]

30 **Hope MD**, Raptis CA, Shah A, Hammer MM, Henry TS; six signatories. A role for CT in COVID-19? *Lancet* 2020; **395**: 1189-1190 [PMID: 32224299 DOI: 10.1016/S0140-6736(20)30728-5]

31 **Adams HJA**, Kwee TC, Yakar D, Hope MD, Kwee RM. Systematic Review and Meta-Analysis on the Value of Chest CT in the Diagnosis of Coronavirus Disease (COVID-19): *Sol Scientiae, Illustra Nos*. *AJR Am J Roentgenol* 2020; **215**: 1342-1350 [PMID: 32478562 DOI: 10.2214/AJR.20.23391]

32 **Akl EA**, Blažić I, Yaacoub S, Frija G, Chou R, Appiah JA, Fatehi M, Flor N, Hitti E, Jafri H, Jin ZY, Kauczor HU, Kawooya M, Kazerooni EA, Ko JP, Mahfouz R, Muglia V, Nyabanda R, Sanchez M, Shete PB, Ulla M, Zheng C, van Deventer E, Perez MDR. Use of Chest Imaging in the Diagnosis and Management of COVID-19: A WHO Rapid Advice Guide. *Radiology* 2021; **298**: E63-E69 [PMID: 32729811 DOI: 10.1148/radiol.2020203173]

33 **American College of Radiology**. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. [cited 25 January 2021]. In: American College of Radiology [Internet]. Available from: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection

34 **Salaffi F**, Carotti M, Tardella M, Borgheresi A, Agostini A, Minorati D, Marotto D, Di Carlo M,

Galli M, Giovagnoni A, Sarzi-Puttini P. The role of a chest computed tomography severity score in coronavirus disease 2019 pneumonia. *Medicine (Baltimore)* 2020; **99**: e22433 [PMID: 33080676 DOI: 10.1097/MD.0000000000022433]

35 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin J, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest* 2020; **158**: 106-116 [PMID: 32275978 DOI: 10.1016/j.chest.2020.04.003]

36 **Jajodia A**, Ebner L, Heidinger B, Chaturvedi A, Prosch H. Imaging in corona virus disease 2019 (COVID-19)-A Scoping review. *Eur J Radiol Open* 2020; **7**: 100237 [PMID: 32395567 DOI: 10.1016/j.ejro.2020.100237]

37 **Awulachew E**, Diriba K, Anja A, Getu E, Belayneh F. Computed Tomography (CT) Imaging Features of Patients with COVID-19: Systematic Review and Meta-Analysis. *Radiol Res Pract* 2020; **2020**: 1023506 [PMID: 32733706 DOI: 10.1155/2020/1023506]

38 **Salehi S**, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *AJR Am J Roentgenol* 2020; **215**: 87-93 [PMID: 32174129 DOI: 10.2214/AJR.20.23034]

39 **Wang Y**, Dong C, Hu Y, Li C, Ren Q, Zhang X, Shi H, Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296**: E55-E64 [PMID: 32191587 DOI: 10.1148/radiol.2020200843]

40 **El Homsi M**, Chung M, Bernheim A, Jacobi A, King MJ, Lewis S, Taouli B. Review of chest CT manifestations of COVID-19 infection. *Eur J Radiol Open* 2020; **7**: 100239 [PMID: 32550256 DOI: 10.1016/j.ejro.2020.100239]

41 **Li K**, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. *Invest Radiol* 2020; **55**: 327-331 [PMID: 32118615 DOI: 10.1097/RLI.0000000000000672]

42 **Ojha V**, Mani A, Pandey NN, Sharma S, Kumar S. CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients. *Eur Radiol* 2020; **30**: 6129-6138 [PMID: 32474632 DOI: 10.1007/s00330-020-06975-7]

43 **Oudkerk M**, Büller HR, Kuijpers D, van Es N, Oudkerk SF, McLoud T, Gommers D, van Dissel J, Ten Cate H, van Beek EJR. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. *Radiology* 2020; **297**: E216-E222 [PMID: 32324101 DOI: 10.1148/radiol.2020201629]

44 **Carsana L**, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, Rech R, Colombo R, Antinori S, Corbellino M, Galli M, Catena E, Tosoni A, Gianatti A, Nebuloni M. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020; **20**: 1135-1140 [PMID: 32526193 DOI: 10.1016/S1473-3099(20)30434-5]

45 **Hani C**, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, Revel MP. COVID-19 pneumonia: A review of typical CT findings and differential diagnosis. *Diagn Interv Imaging* 2020; **101**: 263-268 [PMID: 32291197 DOI: 10.1016/j.diii.2020.03.014]

46 **Larici AR**, Cicchetti G, Marano R, Merlino B, Elia L, Calandriello L, Del Ciello A, Farchione A, Savino G, Infante A, Larosa L, Colosimo C, Manfredi R, Natale L. Multimodality imaging of COVID-19 pneumonia: from diagnosis to follow-up. A comprehensive review. *Eur J Radiol* 2020; **131**: 109217 [PMID: 32861174 DOI: 10.1016/j.ejrad.2020.109217]

47 **Hosseiny M**, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology Perspective of Coronavirus Disease 2019 (COVID-19): Lessons From Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome. *AJR Am J Roentgenol* 2020; **214**: 1078-1082 [PMID: 32108495 DOI: 10.2214/AJR.20.22969]

48 **Aljondi R**, Alghamdi S. Diagnostic Value of Imaging Modalities for COVID-19: Scoping Review. *J Med Internet Res* 2020; **22**: e19673 [PMID: 32716893 DOI: 10.2196/19673]

49 **Yin Z**, Kang Z, Yang D, Ding S, Luo H, Xiao E. A Comparison of Clinical and Chest CT Findings in Patients With Influenza A (H1N1) Virus Infection and Coronavirus Disease (COVID-19). *AJR Am J Roentgenol* 2020; **215**: 1065-1071 [PMID: 32452731 DOI: 10.2214/AJR.20.23214]

50 **Koo HJ**, Lim S, Choe J, Choi SH, Sung H, Do KH. Radiographic and CT Features of Viral Pneumonia. *Radiographics* 2018; **38**: 719-739 [PMID: 29757717 DOI: 10.1148/rg.2018170048]

51 **Ciccarese F**, Coppola F, Spinelli D, Galletta GL, Lucidi V, Paccapelo A, De Benedittis C, Balacchi C, Golfieri R. Diagnostic Accuracy of North America Expert Consensus Statement on Reporting CT Findings in Patients Suspected of Having COVID-19 Infection: An Italian Single-Center Experience. *Radiol Cardiothorac Imaging* 2020; **2**: e200312 [PMID: 33778611 DOI: 10.1148/ryct.2020200312]

52 **Prokop M**, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**: E97-E104 [PMID: 32339082 DOI: 10.1148/radiol.2020201473]

53 **De Smet K**, De Smet D, Ryckaert T, Laridon E, Heremans B, Vandenbulcke R, Demedts I, Bouckaert B, Gryspeerdt S, Martens GA. Diagnostic Performance of Chest CT for SARS-CoV-2 Infection in Individuals with or without COVID-19 Symptoms. *Radiology* 2021; **298**: E30-E37 [PMID: 32776832 DOI: 10.1148/radiol.2020202708]

54 **Schalekamp S**, Bleeker-Rovers CP, Beenen LFM, Quarles van Ufford HME, Gietema HA, Stöger JL, Harris V, Reijers MHE, Rahamat-Langendoen J, Korevaar DA, Smits LP, Korteweg C, van Rees Vellinga TFD, Vermaat M, Stassen PM, Scheper H, Wijnakker R, Borm FJ, Dofferhoff ASM, Prokop M. Chest CT in the Emergency Department for Diagnosis of COVID-19 Pneumonia: Dutch Experience. *Radiology* 2021; **298**: E98-E106 [PMID: 33201791 DOI: 10.1148/radiol.2020203465]

55 **Wu X**, Liu X, Zhou Y, Yu H, Li R, Zhan Q, Ni F, Fang S, Lu Y, Ding X, Liu H, Ewing RM, Jones MG, Hu Y, Nie H, Wang Y. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 2021 [PMID: 33964245 DOI: 10.1016/s2213-2600(21)00174-0]

56 **Hare SS**, Rodrigues JCL, Nair A, Jacob J, Upile S, Johnstone A, Mcstay R, Edey A, Robinson G. The continuing evolution of COVID-19 imaging pathways in the UK: a British Society of Thoracic Imaging expert reference group update. *Clin Radiol* 2020; **75**: 399-404 [PMID: 32321645 DOI: 10.1016/j.crad.2020.04.002]

57 **Bernheim A**, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020; **295**: 200463 [PMID: 32077789 DOI: 10.1148/radiol.2020200463]

58 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]

59 **Fang Y**, Zhou J, Ding X, Ling G, Yu S. Pulmonary fibrosis in critical ill patients recovered from COVID-19 pneumonia: Preliminary experience. *Am J Emerg Med* 2020; **38**: 2134-2138 [PMID: 33071084 DOI: 10.1016/j.ajem.2020.05.120]

60 **Hwang DM**, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. Pulmonary pathology of severe acute respiratory syndrome in Toronto. *Mod Pathol* 2005; **18**: 1-10 [PMID: 15272286 DOI: 10.1038/modpathol.3800247]

61 **Cornejo R**, Llanos O, Fernández C, Carlos Díaz J, Cardemil G, Salguero J, Luengo C, Tobar E, Romero C, Gálvez LR. Organizing pneumonia in patients with severe respiratory failure due to novel A (H1N1) influenza. *BMJ Case Rep* 2010; **2010** [PMID: 22767562 DOI: 10.1136/bcr.02.2010.2708]

62 **Torrealba JR**, Fisher S, Kanne JP, Butt YM, Glazer C, Kershaw C, Burguete D, Gokaslan T, Batra K. Pathology-radiology correlation of common and uncommon computed tomographic patterns of organizing pneumonia. *Hum Pathol* 2018; **71**: 30-40 [PMID: 29122655 DOI: 10.1016/j.humpath.2017.10.028]

63 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

64 **Kory P**, Kanne JP. SARS-CoV-2 organising pneumonia: 'Has there been a widespread failure to identify and treat this prevalent condition in COVID-19? *BMJ Open Respir Res* 2020; **7** [PMID: 32963028 DOI: 10.1136/bmjresp-2020-000724]

65 **Li X**, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Crit Care* 2020; **24**: 198 [PMID: 32375845 DOI: 10.1186/s13054-020-02911-9]

66 **Sekhawat V**, Green A, Mahadeva U. COVID-19 autopsies: conclusions from international studies. *Diagn Histopathol (Oxf)* 2021; **27**: 103-107 [PMID: 33312230 DOI: 10.1016/j.mpdhp.2020.11.008]

67 **McGuinness G**, Zhan C, Rosenberg N, Azour L, Wickstrom M, Mason DM, Thomas KM, Moore WH. Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. *Radiology* 2020; **297**: E252-E262 [PMID: 32614258 DOI: 10.1148/radiol.2020202352]

68 **Han X**, Fan Y, Alwalid O, Li N, Jia X, Yuan M, Li Y, Cao Y, Gu J, Wu H, Shi H. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology* 2021; **299**: E177-E186 [PMID: 33497317 DOI: 10.1148/radiol.2021203153]

69 **Henry BM**, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta* 2020; **507**: 167-173 [PMID: 32348783 DOI: 10.1016/j.cca.2020.04.027]

70 **Léonard-Lorant I**, Delabranche X, Séverac F, Helms J, Pauzet C, Collange O, Schneider F, Labani A, Bilbault P, Molière S, Leyendecker P, Roy C, Ohana M. Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. *Radiology* 2020; **296**: E189-E191 [PMID: 32324102 DOI: 10.1148/radiol.2020201561]

71 **Poyiadji N**, Cormier P, Patel PY, Hadied MO, Bhargava P, Khanna K, Nadig J, Keimig T, Spizarny D, Reeser N, Klochko C, Peterson EL, Song T. Acute Pulmonary Embolism and COVID-19. *Radiology* 2020; **297**: E335-E338 [PMID: 32407256 DOI: 10.1148/radiol.2020201955]

72 **Planquette B**, Le Berre A, Khider L, Yannoutsos A, Gendron N, de Torcy M, Mohamedi N, Jouveshomme S, Smadja DM, Lazareth I, Goudot G, Fournier L, Bruel C, Diehl JL, Mourad JJ, Meyer G, Priollet P, Messas E, Sanchez O, Beaussier H, Mirault T, Zins M, Chatelier G, Emmerich J. Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with respiratory symptoms: A nested case-control study. *Thromb Res* 2021; **197**: 94-99 [PMID: 33190025 DOI: 10.1016/j.thromres.2020.11.001]

73 **Lippi G**, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. *Thromb Haemost* 2020; **120**: 876-878 [PMID: 32246450 DOI: 10.1055/s-0040-1709650]

74 **Aycock RD**, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR. Acute Kidney Injury After Computed Tomography: A Meta-analysis. *Ann Emerg Med* 2018; **71**: 44-53.e4 [PMID: 28811122 DOI: 10.1016/j.annemergmed.2017.06.041]

75 **Lang M**, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, Li MD, Witkin A, Rodriguez-Lopez JM, Shepard JO, Little BP. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis* 2020; **20**: 1365-1366 [PMID: 32359410 DOI: 10.1016/S1473-3099(20)30367-4]

76 **American College of Radiology**. COVID-19: ACR Statement on Nuclear Medicine Ventilation Scans. [cited 25 January 2021]. In: American College of Radiology [Internet]. Available from: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/COVID19-Nuclear-Medicine-Ventilation-Scans

77 **Lu Y**, Lorenzoni A, Fox JJ, Rademaker J, Vander Els N, Grewal RK, Strauss HW, Schöder H. Noncontrast perfusion single-photon emission CT/CT scanning: a new test for the expedited, high-accuracy diagnosis of acute pulmonary embolism. *Chest* 2014; **145**: 1079-1088 [PMID: 24798835 DOI: 10.1378/chest.13-2090]

78 **Das JP**, Yeh R, Schöder H. Clinical utility of perfusion (Q)-single-photon emission computed tomography (SPECT)/CT for diagnosing pulmonary embolus (PE) in COVID-19 patients with a moderate to high pre-test probability of PE. *Eur J Nucl Med Mol Imaging* 2021; **48**: 794-799 [PMID: 32959115 DOI: 10.1007/s00259-020-05043-y]

79 **Carotti M**, Salaffi F, Sarzi-Puttini P, Agostini A, Borgheresi A, Minorati D, Galli M, Marotto D, Giovagnoni A. Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med* 2020; **125**: 636-646 [PMID: 32500509 DOI: 10.1007/s11547-020-01237-4]

80 **Kalra MK**, Homayounieh F, Arru C, Holmberg O, Vassileva J. Chest CT practice and protocols for COVID-19 from radiation dose management perspective. *Eur Radiol* 2020; **30**: 6554-6560 [PMID: 32621238 DOI: 10.1007/s00330-020-07034-x]

81 **Lee C**. Managing Radiation Dose from Chest CT in Patients with COVID-19. *Radiology* 2021; **298**: E158-E159 [PMID: 33174811 DOI: 10.1148/radiol.2020204129]

82 **Homayounieh F**, Holmberg O, Umairi RA, Aly S, Basevičius A, Costa PR, Darweesh A, Gershan V, Ilves P, Kostova-Lefterova D, Renha SK, Mohseni I, Rampado O, Rotaru N, Shirazu I, Sinitsyn V, Turk T, Van Ngoc Ty C, Kalra MK, Vassileva J. Variations in CT Utilization, Protocols, and Radiation Doses in COVID-19 Pneumonia: Results from 28 Countries in the IAEA Study. *Radiology* 2021; **298**: E141-E151 [PMID: 33170104 DOI: 10.1148/radiol.2020203453]

83 **Kang Z**, Li X, Zhou S. Recommendation of low-dose CT in the detection and management of COVID-2019. *Eur Radiol* 2020; **30**: 4356-4357 [PMID: 32193637 DOI: 10.1007/s00330-020-06809-6]

84 **Agostini A**, Floridi C, Borgheresi A, Badaloni M, Esposto Pirani P, Terilli F, Ottaviani L, Giovagnoni A. Proposal of a low-dose, long-pitch, dual-source chest CT protocol on third-generation dual-source CT using a tin filter for spectral shaping at 100 kVp for CoronaVirus Disease 2019 (COVID-19) patients: a feasibility study. *Radiol Med* 2020; **125**: 365-373 [PMID: 32239472 DOI: 10.1007/s11547-020-01179-x]

85 **Kerpel A**, Apter S, Nissan N, Houri-Levi E, Klug M, Amit S, Konen E, Marom EM. Diagnostic and Prognostic Value of Chest Radiographs for COVID-19 at Presentation. *West J Emerg Med* 2020; **21**: 1067-1075 [PMID: 32970556 DOI: 10.5811/westjem.2020.7.48842]

86 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

87 **Jacobi A**, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. *Clin Imaging* 2020; **64**: 35-42 [PMID: 32302927 DOI: 10.1016/j.clinimag.2020.04.001]

88 **Yates A**, Dempsey PJ, Vencken S, MacMahon PJ, Hutchinson BD. Structured reporting in portable chest radiographs: An essential tool in the diagnosis of COVID-19. *Eur J Radiol* 2021; **134**: 109414 [PMID: 33246271 DOI: 10.1016/j.ejrad.2020.109414]

89 **Warren MA**, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, Rice TW, Matthay MA, Calfee CS, Ware LB. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax* 2018; **73**: 840-846 [PMID: 29903755 DOI: 10.1136/thoraxjnl-2017-211280]

90 **Joseph NP**, Reid NJ, Som A, Li MD, Hyle EP, Dugdale CM, Lang M, Betancourt JR, Deng F, Mendoza DP, Little BP, Narayan AK, Flores EJ. Racial and Ethnic Disparities in Disease Severity on Admission Chest Radiographs among Patients Admitted with Confirmed Coronavirus Disease 2019: A Retrospective Cohort Study. *Radiology* 2020; **297**: E303-E312 [PMID: 32673191 DOI: 10.1148/radiol.2020202602]

91 **Zhu F**, Zhao X, Wang T, Wang Z, Guo F, Xue H, Chang P, Liang H, Ni W, Wang Y, Chen L, Jiang B. Ultrasonic Characteristics and Severity Assessment of Lung Ultrasound in COVID-19 Pneumonia in Wuhan, China: A Retrospective, Observational Study. *Engineering (Beijing)* 2021; **7**: 367-375 [PMID: 33101757 DOI: 10.1016/j.eng.2020.09.007]

92 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for International Standardization of the Use of Lung Ultrasound for Patients With COVID-19: A Simple, Quantitative, Reproducible Method. *J Ultrasound Med* 2020; **39**: 1413-1419 [PMID: 32227492 DOI: 10.1002/jum.15285]

93 **Allinovi M**, Parise A, Giacalone M, Amerio A, Delsante M, Odone A, Franci A, Gigliotti F, Amadasi S, Delmonte D, Parri N, Mangia A. Lung Ultrasound May Support Diagnosis and Monitoring of COVID-19 Pneumonia. *Ultrasound Med Biol* 2020; **46**: 2908-2917 [PMID: 32807570 DOI: 10.1016/j.ultrasmedbio.2020.07.018]

94 **Bennett D**, De Vita E, Mezzasalma F, Lanzarone N, Cameli P, Bianchi F, Perillo F, Bargagli E, Mazzei MA, Volterrani L, Scolletta S, Valente S, Franchi F, Frediani B, Sestini P. Portable Pocket-Sized Ultrasound Scanner for the Evaluation of Lung Involvement in Coronavirus Disease 2019 Patients. *Ultrasound Med Biol* 2021; **47**: 19-24 [PMID: 33082053 DOI: 10.1016/j.ultrasmedbio.2020.09.014]

95 **Bar S**, Lecourtois A, Diouf M, Goldberg E, Bourbon C, Arnaud E, Domisse L, Dupont H, Gosset P. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. *Anaesthesia* 2020; **75**: 1620-1625 [PMID: 32520406 DOI: 10.1111/anae.15175]

96 **Haak SL**, Renken IJ, Jager LC, Lameijer H, van der Kolk BBY. Diagnostic accuracy of point-of-care lung ultrasound in COVID-19. *Emerg Med J* 2020 [PMID: 33208399 DOI: 10.1136/emermed-2020-210125]

97 **Lu W**, Zhang S, Chen B, Chen J, Xian J, Lin Y, Shan H, Su ZZ. A Clinical Study of Noninvasive Assessment of Lung Lesions in Patients with Coronavirus Disease-19 (COVID-19) by Bedside Ultrasound. *Ultraschall Med* 2020; **41**: 300-307 [PMID: 32294796 DOI: 10.1055/a-1154-8795]

98 **Tung-Chen Y**, Martí de Gracia M, Díez-Tascón A, Alonso-González R, Agudo-Fernández S, Parra-Gordo ML, Ossaba-Vélez S, Rodríguez-Fuertes P, Llamas-Fuentes R. Correlation between Chest Computed Tomography and Lung Ultrasonography in Patients with Coronavirus Disease 2019 (COVID-19). *Ultrasound Med Biol* 2020; **46**: 2918-2926 [PMID: 32771222 DOI: 10.1016/j.ultrasmedbio.2020.07.003]

99 **Gandhi D**, Ahuja K, Grover H, Sharma P, Solanki S, Gupta N, Patel L. Review of X-ray and computed tomography scan findings with a promising role of point of care ultrasound in COVID-19 pandemic. *World J Radiol* 2020; **12**: 195-203 [PMID: 33033574 DOI: 10.4329/wjr.v12.i9.195]

100 **Gandhi D**, Jain N, Khanna K, Li S, Patel L, Gupta N. Current role of imaging in COVID-19 infection with recent recommendations of point of care ultrasound in the contagion: a narrative review. *Ann Transl Med* 2020; **8**: 1094 [PMID: 33145313 DOI: 10.21037/atm-20-3043]

101 **Li J**, Long X, Wang X, Fang F, Lv X, Zhang D, Sun Y, Hu S, Lin Z, Xiong N. Radiology indispensable for tracking COVID-19. *Diagn Interv Imaging* 2021; **102**: 69-75 [PMID: 33281082 DOI: 10.1016/j.diii.2020.11.008]

102 **Torkian P**, Rajebi H, Zamani T, Ramezani N, Kiani P, Akhlaghpoor S. Magnetic resonance imaging features of coronavirus disease 2019 (COVID-19) pneumonia: The first preliminary case series. *Clin Imaging* 2021; **69**: 261-265 [PMID: 33002753 DOI: 10.1016/j.clinimag.2020.09.002]

103 **Yang S**, Zhang Y, Shen J, Dai Y, Ling Y, Lu H, Zhang R, Ding X, Qi H, Shi Y, Zhang Z, Shan F. Clinical Potential of UTE-MRI for Assessing COVID-19: Patient- and Lesion-Based Comparative Analysis. *J Magn Reson Imaging* 2020; **52**: 397-406 [PMID: 32491257 DOI: 10.1002/jmri.27208]

104 **Fields BKK**, Demirjian NL, Dadgar H, Gholamrezanezhad A. Imaging of COVID-19: CT, MRI, and PET. *Semin Nucl Med* 2021; **51**: 312-320 [PMID: 33288215 DOI: 10.1053/j.semnuclmed.2020.11.003]

105 **Rafiee F**, Keshavarz P, Katal S, Assadi M, Nejati SF, Ebrahimian Sadabad F, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19) in Molecular Imaging: A Systematic Review of Incidental Detection of SARS-CoV-2 Pneumonia on PET Studies. *Semin Nucl Med* 2021; **51**: 178-191 [PMID: 33509374 DOI: 10.1053/j.semnuclmed.2020.10.002]

106 **Revzin MV**, Raza S, Srivastava NC, Warshawsky R, D'Agostino C, Malhotra A, Bader AS, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 2: From Cardiac Complications to Pediatric Manifestations. *Radiographics* 2020; **40**: 1866-1892 [PMID: 33136488 DOI: 10.1148/rg.2020200195]

107 **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]

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

109 **Ruan Q**, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46**: 846-848 [PMID: 32125452 DOI: 10.1007/s00134-020-05991-x]

110 **Wei JF**, Huang FY, Xiong TY, Liu Q, Chen H, Wang H, Huang H, Luo YC, Zhou X, Liu ZY, Peng Y, Xu YN, Wang B, Yang YY, Liang ZA, Lei XZ, Ge Y, Yang M, Zhang L, Zeng MQ, Yu H, Liu K, Jia YH, Prendergast BD, Li WM, Chen M. Acute myocardial injury is common in patients with COVID-19 and impairs their prognosis. *Heart* 2020; **106**: 1154-1159 [PMID: 32354798 DOI: 10.1136/heartjnl-2020-317007]

111 **Skulstad H**, Cosyns B, Popescu BA, Galderisi M, Salvo GD, Donal E, Petersen S, Gimelli A,

Haugaa KH, Muraru D, Almeida AG, Schulz-Menger J, Dweck MR, Pontone G, Sade LE, Gerber B, Maurovich-Horvat P, Bharucha T, Cameli M, Magne J, Westwood M, Maurer G, Edvardsen T. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. *Eur Heart J Cardiovasc Imaging* 2020; **21**: 592-598 [PMID: 32242891 DOI: 10.1093/ehjci/jeaa072]

112 **Vrettou AR**, Parissis J, Ikonomidis I. The Dual Role of Echocardiography in the Diagnosis of Acute Cardiac Complications and Treatment Monitoring for Coronavirus Disease 2019 (COVID-19). *Front Cardiovasc Med* 2020; **7**: 129 [PMID: 32984405 DOI: 10.3389/fcvm.2020.00129]

113 **Cau R**, Bassareo PP, Mannelli L, Suri JS, Saba L. Imaging in COVID-19-related myocardial injury. *Int J Cardiovasc Imaging* 2021; **37**: 1349-1360 [PMID: 33211242 DOI: 10.1007/s10554-020-02089-9]

114 **Beitzke D**, Salgado R, Francone M, Kreitner KF, Natale L, Bremerich J, Gutberlet M, Mousseaux E, Nikolaou K, Peebles C, Velthuis B, Vliegenthart R, Loewe C, Emrich T; Executive Committee of the European Society of Cardiovascular Radiology (ESCR):, Luigi N, Matthias G, Rozemarijn V, Konstantin N, Marco F, Christian L, Brigitta V, Rodrigo S, Charles P, Ellie M. Cardiac imaging procedures and the COVID-19 pandemic: recommendations of the European Society of Cardiovascular Radiology (ESCR). *Int J Cardiovasc Imaging* 2020; **36**: 1801-1810 [PMID: 32451877 DOI: 10.1007/s10554-020-01892-8]

115 **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]

116 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]

117 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

118 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]

119 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]

120 **Barkmeier DT**, Stein EB, Bojicic K, Otemuyiwa B, Vummidi D, Chughtai A, Ellis JH. Abdominal CT in COVID-19 patients: incidence, indications, and findings. *Abdom Radiol (NY)* 2021; **46**: 1256-1262 [PMID: 32949274 DOI: 10.1007/s00261-020-02747-5]

121 **Lui K**, Wilson MP, Low G. Abdominal imaging findings in patients with SARS-CoV-2 infection: a scoping review. *Abdom Radiol (NY)* 2021; **46**: 1249-1255 [PMID: 32926211 DOI: 10.1007/s00261-020-02739-5]

122 **Bhayana R**, Som A, Li MD, Carey DE, Anderson MA, Blake MA, Catalano O, Gee MS, Hahn PF, Harisinghani M, Kilcoyne A, Lee SI, Mojtahed A, Pandharipande PV, Pierce TT, Rosman DA, Saini S, Samir AE, Simeone JF, Gervais DA, Velmahos G, Misdraji J, Kambadakone A. Abdominal Imaging Findings in COVID-19: Preliminary Observations. *Radiology* 2020; **297**: E207-E215 [PMID: 32391742 DOI: 10.1148/radiol.2020201908]

123 **Parry AH**, Wani AH, Yaseen M. Acute Mesenteric Ischemia in Severe Coronavirus-19 (COVID-19): Possible Mechanisms and Diagnostic Pathway. *Acad Radiol* 2020; **27**: 1190 [PMID: 32475635 DOI: 10.1016/j.acra.2020.05.016]

124 **Fan Z**, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]

125 **Wang F**, Wang H, Fan J, Zhang Y, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. *Gastroenterology* 2020; **159**: 367-370 [PMID: 32247022 DOI: 10.1053/j.gastro.2020.03.055]

126 **Kunutsor SK**, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. *Ann Med* 2020; **52**: 345-353 [PMID: 32643418 DOI: 10.1080/07853890.2020.1790643]

127 **Hirsch JS**, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; **98**: 209-218 [PMID: 32416116 DOI: 10.1016/j.kint.2020.05.006]

128 **Capaccione KM**, Yang H, West E, Patel H, Ma H, Patel S, Fruauff A, Loeb G, Maddocks A, Borowski A, Lala S, Nguyen P, Lignelli A, D'souza B, Desperito E, Ruzal-Shapiro C, Salvatore MM. Pathophysiology and Imaging Findings of COVID-19 Infection: An Organ-system Based Review. *Acad Radiol* 2021; **28**: 595-607 [PMID: 33583712 DOI: 10.1016/j.acra.2021.01.022]

129 **Puelles VG**, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfefferle S, Schröder AS, Edler C, Gross O, Glatzel M, Wichmann D, Wiech T, Kluge S, Pueschel K, Aepfelbacher M, Huber TB. Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med* 2020; **383**: 590-592 [PMID: 32402155 DOI: 10.1056/NEJMc2011400]

130 **Lima M**, Siokas V, Aloizou AM, Liampas I, Mentis AA, Tsouris Z, Papadimitriou A, Mitsias PD, Tsatsakis A, Bogdanos DP, Baloyannis SJ, Dardiotis E. Unraveling the Possible Routes of SARS-COV-2 Invasion into the Central Nervous System. *Curr Treat Options Neurol* 2020; **22**: 37 [PMID: 32994698 DOI: 10.1007/s11940-020-00647-z]

131 **Li Z**, Liu T, Yang N, Han D, Mi X, Li Y, Liu K, Vuylsteke A, Xiang H, Guo X. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. *Front Med* 2020; **14**: 533-541 [PMID: 32367431 DOI: 10.1007/s11684-020-0786-5]

132 **Eskandar EN**, Altschul DJ, de la Garza Ramos R, Cezayirli P, Unda SR, Benton J, Dardick J, Toma A, Patel N, Malaviya A, Flomenbaum D, Fernandez-Torres J, Lu J, Holland R, Burchi E, Zampolin R, Hsu K, McClelland A, Burns J, Erdfarb A, Malhotra R, Gong M, Semczuk P, Gursky J, Ferastraoaru V, Rosengard J, Antoniello D, Labovitz D, Esenwa C, Milstein M, Boro A, Mehler MF. Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19. *Neurology* 2021; **96**: e1527-e1538 [PMID: 33443111 DOI: 10.1212/WNL.0000000000011356]

133 **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683-690 [PMID: 32275288 DOI: 10.1001/jamaneurol.2020.1127]

134 **Helms J**, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, Meziani F. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020; **382**: 2268-2270 [PMID: 32294339 DOI: 10.1056/NEJMc2008597]

135 **Sawlani V**, Scotton S, Nader K, Jen JP, Patel M, Gokani K, Denno P, Thaller M, Englezou C, Janjua U, Bowen M, Hoskote C, Veenith T, Hassan-Smith G, Jacob S. COVID-19-related intracranial imaging findings: a large single-centre experience. *Clin Radiol* 2021; **76**: 108-116 [PMID: 33023738 DOI: 10.1016/j.crad.2020.09.002]

136 **Kremer S**, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, Collange O, Bonneville F, Adam G, Martin-Blondel G, Rafiq M, Geeraerts T, Delamarre L, Grand S, Krainik A, Caillard S, Constans JM, Metanbou S, Heintz A, Helms J, Schenck M, Lefèbvre N, Boutet C, Fabre X, Forestier G, de Beaurepaire I, Bornet G, Lacalm A, Oesterlé H, Bolognini F, Messié J, Hmeydia G, Benzakoun J, Oppenheim C, Bapst B, Megdiche I, Henry Feugeas MC, Khalil A, Gaudemer A, Jager L, Nesser P, Talla Mba Y, Hemmert C, Feuerstein P, Sebag N, Carré S, Alleg M, Lecocq C, Schmitt E, Anxionnat R, Zhu F, Comby PO, Ricolfi F, Thouant P, Desal H, Boulouis G, Berge J, Kazémi A, Pyatigorskaya N, Lecler A, Saleme S, Edjlali-Goujon M, Kerleroux B, Zorn PE, Matthieu M, Baloglu S, Ardellier FD, Willaume T, Brisset JC, Boulay C, Mutschler V, Hansmann Y, Mertes PM, Schneider F, Fafi-Kremer S, Ohana M, Meziani F, David JS, Meyer N, Anheim M, Cotton F. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. *Radiology* 2020; **297**: E242-E251 [PMID: 32544034 DOI: 10.1148/radiol.2020202222]

137 **Radmanesh A**, Derman A, Lui YW, Raz E, Loh JP, Hagiwara M, Borja MJ, Zan E, Fatterpekar GM. COVID-19-associated Diffuse Leukoencephalopathy and Microhemorrhages. *Radiology* 2020; **297**: E223-E227 [PMID: 32437314 DOI: 10.1148/radiol.2020202040]

138 **Aghagoli G**, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological Involvement in COVID-19 and Potential Mechanisms: A Review. *Neurocrit Care* 2021; **34**: 1062-1071 [PMID: 32661794 DOI: 10.1007/s12028-020-01049-4]

139 **De Sanctis P**, Doneddu PE, Viganò L, Selmi C, Nobile-Orazio E. Guillain-Barré syndrome associated with SARS-CoV-2 infection. A systematic review. *Eur J Neurol* 2020; **27**: 2361-2370 [PMID: 32757404 DOI: 10.1111/ene.14462]

140 **Andalib S**, Biller J, Di Napoli M, Moghimi N, McCullough LD, Rubinos CA, O'Hana Nobleza C, Azarpazhooh MR, Catanese L, Elicer I, Jafari M, Liberati F, Camejo C, Torbey M, Divani AA. Peripheral Nervous System Manifestations Associated with COVID-19. *Curr Neurol Neurosci Rep* 2021; **21**: 9 [PMID: 33586020 DOI: 10.1007/s11910-021-01102-5]

141 **Ramani SL**, Samet J, Franz CK, Hsieh C, Nguyen CV, Horbinski C, Deshmukh S. Musculoskeletal involvement of COVID-19: review of imaging. *Skeletal Radiol* 2021 [PMID: 33598718 DOI: 10.1007/s00256-021-03734-7]

142 **Sansone P**, Giaccari LG, Aurilio C, Coppolino F, Esposito V, Fiore M, Paladini A, Passavanti MB, Pota V, Pace MC. Post-Infectious Guillain-Barré Syndrome Related to SARS-CoV-2 Infection: A Systematic Review. *Life (Basel)* 2021; **11** [PMID: 33670000 DOI: 10.3390/Life11020167]

143 **Restivo DA**, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia Gravis Associated With SARS-CoV-2 Infection. *Ann Intern Med* 2020; **173**: 1027-1028 [PMID: 32776781 DOI: 10.7326/L20-0845]

144 **Zhou C**, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. *Neural Regen Res* 2014; **9**: 101-110 [PMID: 25206749 DOI: 10.4103/1673-5374.125337]

145 **Cabañes-Martínez L**, Villadóniga M, González-Rodríguez L, Araque L, Díaz-Cid A, Ruz-Caracuel I, Pian H, Sánchez-Alonso S, Fanjul S, Del Álamo M, Regidor I. Neuromuscular involvement in

COVID-19 critically ill patients. *Clin Neurophysiol* 2020; **131**: 2809-2816 [PMID: 33137571 DOI: 10.1016/j.clinph.2020.09.017]

146 **Lechien JR**, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souchay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020; **277**: 2251-2261 [PMID: 32253535 DOI: 10.1007/s00405-020-05965-1]

147 **Politi LS**, Salsano E, Grimaldi M. Magnetic Resonance Imaging Alteration of the Brain in a Patient With Coronavirus Disease 2019 (COVID-19) and Anosmia. *JAMA Neurol* 2020; **77**: 1028-1029 [PMID: 32469400 DOI: 10.1001/jamaneurol.2020.2125]

148 **Altundag A**, Yıldırım D, Tekcan Sanli DE, Cayonu M, Kandemirli SG, Sanli AN, Arici Duz O, Saatci O. Olfactory Cleft Measurements and COVID-19-Related Anosmia. *Otolaryngol Head Neck Surg* 2021; **164**: 1337-1344 [PMID: 33045908 DOI: 10.1177/0194599820965920]

149 **Gogia B**, Gil Guevara A, Rai PK, Fang X. A case of COVID-19 with multiple cranial neuropathies. *Int J Neurosci* 2020; 1-3 [PMID: 33372575 DOI: 10.1080/00207454.2020.1869001]

150 **Ling XC**, Kang EY, Lin JY, Chen HC, Lai CC, Ma DH, Wu WC. Ocular manifestation, comorbidities, and detection of severe acute respiratory syndrome-coronavirus 2 from conjunctiva in coronavirus disease 2019: A systematic review and meta-analysis. *Taiwan J Ophthalmol* 2020; **10**: 153-166 [PMID: 33110745 DOI: 10.4103/tjo.tjo_53_20]

151 **Landecho MF**, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, García-Layana A. COVID-19 retinal microangiopathy as an *in vivo* biomarker of systemic vascular disease? *J Intern Med* 2021; **289**: 116-120 [PMID: 32729633 DOI: 10.1111/joim.13156]

152 **Sanghi P**, Malik M, Hossain IT, Manzouri B. Ocular Complications in the Prone Position in the Critical Care Setting: The COVID-19 Pandemic. *J Intensive Care Med* 2021; **36**: 361-372 [PMID: 32985317 DOI: 10.1177/0885066620959031]

153 **Saritas TB**, Bozkurt B, Simsek B, Cakmak Z, Ozdemir M, Yosunkaya A. Ocular surface disorders in intensive care unit patients. *ScientificWorldJournal* 2013; **2013**: 182038 [PMID: 24285933 DOI: 10.1155/2013/182038]

154 **Lecler A**, Cotton F, Lersy F, Kremer S, Héran F; SFNR's COVID Study Group. Ocular MRI Findings in Patients with Severe COVID-19: A Retrospective Multicenter Observational Study. *Radiology* 2021; **299**: E226-E229 [PMID: 33591889 DOI: 10.1148/radiol.2021204394]

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

156 **Husain R**, Corcuera-Solano I, Dayan E, Jacobi AH, Huang M. Rhabdomyolysis as a manifestation of a severe case of COVID-19: A case report. *Radiol Case Rep* 2020; **15**: 1633-1637 [PMID: 32690987 DOI: 10.1016/j.radcr.2020.07.003]

157 **De Giorgi V**, Recalcati S, Jia Z, Chong W, Ding R, Deng Y, Scarfì F, Venturi F, Trane L, Gori A, Silvestri F, Gao XH, Lotti T. Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): A prospective study from China and Italy. *J Am Acad Dermatol* 2020; **83**: 674-675 [PMID: 32442696 DOI: 10.1016/j.jaad.2020.05.073]

158 **Marzano AV**, Genovese G, Moltrasio C, Gaspari V, Vezzoli P, Maione V, Misciali C, Sena P, Patrizi A, Offidani A, Quaglino P, Arco R, Caproni M, Rovesti M, Bordin G, Recalcati S, Potenza C, Guarneri C, Fabbrocini G, Tomasini C, Sorci M, Lombardo M, Gisondi P, Conti A, Casazza G, Peris K, Calzavara-Pinton P, Berti E; Italian Skin COVID-19 Network of the Italian Society of Dermatology and Sexually Transmitted Diseases. The clinical spectrum of COVID-19-associated cutaneous manifestations: An Italian multicenter study of 200 adult patients. *J Am Acad Dermatol* 2021; **84**: 1356-1363 [PMID: 33476725 DOI: 10.1016/j.jaad.2021.01.023]

159 **Dong Y**, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020; **145** [PMID: 32179660 DOI: 10.1542/peds.2020-0702]

160 **Ludvigsson JF**. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr* 2020; **109**: 1088-1095 [PMID: 32202343 DOI: 10.1111/apa.15270]

161 **Bayramoglu Z**, Canıpek E, Comert RG, Gasimli N, Kaba O, Sarı Yanartaş M, Hançerli Torun S, Somer A, Erturk SM. Imaging Features of Pediatric COVID-19 on Chest Radiography and Chest CT: A Retrospective, Single-Center Study. *Acad Radiol* 2021; **28**: 18-27 [PMID: 33067091 DOI: 10.1016/j.acra.2020.10.002]

162 **Peng X**, Guo Y, Xiao H, Xia W, Zhai A, Zhu B, Zhang W, Shao J. Overview of chest involvement at computed tomography in children with coronavirus disease 2019 (COVID-19). *Pediatr Radiol* 2021; **51**: 222-230 [PMID: 33084963 DOI: 10.1007/s00247-020-04826-7]

163 **Raissaki M**, Shelmerdine SC, Damasio MB, Toso S, Kvist O, Lovrenski J, Hirsch FW, Görkem SB, Paterson A, Arthurs OJ, Rossi A, van Schuppen J, Petit P, Argyropoulou MI, Offiah AC, Rosendahl K, Caro-Domínguez P. Management strategies for children with COVID-19: ESPR practical recommendations. *Pediatr Radiol* 2020; **50**: 1313-1323 [PMID: 32621013 DOI: 10.1007/s00247-020-04749-3]

164 **Katal S**, Johnston SK, Johnston JH, Gholamrezanezhad A. Imaging Findings of SARS-CoV-2

Infection in Pediatrics: A Systematic Review of Coronavirus Disease 2019 (COVID-19) in 850 Patients. *Acad Radiol* 2020; **27**: 1608-1621 [PMID: 32773328 DOI: 10.1016/j.acra.2020.07.031]

165 **Xia W**, Guo Y, Tian Z, Luo Y, Hu D, Shao J, Li Z, Kamel IR. Clinical Features and Temporal Changes of RT-PCR and Chest CT in COVID-19 Pediatric Patients. *Front Pediatr* 2020; **8**: 579512 [PMID: 33163466 DOI: 10.3389/fped.2020.579512]

166 **Zuo H**. Contribution of CT Features in the Diagnosis of COVID-19. *Can Respir J* 2020; **2020**: 1237418 [PMID: 33224361 DOI: 10.1155/2020/1237418]

167 **Hizal M**, Aykac K, Yayla BCC, Yilmaz A, Altun D, Akkaya HE, Bayhan GI, Kurt ANC, Karakaya J, Ozsurekci Y, Ceyhan M. Diagnostic value of lung ultrasonography in children with COVID-19. *Pediatr Pulmonol* 2021; **56**: 1018-1025 [PMID: 33085218 DOI: 10.1002/ppul.25127]

168 **Musolino AM**, Supino MC, Buonsenso D, Papa RE, Chiurchiù S, Magistrelli A, Barbieri MA, Raponi M, D'Argenio P, Villani A, Tomà P; LUS COVID Group. Lung ultrasound in the diagnosis and monitoring of 30 children with coronavirus disease 2019. *Pediatr Pulmonol* 2021; **56**: 1045-1052 [PMID: 33404197 DOI: 10.1002/ppul.25255]

169 **Simoni P**, Bazzocchi A, Boitsios G, De Leucio A, Preziosi M, Aparisi Gómez MP. Chest computed tomography (CT) features in children with reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19: A systematic review. *J Med Imaging Radiat Oncol* 2020; **64**: 649-659 [PMID: 33000560 DOI: 10.1111/1754-9485.13098]

170 **World Health Organization**. Multisystem inflammatory syndrome in children and adolescents with COVID-19. [cited 26 January 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

171 **Hameed S**, Elbaaly H, Reid CEL, Santos RMF, Shivamurthy V, Wong J, Jogeesvaran KH. Spectrum of Imaging Findings at Chest Radiography, US, CT, and MRI in Multisystem Inflammatory Syndrome in Children Associated with COVID-19. *Radiology* 2021; **298**: E1-E10 [PMID: 32584166 DOI: 10.1148/radiol.2020202543]

172 **Ahmed M**, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, Acosta S, Naqvi R, Burmeister-Morton F, Burmeister F, Tarriela A, Petershack M, Evans M, Hoang A, Rajasekaran K, Ahuja S. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine* 2020; **26**: 100527 [PMID: 32923992 DOI: 10.1016/j.eclinm.2020.100527]

173 **Fenlon Iii EP**, Chen S, Ruzal-Shapiro CB, Jaramillo D, Maddocks ABR. Extracardiac imaging findings in COVID-19-associated multisystem inflammatory syndrome in children. *Pediatr Radiol* 2021; **51**: 831-839 [PMID: 33433671 DOI: 10.1007/s00247-020-04929-1]

174 **Yu J**, Ding N, Chen H, Liu XJ, He WJ, Dai WC, Zhou ZG, Lin F, Pu ZH, Li DF, Xu HJ, Wang YL, Zhang HW, Lei Y. Infection Control against COVID-19 in Departments of Radiology. *Acad Radiol* 2020; **27**: 614-617 [PMID: 32276755 DOI: 10.1016/j.acra.2020.03.025]

175 **Goh Y**, Chua W, Lee JKT, Ang BWL, Liang CR, Tan CA, Choong DAW, Hoon HX, Ong MKL, Quek ST. Operational Strategies to Prevent Coronavirus Disease 2019 (COVID-19) Spread in Radiology: Experience From a Singapore Radiology Department After Severe Acute Respiratory Syndrome. *J Am Coll Radiol* 2020; **17**: 717-723 [PMID: 32298643 DOI: 10.1016/j.jacr.2020.03.027]

176 **Tsou IYY**, Liew CJY, Tan BP, Chou H, Wong SBS, Loke KSH, Quah RCW, Tan AGS, Tay KH. Planning and coordination of the radiological response to the coronavirus disease 2019 (COVID-19) pandemic: the Singapore experience. *Clin Radiol* 2020; **75**: 415-422 [PMID: 32291080 DOI: 10.1016/j.crad.2020.03.028]

177 **Mossa-Basha M**, Meltzer CC, Kim DC, Tuite MJ, Kolli KP, Tan BS. Radiology Department Preparedness for COVID-19: *Radiology* Scientific Expert Review Panel. *Radiology* 2020; **296**: E106-E112 [PMID: 32175814 DOI: 10.1148/radiol.2020200988]

178 **American Cancer Society**. Cancer Screening During the COVID-19 Pandemic. [cited 4 January 2021]. In: American Cancer Society [Internet]. Available from: https://www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/cancer-screening-during-covid-19-pandemic.html

179 **The American Society of Breast Surgeons**. ASBrS and ACR Joint Statement on Breast Screening Exams During the COVID-19 Pandemic. [cited 3 January 2021]. In: The American Society of Breast Surgeons [Internet]. Available from: https://www.breastsurgeons.org/news/?id=45

180 **Mazzone PJ**, Gould MK, Arenberg DA, Chen AC, Choi HK, Detterbeck FC, Farjah F, Fong KM, Iaccarino JM, Janes SM, Kanne JP, Kazerooni EA, MacMahon H, Naidich DP, Powell CA, Raoof S, Rivera MP, Tanner NT, Tanoue LK, Tremblay A, Vachani A, White CS, Wiener RS, Silvestri GA. Management of Lung Nodules and Lung Cancer Screening During the COVID-19 Pandemic: CHEST Expert Panel Report. *Chest* 2020; **158**: 406-415 [PMID: 32335067 DOI: 10.1016/j.chest.2020.04.020]

181 **Patt D**, Gordan L, Diaz M, Okon T, Grady L, Harmison M, Markward N, Sullivan M, Peng J, Zhou A. Impact of COVID-19 on Cancer Care: How the Pandemic Is Delaying Cancer Diagnosis and Treatment for American Seniors. *JCO Clin Cancer Inform* 2020; **4**: 1059-1071 [PMID: 33253013 DOI: 10.1200/CCI.20.00134]

182 **Tsai HY**, Chang YL, Shen CT, Chung WS, Tsai HJ, Chen FM. Effects of the COVID-19 pandemic on breast cancer screening in Taiwan. *Breast* 2020; **54**: 52-55 [PMID: 32919172 DOI: 10.1016/j.breast.2020.08.014]

183 **Peng SM**, Yang KC, Chan WP, Wang YW, Lin LJ, Yen AM, Smith RA, Chen TH. Impact of the COVID-19 pandemic on a population-based breast cancer screening program. *Cancer* 2020; **126**:

5202-5205 [PMID: 32914864 DOI: 10.1002/cncr.33180]
184 **Lauby-Secretan B**, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group. Breast-cancer screening--viewpoint of the IARC Working Group. *N Engl J Med* 2015; **372**: 2353-2358 [PMID: 26039523 DOI: 10.1056/NEJMsr1504363]
185 **Maringe C**, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, Rachet B, Aggarwal A. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol* 2020; **21**: 1023-1034 [PMID: 32702310 DOI: 10.1016/S1470-2045(20)30388-0]
186 **Lang M**, Yeung T, Shepard JO, Sharma A, Petranovic M, Flores EJ, McLoud TC, Som A, Saini S, Prabhakar AM, D Succi M, Little BP. Operational Challenges of a Low-Dose CT Lung Cancer Screening Program During the Coronavirus Disease 2019 Pandemic. *Chest* 2021; **159**: 1288-1291 [PMID: 33121979 DOI: 10.1016/j.chest.2020.10.045]
187 **Toyoda H**, Huang DQ, Le MH, Nguyen MH. Liver Care and Surveillance: The Global Impact of the COVID-19 Pandemic. *Hepatol Commun* 2020 [PMID: 32838107 DOI: 10.1002/hep4.1579]
188 **Mehta N**, Parikh N, Kelley RK, Hameed B, Singal AG. Surveillance and Monitoring of Hepatocellular Carcinoma During the COVID-19 Pandemic. *Clin Gastroenterol Hepatol* 2020 [PMID: 32652308 DOI: 10.1016/j.cgh.2020.06.072]
189 **Mast C**, Munoz del Rio A. Delayed Cancer Screenings—A Second Look. [cited 25 January 2021]. In: Epic Health Research Network [Internet]. Available from: https://ehrn.org/articles/delayed-cancer-screenings-a-second-look/
190 **Moreno CC**, Yee J, Ahmed FS, Barish MA, Brewington C, Dachman AH, Gollub MJ, Kim DH, McFarland E, Pickhardt PJ, Reddy S, Zalis M, Chang KJ. CT colonography's role in the COVID-19 pandemic: a safe(r), socially distanced total colon examination. *Abdom Radiol (NY)* 2021; **46**: 486-490 [PMID: 32748251 DOI: 10.1007/s00261-020-02674-5]
191 **Luker GD**, Boettcher AN. Impact of COVID-19 on Clinical Care and Research in Cancer Imaging: Where We Are Now. *Radiol Imaging Cancer* 2021; **3**: e210003 [PMID: 33778764 DOI: 10.1148/rycan.2021210003]
192 **Selway WG**, Stenson KM, Holt PJ, Loftus IM. Willingness of patients to attend abdominal aortic aneurysm surveillance: The implications of COVID-19 on restarting the National Abdominal Aortic Aneurysm Screening Programme. *Br J Surg* 2020; **107**: e646-e647 [PMID: 32990339]
193 **Tan KK**, Lau J. Cessation of cancer screening: An unseen cost of the COVID-19 pandemic? *Eur J Surg Oncol* 2020; **46**: 2154-2155 [PMID: 32409112 DOI: 10.1016/j.ejso.2020.05.004]
194 **Our World In Data**. Coronavirus (COVID-19) Vaccinations. June 3, 2021. [cited 4 June 2021]. In: Our World In Data [Internet]. Available from: https://ourworldindata.org/covid-vaccinations
195 **Tu W**, Gierada DS, Joe BN. COVID-19 Vaccination-Related Lymphadenopathy: What To Be Aware Of. *Radiol Imaging Cancer* 2021; **3**: e210038 [PMID: 33874733 DOI: 10.1148/rycan.2021210038]
196 **Eifer M**, Eshet Y. Imaging of COVID-19 Vaccination at FDG PET/CT. *Radiology* 2021; **299**: E248 [PMID: 33507123 DOI: 10.1148/radiol.2020210030]
197 **Özütemiz C**, Krystosek LA, Church AL, Chauhan A, Ellermann JM, Domingo-Musibay E, Steinberger D. Lymphadenopathy in COVID-19 Vaccine Recipients: Diagnostic Dilemma in Oncology Patients. *Radiology* 2021; 210275 [PMID: 33625300 DOI: 10.1148/radiol.2021210275]
198 **Becker AS**, Perez-Johnston R, Chikarmane SA, Chen MM, El Homsi M, Feigin KN, Gallagher KM, Hanna EY, Hicks M, Ilica AT, Mayer EL, Shinagare AB, Yeh R, Mayerhoefer ME, Hricak H, Vargas HA. Multidisciplinary Recommendations Regarding Post-Vaccine Adenopathy and Radiologic Imaging: *Radiology* Scientific Expert Panel. *Radiology* 2021; 210436 [PMID: 33625298 DOI: 10.1148/radiol.2021210436]
199 **Lehman CD**, D'Alessandro HA, Mendoza DP, Succi MD, Kambadakone A, Lamb LR. Unilateral Lymphadenopathy After COVID-19 Vaccination: A Practical Management Plan for Radiologists Across Specialties. *J Am Coll Radiol* 2021; **18**: 843-852 [PMID: 33713605 DOI: 10.1016/j.jacr.2021.03.001]
200 **Grimm L**, Destounis S, Dogan B, Nicholson B, Dontchos B, Sonnenblick E, Milch H, Pushkin J, Benson J, Dodelzon K, Modi N, Yang R, Dialani V, Perera V. SBI Recommendations for the Management of Axillary Adenopathy in Patients with Recent COVID-19 Vaccination. [cited 25 March 2021]. In: Society of Breast Imaging [Internet]. Available from: https://www.sbi-online.org/Portals/0/Position%20Statements/2021/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination.pdf
201 **Lehman CD**, Lamb LR, D'Alessandro HA. Mitigating the Impact of Coronavirus Disease (COVID-19) Vaccinations on Patients Undergoing Breast Imaging Examinations: A Pragmatic Approach. *AJR Am J Roentgenol* 2021 [PMID: 33617288 DOI: 10.2214/AJR.21.25688]
202 **Zhang R**, Tie X, Qi Z, Bevins NB, Zhang C, Griner D, Song TK, Nadig JD, Schiebler ML, Garrett JW, Li K, Reeder SB, Chen GH. Diagnosis of Coronavirus Disease 2019 Pneumonia by Using Chest Radiography: Value of Artificial Intelligence. *Radiology* 2021; **298**: E88-E97 [PMID: 32969761 DOI: 10.1148/radiol.2020202944]
203 **Wehbe RM**, Sheng J, Dutta S, Chai S, Dravid A, Barutcu S, Wu Y, Cantrell DR, Xiao N, Allen BD, MacNealy GA, Savas H, Agrawal R, Parekh N, Katsaggelos AK. DeepCOVID-XR: An Artificial Intelligence Algorithm to Detect COVID-19 on Chest Radiographs Trained and Tested on a Large U.S. Clinical Data Set. *Radiology* 2021; **299**: E167-E176 [PMID: 33231531 DOI:

10.1148/radiol.2020203511]
204 **Jaiswal A**, Gianchandani N, Singh D, Kumar V, Kaur M. Classification of the COVID-19 infected patients using DenseNet201 based deep transfer learning. *J Biomol Struct Dyn* 2020; 1-8 [PMID: 32619398 DOI: 10.1080/07391102.2020.1788642]
205 **Wang Y**, Chen Y, Wei Y, Li M, Zhang Y, Zhang N, Zhao S, Zeng H, Deng W, Huang Z, Ye Z, Wan S, Song B. Quantitative analysis of chest CT imaging findings with the risk of ARDS in COVID-19 patients: a preliminary study. *Ann Transl Med* 2020; **8**: 594 [PMID: 32566621 DOI: 10.21037/atm-20-3554]
206 **Li L**, Qin L, Xu Z, Yin Y, Wang X, Kong B, Bai J, Lu Y, Fang Z, Song Q, Cao K, Liu D, Wang G, Xu Q, Fang X, Zhang S, Xia J. Using Artificial Intelligence to Detect COVID-19 and Community-acquired Pneumonia Based on Pulmonary CT: Evaluation of the Diagnostic Accuracy. *Radiology* 2020; **296**: E65-E71 [PMID: 32191588 DOI: 10.1148/radiol.2020200905]
207 **Bai HX**, Wang R, Xiong Z, Hsieh B, Chang K, Halsey K, Tran TML, Choi JW, Wang DC, Shi LB, Mei J, Jiang XL, Pan I, Zeng QH, Hu PF, Li YH, Fu FX, Huang RY, Sebro R, Yu QZ, Atalay MK, Liao WH. Artificial Intelligence Augmentation of Radiologist Performance in Distinguishing COVID-19 from Pneumonia of Other Origin at Chest CT. *Radiology* 2020; **296**: E156-E165 [PMID: 32339081 DOI: 10.1148/radiol.2020201491]
208 **Apostolopoulos ID**, Aznaouridis SI, Tzani MA. Extracting Possibly Representative COVID-19 Biomarkers from X-ray Images with Deep Learning Approach and Image Data Related to Pulmonary Diseases. *J Med Biol Eng* 2020; 1-8 [PMID: 32412551 DOI: 10.1007/s40846-020-00529-4]
209 **Chassagnon G**, Vakalopoulou M, Battistella E, Christodoulidis S, Hoang-Thi TN, Dangeard S, Deutsch E, Andre F, Guillo E, Halm N, El Hajj S, Bompard F, Neveu S, Hani C, Saab I, Campredon A, Koulakian H, Bennani S, Freche G, Barat M, Lombard A, Fournier L, Monnier H, Grand T, Gregory J, Nguyen Y, Khalil A, Mahdjoub E, Brillet PY, Tran Ba S, Bousson V, Mekki A, Carlier RY, Revel MP, Paragios N. AI-driven quantification, staging and outcome prediction of COVID-19 pneumonia. *Med Image Anal* 2021; **67**: 101860 [PMID: 33171345 DOI: 10.1016/j.media.2020.101860]
210 **Homayounieh F**, Babaei R, Karimi Mobin H, Arru CD, Sharifian M, Mohseni I, Zhang E, Digumarthy SR, Kalra MK. Computed Tomography Radiomics Can Predict Disease Severity and Outcome in Coronavirus Disease 2019 Pneumonia. *J Comput Assist Tomogr* 2020; **44**: 640-646 [PMID: 32842058 DOI: 10.1097/RCT.0000000000001094]
211 **The Cancer Imaging Archive**. Medical Imaging Data Resource Center - RSNA International COVID Radiology Database Release 1a - Chest CT Covid+ (MIDRC-RICORD-1a). [cited 6 February 2021]. In: The Cancer Imaging Archive [Internet]. Available from: https://wiki.cancerimagingarchive.net/pages/viewpage.action?pageId=80969742
212 **Greenspan H**, San José Estépar R, Niessen WJ, Siegel E, Nielsen M. Position paper on COVID-19 imaging and AI: From the clinical needs and technological challenges to initial AI solutions at the lab and national level towards a new era for AI in healthcare. *Med Image Anal* 2020; **66**: 101800 [PMID: 32890777 DOI: 10.1016/j.media.2020.101800]
213 **Pesapane F**, Volonté C, Codari M, Sardanelli F. Artificial intelligence as a medical device in radiology: ethical and regulatory issues in Europe and the United States. *Insights Imaging* 2018; **9**: 745-753 [PMID: 30112675 DOI: 10.1007/s13244-018-0645-y]
214 **Naudé W**. Artificial intelligence *vs* COVID-19: limitations, constraints and pitfalls. *AI Soc* 2020; 1-5 [PMID: 32346223 DOI: 10.1007/s00146-020-00978-0]
215 **Jaremko JL**, Azar M, Bromwich R, Lum A, Alicia Cheong LH, Gibert M, Laviolette F, Gray B, Reinhold C, Cicero M, Chong J, Shaw J, Rybicki FJ, Hurrell C, Lee E, Tang A; Canadian Association of Radiologists (CAR) Artificial Intelligence Working Group. Canadian Association of Radiologists White Paper on Ethical and Legal Issues Related to Artificial Intelligence in Radiology. *Can Assoc Radiol J* 2019; **70**: 107-118 [PMID: 30962048 DOI: 10.1016/j.carj.2019.03.001]
216 **Chen J**, See KC. Artificial Intelligence for COVID-19: Rapid Review. *J Med Internet Res* 2020; **22**: e21476 [PMID: 32946413 DOI: 10.2196/21476]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 July 28; 13(7): 223-242

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 7 July 28, 2021

World Journal of Radiology

Monthly Volume 13 Number 7 July 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Ioannis A Tsalafoutas, PhD, Medical Physicist, Medical Physics Section, OHS department, Hamad Medical Corporation, Doha 3050, Qatar. itsalafoutas@hamad.qa

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJR* as 0.51.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
July 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 July 28; 13(7): 223-226

DOI: 10.4329/wjr.v13.i7.223

ISSN 1949-8470 (online)

EDITORIAL

Imaging in multiple myeloma: Computed tomography or magnetic resonance imaging?

Alberto Stefano Tagliafico

ORCID number: Alberto Stefano Tagliafico 0000-0003-1736-0697.

Author contributions: Tagliafico AS wrote this editorial.

Conflict-of-interest statement: Dr. Tagliafico has no conflicts of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Alberto Stefano Tagliafico, Department of Health Sciences (DISSAL), University of Genova, Genova 16138, Italy

Corresponding author: Alberto Stefano Tagliafico, MD, Associate Professor, Staff Physician, Department of Health Sciences (DISSAL), University of Genova, Via Balbi, 5, Genova 16138, Italy. alberto.tagliafico@unige.it

Abstract

Multiple myeloma (MM) is the second most common type of hematological disease with its incidence rising in the elderly. In MM, the extent of the bone disease increases both morbidity and mortality. The detection of lytic bone lesions on imaging, especially computerized tomography (CT) and magnetic resonance imaging (MRI) is crucial to separate asymptomatic from symptomatic MM patients even when no clinical symptoms are present. Although radiology is essential in the staging and management of patients with MM there is still high variability in the choice between MRI and CT. In addition, there is still suboptimal agreement among readers. The potential of medical imaging in MM is largely under-evaluated: artificial intelligence, radiomics and new quantitative methods to report CT and MRI will improve imaging usage.

Key Words: Multiple myeloma; Imaging; Magnetic resonance imaging; Computed tomography; Quantitative imaging

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Introduction of new quantitative scores and biomarkers to predict multiple myeloma (MM) prognosis, possibly outperforming current staging methods to create new reliable standards for disease prediction and monitoring is an opportunity for further research in MM imaging.

Citation: Tagliafico AS. Imaging in multiple myeloma: Computed tomography or magnetic resonance imaging? *World J Radiol* 2021; 13(7): 223-226

URL: https://www.wjgnet.com/1949-8470/full/v13/i7/223.htm

DOI: https://dx.doi.org/10.4329/wjr.v13.i7.223

Grade C (Good): C, C, C
Grade D (Fair): D
Grade E (Poor): 0

Received: March 15, 2021
Peer-review started: March 15, 2021
First decision: April 6, 2021
Revised: April 10, 2021
Accepted: June 18, 2021
Article in press: June 18, 2021
Published online: July 28, 2021

P-Reviewer: Karavaş E, Xiao B
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Yuan YY

INTRODUCTION

Multiple myeloma belongs to the so-called plasma cell dyscrasias which are pathological conditions including monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and full-blown multiple myeloma (MM)[1]. Epidemiological studies show that, on the one hand, around 5% population over 70 is MGUS carriers and around 1% of them will turn into MM every year. On the other hand, around 10% SMM population evolves into full-blown MM[1]. Finally, the early MM mortality, *i.e.* the number of MM patients that dye within the first year after diagnosis, is nowadays around 28%, with a peak of 35% among older patients[1]. The single or, more frequently, multiple bone lesions are biologically determined by the proliferation of abnormal cells from a single clone and the excessive and unbalanced activation of osteoclasts eroding the bone starting from the medulla and then reaching the cortical bone and even the extra-osseous soft-tissues. However, MM has a heterogenous genetic architecture which is evident among different patients with the same disease. Genetic heterogenicity is evident also in the same patient where different focal bone lesions may have different genetic patterns[2-4]. MM patients are classically described and defined by the CRAB-criteria (Calcium elevation, Renal insufficiency, Anemia, Bone lesion), indeed symptoms of MM patients vary from bone pain or pathological fractures over renal failure and anemia to calcium elevation and even immune deficiency. It is not known why up to 20% of patients with SMM become symptomatic within 2 years, while one third does not progress to MM within a decade [5], therefore there are several unmet research questions that need to be addressed. In MM patients, having a single focal lesion > 5 mm in diameter identified by mean of computed tomography (CT) or magnetic resonance imaging (MRI) is currently used to identify high-risk SMM patients to upstage them to MM according to the International myeloma working group updated criteria for the diagnosis of multiple myeloma[6]. Therefore, detection of lytic bone lesions on imaging has been recognized crucial since 2003 when the international myeloma working group replaced the classical Durie-Salmon staging system with a more complex and complete revised version called Durie-Salmon plus system. This latter system replaced radiography for identifying bone involvement with the increased sensitivity of MRI, CT or Positron emission tomography (PET)[7]. Therefore, the detection of lytic bone lesions on imaging, especially CT and MRI, is becoming crucial from the clinical viewpoint to separate asymptomatic from symptomatic MM patients. According to Rajkumar *et al*[8] bone imaging in MM is relevant for diagnosis because osteolytic lesion detection justifies the beginning of a treatment. Medical imaging is required for several reasons: (1) Localization of bone pain; (2) Prevention of complications such as pathologic fractures on long bones (*i.e.* femur) and vertebral pathological fractures; (3) Identification of focal lesions with high risk of progression; (4) To identify sites of extra-medullary disease; and (5) Identification of sites at potential risk of neurologic complications (Figure 1). In spite of the pivotal role of medical imaging in MM patient care, there is still considerable heterogeneity in clinical practice regarding imaging usage in MM, essentially due to the high variability in the choice between various imaging methods and the high variability in image interpretation[9,10]. In this editorial, the unmet research questions in the usage of imaging in MM are reported and possible future directions are discussed.

POTENTIAL OF MEDICAL IMAGING IN MM

Firstly, it must be underlined that the detection of lytic bone lesions with a diameter > 5 mm can be done with both CT and MRI and no study directly compared the two modalities regarding patients' outcomes after CT or MRI. At least in theory, MRI could have some advantages, such as the possibility to introduce functional sequences such as diffusion weighted sequences, but, no clear advantage of one technique over another has been found, even when a systematic review approach was adopted[11, 12]. Regelink *et al*[12] found that there was only few additional lesions detected by both PET and MRI if CT was used as reference test (detection rate 1.00 and 1.00-1.25 respectively). In addition, the review by Regelink *et al*[12] review was limited by the suboptimal methodological quality of the involved studies due to lack of a technical details. It could be suggested that both MRI and CT have equal diagnostic value and there is no clear advantage to prefer one of the two techniques (Table 1). The scientific community is waiting for thorough comparative future studies, possibly focusing on prognostic value and follow-up. Furthermore, an analysis of multiple bone lesions

Table 1 Specific advantages and disadvantages or computed tomography and magnetic resonance imaging in multiple myeloma

	Availability	Reader expertise	Radiation dose	Repeatability among different readers	Repeatability among different scanners	Availability of reporting guidelines	Ability to detect > 5 mm focal lesions	Exam duration
CT	High	Medium	Similar to total body CT	High	Medium	Low	High	Less than 10 min
MRI	Medium	Low	None	Medium	Medium	Low	High	More than 30 min

CT: Computed tomography; MRI: Magnetic resonance imaging.

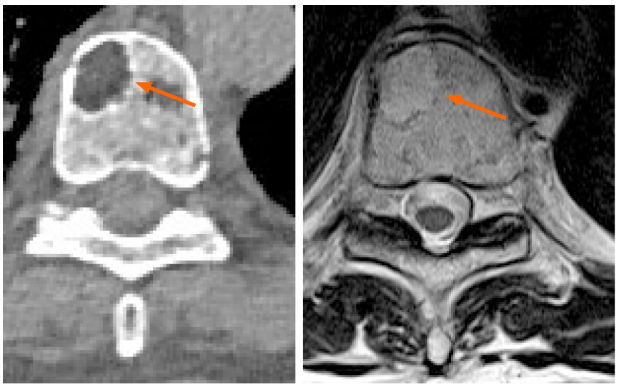


Figure 1 Computed tomography and magnetic resonance imaging of the same lytic lesion located into the vertebral body acquired in the same week for different reasons. No major differences in detection capabilities are evident.

detected on CT and MRI could be performed using artificial intelligence and radiomics [13]. Up-to-date, radiomics[14] is a quantitative radiological promising technique, with the ultimate goal to improve cancer treatment by improving prognostic capabilities of medical imaging. Radiomics is a complex, quantitative feature-based tool for image analysis described as the conversion of images to higher dimensional data and the subsequent mining of these data for improved decision support[14]. In MM, a recent application of radiomics improved the radiological evaluation of focal and diffuse pattern on CT by increasing the area under the curve of radiologists[15]. Accuracy of radiologists compared to the reference standard was lower (64%) than the accuracy using a radiomics approach (79%)[15]. In addition, machine learning-based classifiers resulted a satisfactory in differentiating MM lesions from those of tumor metastasis of the spine evaluated on MRI[16]. Radiomics was also on PET/CT in MM to elaborate a prognosis model predicting outcome in transplant-eligible newly diagnosed patients [17]. Finally, radiomics has been used with MRI to correlate features with the clinical and hematological response in multiple myeloma patients undergoing systemic treatment. In detail, one textural feature (GLSZM large area low gray level emphasis), in the study by Ekert *et al*[18] resulted to be correlated also with the bioptic degree of bone marrow infiltration.

CONCLUSION

Introduction of new quantitative scores and biomarkers to refine diagnosis, to predict MM prognosis, possibly outperforming current staging methods to create new reliable standards for disease prediction and monitoring is an opportunity for further research in MM imaging.

REFERENCES

1 **Jameson J**, Fauci A, Kasper D, Hauser S, Longo D. Harrison's Principles of Internal Medicine. 20th ed. McGraw Hill, 2018

2 **Rasche L**, Chavan SS, Stephens OW, Patel PH, Tytarenko R, Ashby C, Bauer M, Stein C, Deshpande S, Wardell C, Buzder T, Molnar G, Zangari M, van Rhee F, Thanendrarajan S, Schinke C, Epstein J, Davies FE, Walker BA, Meissner T, Barlogie B, Morgan GJ, Weinhold N. Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing. *Nat Commun* 2017; **8**: 268 [PMID: 28814763 DOI: 10.1038/s41467-017-00296-y]

3 **Neben K**, Jauch A, Hielscher T, Hillengass J, Lehners N, Seckinger A, Granzow M, Raab MS, Ho AD, Goldschmidt H, Hose D. Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load. *J Clin Oncol* 2013; **31**: 4325-4332 [PMID: 24145347 DOI: 10.1200/JCO.2012.48.4923]

4 **Fonseca R**, Bergsagel PL, Drach J, Shaughnessy J, Gutierrez N, Stewart AK, Morgan G, Van Ness B, Chesi M, Minvielle S, Neri A, Barlogie B, Kuehl WM, Liebisch P, Davies F, Chen-Kiang S, Durie BG, Carrasco R, Sezer O, Reiman T, Pilarski L, Avet-Loiseau H; International Myeloma Working Group. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia* 2009; **23**: 2210-2221 [PMID: 19798094 DOI: 10.1038/leu.2009.174]

5 **Kyle RA**, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, Larson DR, Plevak MF, Jelinek DF, Fonseca R, Melton LJ 3rd, Rajkumar SV. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007; **356**: 2582-2590 [PMID: 17582068 DOI: 10.1056/NEJMoa070389]

6 **Rajkumar SV**, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG, Miguel JF. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014; **15**: e538-548 [PMID: 25439696 DOI: 10.1016/S1470-2045(14)70442-5]

7 **Rajkumar SV**. Evolving diagnostic criteria for multiple myeloma. *Hematology Am Soc Hematol Educ Program* 2015; **2015**: 272-278 [PMID: 26637733 DOI: 10.1182/asheducation-2015.1.272]

8 **Hillengass J**. Evolving Concepts in the Diagnosis and Staging of Multiple Myeloma. *Natl Compr Cancer Netw* 2020; **18**: 1770-1772 [DOI: 10.6004/jnccn.2020.5041]

9 **Tagliafico AS**, Belgioia L, Bonsignore A, Rossi F, Succio G, Bignotti B, Dominietto A. Subspecialty Second-Opinion in Multiple Myeloma CT: Emphasis on Clinically Significant Lytic Lesions. *Medicina (Kaunas)* 2020; **56** [PMID: 32340143 DOI: 10.3390/medicina56040195]

10 **Tagliafico AS**, Dominietto A, Belgioia L, Campi C, Schenone D, Piana M. Quantitative Imaging and Radiomics in Multiple Myeloma: A Potential Opportunity? *Medicina (Kaunas)* 2021; **57** [PMID: 33494449 DOI: 10.3390/medicina57020094]

11 **Caers J**, Withofs N, Hillengass J, Simoni P, Zamagni E, Hustinx R, Beguin Y. The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. *Haematologica* 2014; **99**: 629-637 [PMID: 24688111 DOI: 10.3324/haematol.2013.091918]

12 **Regelink JC**, Minnema MC, Terpos E, Kamphuis MH, Raijmakers PG, Pieters-van den Bos IC, Heggelman BG, Nievelstein RJ, Otten RH, van Lammeren-Venema D, Zijlstra JM, Arens AI, de Rooy JW, Hoekstra OS, Raymakers R, Sonneveld P, Ostelo RW, Zweegman S. Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. *Br J Haematol* 2013; **162**: 50-61 [PMID: 23617231 DOI: 10.1111/bjh.12346]

13 **Fiz F**, Marini C, Campi C, Massone AM, Podestà M, Bottoni G, Piva R, Bongioanni F, Bacigalupo A, Piana M, Sambuceti G, Frassoni F. Allogeneic cell transplant expands bone marrow distribution by colonizing previously abandoned areas: an FDG PET/CT analysis. *Blood* 2015; **125**: 4095-4102 [PMID: 25957389 DOI: 10.1182/blood-2015-01-618215]

14 **Gillies RJ**, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. *Radiology* 2016; **278**: 563-577 [PMID: 26579733 DOI: 10.1148/radiol.2015151169]

15 **Tagliafico AS**, Cea M, Rossi F, Valdora F, Bignotti B, Succio G, Gualco S, Conte A, Dominietto A. Differentiating diffuse from focal pattern on Computed Tomography in multiple myeloma: Added value of a Radiomics approach. *Eur J Radiol* 2019; **121**: 108739 [PMID: 31733431 DOI: 10.1016/j.ejrad.2019.108739]

16 **Xiong X**, Wang J, Hu S, Dai Y, Zhang Y, Hu C. Differentiating Between Multiple Myeloma and Metastasis Subtypes of Lumbar Vertebra Lesions Using Machine Learning-Based Radiomics. *Front Oncol* 2021; **11**: 601699 [PMID: 33718148 DOI: 10.3389/fonc.2021.601699]

17 **Jamet B**, Morvan L, Nanni C, Michaud AV, Bailly C, Chauvie S, Moreau P, Touzeau C, Zamagni E, Bodet-Milin C, Kraeber-Bodéré F, Mateus D, Carlier T. Random survival forest to predict transplant-eligible newly diagnosed multiple myeloma outcome including FDG-PET radiomics: a combined analysis of two independent prospective European trials. *Eur J Nucl Med Mol Imaging* 2021; **48**: 1005-1015 [PMID: 33006656 DOI: 10.1007/s00259-020-05049-6]

18 **Ekert K**, Hinterleitner C, Baumgartner K, Fritz J, Horger M. Extended Texture Analysis of Non-Enhanced Whole-Body MRI Image Data for Response Assessment in Multiple Myeloma Patients Undergoing Systemic Therapy. *Cancers (Basel)* 2020; **12** [PMID: 32213834 DOI: 10.3390/cancers12030761]

World Journal of Radiology

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

World J Radiol 2021 July 28; 13(7): 227-232

DOI: 10.4329/wjr.v13.i7.227

ISSN 1949-8470 (online)

MINIREVIEWS

Abdominal imaging in COVID-19

Daniel Vasile Balaban, Oana Madalina Baston, Mariana Jinga

ORCID number: Daniel Vasile Balaban 0000-0003-3436-8041; Oana Madalina Baston 0000-0001-6233-1487; Mariana Jinga 0000-0001-5826-0815.

Author contributions: Balaban DV, Baston OM and Jinga M performed the literature search and drafted the manuscript; Jinga M critically reviewed the manuscript; all authors have read and approved the final manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Daniel Vasile Balaban, Mariana Jinga, Department of Internal Medicine and Gastroenterology, Carol Davila University of Medicine and Pharmacy; Dr. Carol Davila Central Military Emergency University Hospital, Bucharest 020021, Romania

Oana Madalina Baston, Department of Radiology, Medical Imaging and Interventional Radiology, Carol Davila University of Medicine and Pharmacy; Dr. Carol Davila Central Military Emergency University Hospital, Bucharest 020021, Romania

Corresponding author: Daniel Vasile Balaban, MD, PhD, Senior Lecturer, Department of Internal Medicine and Gastroenterology, Carol Davila University of Medicine and Pharmacy; Dr. Carol Davila Central Military Emergency University Hospital, 37 Dionisie Lupu, Bucharest 020021, Romania. vbalaban@yahoo.com

Abstract

Initially thought of as a respiratory infection, coronavirus disease-2019 (COVID-19) is now recognized as a complex disease with a wide clinical spectrum, including digestive involvement. While several studies have evaluated chest imaging findings in COVID-19, few papers have looked at the abdominal imaging features of these patients. Liver, biliary, pancreas and bowel involvement have been reported in COVID-19 infected patients. In this review, we aim to summarize currently available data related to abdominal imaging techniques in COVID-19, in accordance with relevant clinical and laboratory workup of these patients. Underlying mechanisms, indications and imaging findings related to COVID-19 are discussed based on published data. Also, practice points for clinicians are highlighted in order to adequately recognize digestive-related injuries of severe acute respiratory syndrome coronavirus 2 infection. While there's been a steady accumulation of data with respect to abdominal imaging findings in COVID-19, currently available recommendations are based on limited research. There is a wide spectrum of abdominal imaging findings in COVID-19, which includes hepato-biliary, pancreatic and luminal pathology.

Key Words: COVID-19; Gastrointestinal; Digestive; Features; Imaging; Ultrasound; Computed tomography

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Initially being thought of as a respiratory infection, coronavirus disease-2019

Country/Territory of origin: Romania

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

Received: February 7, 2021
Peer-review started: February 7, 2021
First decision: May 6, 2021
Revised: May 6, 2021
Accepted: June 23, 2021
Article in press: June 23, 2021
Published online: July 28, 2021

P-Reviewer: Cabezuelo AS, Cure E
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Li X

(COVID-19) is now widely recognized as a complex disease with systemic features. Gastrointestinal manifestations have been reported with high prevalence in severe acute respiratory syndrome coronavirus 2 infected patients, including gut, pancreas, liver and biliary dysfunction. In this review we summarize and analyze currently available evidence on abdominal imaging techniques, indications and findings in COVID-19, in accordance with relevant clinical and laboratory workup of these patients.

Citation: Balaban DV, Baston OM, Jinga M. Abdominal imaging in COVID-19. *World J Radiol* 2021; 13(7): 227-232
URL: https://www.wjgnet.com/1949-8470/full/v13/i7/227.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i7.227

INTRODUCTION

In late December 2019, a cluster of pneumonia cases of unknown origin was reported in Wuhan, Hubei province, China. The causative agent was identified as a novel coronavirus, linked to the severe acute respiratory syndrome (SARS). The virus was named SARS coronavirus 2 (SARS-CoV-2) and the related disease coronavirus disease-2019 (COVID-19). The novel coronavirus rapidly spread worldwide, and since March 11th 2020, the date on which COVID-19 was declared a pandemic[1], over 150 million cases and 3.2 million COVID-19 associated deaths have been reported[2].

Initially being thought of as a respiratory infection, COVID-19 is now recognized as a complex disease with a wide spectrum of presentations, from viral pneumonia and flu-like symptoms to acute hepatitis and Kawasaki-like disease[3,4]. The systemic nature of COVID-19 is related to the interaction of SARS-CoV-2 with the human body, mediated by angiotensin converting enzyme 2 (ACE2) expressed on cell surfaces[5]. ACE2 is most abundant in alveolar epithelium, but is also found in large amounts in enterocytes, vascular endothelium, liver and biliary epithelium[6]. Binding of SARS-CoV-2 at these susceptible extrapulmonary sites can generate symptoms directly related to the infected organ. Moreover, several reports have identified SARS-CoV-2 to be present in stool samples of infected patients[7-9], and there have been proposals to use anal swabs for SARS-CoV-2 detection and follow-up of infected individuals[10].

With regard to involvement of the gastrointestinal tract, several studies have shown high prevalence of digestive symptoms in COVID-19[7,11,12]. This was explained by the high density of ACE2 receptor (the cell entry point for SARS-CoV-2) in the small bowel and pancreas, but also as a side effect of COVID-19 related therapy and secondary to systemic inflammation and ischemia[13]. Not least, laboratory changes reflecting on gut or hepato-bilio-pancreatic pathology have been reported in COVID-19. In this setting, abdominal imaging has been used to define the cause of symptoms and laboratory abnormalities in these patients.

While an abundance of papers has described chest imaging findings in COVID-19, few articles have focused on abdominal imaging features of these patients. In this review we aim to summarize and analyze current evidence on abdominal imaging techniques, indications and findings in COVID-19, in accordance with relevant clinical and laboratory workup of these patients.

ABDOMINAL IMAGING

Abdominal imaging reported in COVID-19 patients include abdominal ultrasound and cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). A literature search on the topic also revealed isolated reports of plain abdominal X-ray, endoscopy or positron emission tomography CT (PET-CT) findings in COVID-19 patients.

Ultrasound

Abdominal ultrasound is being routinely used in patients with abdominal complaints. With regard to COVID-19, ultrasound (US) has been mostly indicated to evaluate for

abdominal pain and abnormal liver function tests. While sometimes the abdominal pain does not reflect digestive pathology and is probably referred pain as the one seen in basilar pneumonias, the prevalence of transaminitis in COVID-19 has been estimated at 15%[14]. Sonographic examination has been also ordered for abdominal distention, suspected sepsis, increase in renal function tests or drop in hemoglobin [15]. Abdominal sonographic scanning also includes evaluation of hydration status by assessment of the inferior vena cava, presence of ascites (also pericardial or pleural effusions) or hydronephrosis[16].

In the study by Abdelmohsen *et al*[15] which aimed to characterize the sonographic abdominal imaging findings in COVID-19 intensive care patients, the most frequent sonographic finding was hepatomegaly (56.09%), followed by biliary system disease (41.4%) consisting of gallbladder wall thickening, mural hyperemia, intraluminal mud and pericholecystic fluid. Results are similar to those reported by Bhayana *et al*[17], with gallbladder sludge and distention being seen in 54% of right upper quadrant ultrasound studies. In this latter study, US also detected portal venous gas in one patient, which was confirmed by CT scan. US can also be used for guiding drainage procedures, as reported in cases of COVID-19-related acute cholecystitis[18].

A rather high prevalence of fatty liver has been reported in COVID-19 patients who underwent US examination, likely attributable to the established association between SARS-CoV-2 infection and obesity[17,19].

Taking into account the altered coagulation in COVID-19 and the potential thrombotic complications, US can be of value in evaluating the abdominal vasculature. Doppler US can be used to assess for venous or arterial thrombosis. Decreased vascularity at Doppler examination can indicate infarction and needs further studies. Contrast-enhanced US has been reported to adequately detect abdominal microcirculatory disorders by assessing mesenteric blood flow, liver and kidney perfusion[20].

A concern regarding US in COVID-19 patients was related to sonographer exposure while performing the examination. In order to minimize the scanning time, there have been proposals to capture cine clips and proceed with postprocessing of images after the examination[21].

CT

Several papers have looked at abdominal CT findings in COVID-19. Most frequent features seen on abdominal CT in COVID-19 patients were bowel wall thickening, fluid-filled colon, pneumatosis, pneumoperitoneum, intussusception, and ascites[22]. Abdominal findings in COVID-19 are detected either by ordering an abdominal scan in a SARS-CoV-2 positive patient, or by incidentally detecting ground-glass opacities in lung bases during an abdominal scan ordered for non-COVID related reasons.

CT scan has been usually indicated for prominent, otherwise unexplained digestive pain or for suspected complications such as mesenteric thrombosis or bowel ischemia [12,17]. Also, elevations in serum amylase and lipase have been reported in COVID-19; while the increased values of pancreatic enzymes did not usually reflect pancreatitis, there are reports of COVID-19 associated acute pancreatitis documented by CT[23-29]. Others, however, have considered inappropriate to define a causal relationship between SARS-CoV-2 and acute pancreatitis, due to insufficient etiological workup [30].

MRI

MRI has been rarely reported in COVID-19 patients, significantly less than US and CT [17]. In a study by Shiralkar *et al*[31], MRI was indicated for liver dysfunction; no acute findings were seen. A potential limitation of abdominal MRI studies in COVID-19 is the prolonged examination time in patients suffering from respiratory failure. Although MRI is an excellent modality for the evaluation of biliary disease, findings are usually non-specific as cholestasis is related to the high expression of ACE2 receptor in cholangiocytes.

DISCUSSIONS

In front of this novel threat for humanity, knowledge is continuously evolving with unprecedented efforts from the academic community. Despite good evidence on gastrointestinal involvement in COVID-19, related to the abundant expression of ACE2 receptors in the gut and biliary endothelium, there is a paucity of data regarding the imaging approach of digestive-related symptoms or laboratory test abnormalities of these patients. Moreover, currently available data on abdominal imaging in COVID-

Table 1 Summary of proposed mechanisms and abdominal imaging techniques recommended for gastrointestinal involvement in coronavirus disease-2019[13,34,35]

	Proposed mechanism	Abdominal imaging
Hepato-biliary	Direct viral cytopathic injury; Congestive hepatopathy; Drug-induced liver injury; Systemic inflammatory response; Exacerbation of preexistent chronic liver disease	Ultrasound to check gallbladder and biliary tree; CT/MRI to asses for perfusion injury and complications
Pancreas	Direct viral cytopathic injury; Systemic inflammation; Dehydration	CT scan to assess severity and complications of pancreatitis, and evaluate for alternative diagnosis; Ultrasound to check for biliary etiology or alternative diagnosis, also for diagnosis and follow-up of complications in pancreatitis
Gastrointestinal tract	Direct viral cytopathic injury; Systemic inflammation; Thrombosis; Adverse effects of COVID-19-related drugs	CT scan to assess for clinically similar alternative diagnosis, to detect extension and severity of bowel inflammation and to check the vascular patency

COVID-19: Coronavirus disease-2019; CT: Computed tomography; MRI: Magnetic resonance imaging.

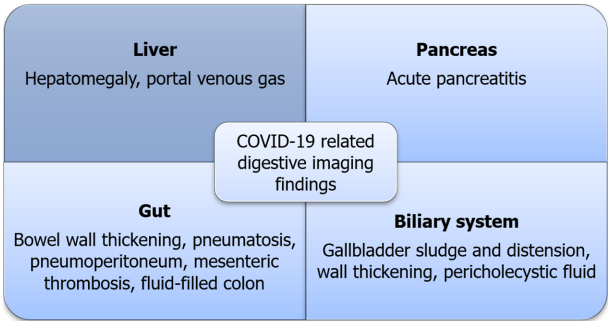


Figure 1 Summary of coronavirus disease-2019 related abdominal imaging findings.

19 is retrospective in nature and limited by significant heterogeneity with respect to indications, protocol and follow-up of pathological findings.

Most frequent indications for US examination in SARS-CoV-2 positive patients were upper abdominal pain and altered liver function tests. COVID-19-related liver injury is usually mild and transient, but liver failure can occur in the setting of sepsis or coagulopathy with microthrombosis[21]. While Doppler examination might be limited in detecting small vessel thrombosis, assessment of mesenteric and liver vasculature patency is well done by contrast-enhanced CT scan or gadolinium-enhanced MRI. Usually, abdominal CT scan is indicated in cases of suspected bowel ischemia/perforation, solid organ infarction (spleen, kidney), sepsis or cholestasis-related complications[21]. Segmental or diffuse thickening of the gut wall, along with distended intestinal lumen is a frequent finding in COVID-19 and can present as gastritis, enteritis, colitis or combination of these[21]. Bowel findings in COVID-19 are supposed to be caused be either direct viral infection of gut epithelium or by small-vessel thrombosis with consecutive ischemia[17].

Along with ischemic complications, CT scan can also depict hemorrhagic complications such as hematomas or hemorrhagic transformation of bowel ischemia[21]. Besides its diagnostic role, abdominal imaging has also demonstrated prognostic value upon detection of ischemic gastrointestinal complications in COVID-19, which has been shown to be associated with higher mortality[32,33]. The most frequent findings on abdominal imaging in COVID-19 are summarized in Figure 1.

Not least, cross-sectional abdominal imaging performed in symptomatic individuals not suspected of having COVID-19 can alert clinicians of the possibility of SARS-CoV-2 infection by detection of ground-glass opacities on sections of the upper abdomen which are also capturing the lung bases. Thus, a CT scan ordered for a non-pulmonary indication can incidentally detect COVID-19 patients, before occurrence of respiratory manifestations.

To sum up, abdominal ultrasound and cross-sectional imaging techniques such as CT scan can accurately assess for gastrointestinal involvement in SARS-CoV-2 infected patients, particularly in a clinically significant setting; knowledge of the underlying mechanisms of hepatobiliary, pancreatic and gut alterations in COVID-19 and a high

index of suspicion is mandatory for prompt detection of digestive-related injuries of SARS-CoV-2 infection (Table 1). Further studies looking at abdominal microvasculature and follow-up of patients with abdominal features related to COVID-19 are warranted to better depict the imaging features of this infection.

CONCLUSION

While there's been a steady accumulation of data with respect to abdominal imaging findings in COVID-19, currently available recommendations are based on limited research. There is a wide spectrum of abdominal imaging findings in COVID-19, which includes hepato-biliary, pancreatic and luminal pathology. Underlying mechanisms behind the wide spectrum of digestive involvement in COVID-19 include direct viral infection, small-vessel thrombosis and systemic inflammation. Prompt recognition of abdominal imaging findings in COVID-19 is mandatory to adequately guide management and improve prognosis of these patients. Also, abdominal imaging in patients with primarily digestive symptoms not initially suspected of COVID-19 can alert clinicians about the possibility of SARS-CoV-2 infection if typical lesions are found on evaluation of lung bases.

REFERENCES

1 **World Health Organization**. WHO Director-General's opening remarks at the media briefing on COVID-19. [cited 6 Nov 2020]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

2 **Dong E**, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20**: 533-534 [PMID: 32087114 DOI: 10.1016/S1473-3099(20)30120-1]

3 **Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]

4 **Consiglio CR**, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, Tan Z, Zicari S, Ruggiero A, Pascucci GR, Santilli V, Campbell T, Bryceson Y, Eriksson D, Wang J, Marchesi A, Lakshmikanth T, Campana A, Villani A, Rossi P; CACTUS Study Team, Landegren N, Palma P, Brodin P. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell* 2020; **183**: 968-981.e7 [PMID: 32966765 DOI: 10.1016/j.cell.2020.09.016]

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

6 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

7 **Han C**, Duan C, Zhang S, Spiegel B, Shi H, Wang W, Zhang L, Lin R, Liu J, Ding Z, Hou X. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. *Am J Gastroenterol* 2020; **115**: 916-923 [PMID: 32301761 DOI: 10.14309/ajg.0000000000000664]

8 **Wang W**, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020; **323**: 1843-1844 [PMID: 32159775 DOI: 10.1001/jama.2020.3786]

9 **Wu Y**, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**: 434-435 [PMID: 32199469 DOI: 10.1016/S2468-1253(20)30083-2]

10 **Sun M**, Guo D, Zhang J, Teng HF, Xia J, Liu P, Ge QX, Wang MY. Anal swab as a potentially optimal specimen for SARS-CoV-2 detection to evaluate hospital discharge of COVID-19 patients. *Future Microbiol* 2020; **15**: 1101-1107 [PMID: 32795131 DOI: 10.2217/fmb-2020-0090]

11 **Tariq R**, Saha S, Furqan F, Hassett L, Pardi D, Khanna S. Prevalence and Mortality of COVID-19 Patients With Gastrointestinal Symptoms: A Systematic Review and Meta-analysis. *Mayo Clin Proc* 2020; **95**: 1632-1648 [PMID: 32753138 DOI: 10.1016/j.mayocp.2020.06.003]

12 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]

13 **Pasha SB**, Swi A, Hammoud GM. Gastrointestinal and hepatic manifestations of COVID-19 infection: Lessons for practitioners. *World J Meta-Anal* 2020; **8**: 348-374

14 **Sultan S**, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, Falck-Ytter Y, El-Serag HB;

AGA Institute. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. *Gastroenterology* 2020; **159**: 320-334.e27 [PMID: 32407808 DOI: 10.1053/j.gastro.2020.05.001]

15 **Abdelmohsen MA**, Alkandari BM, Gupta VK, ElBeheiry AA. Diagnostic value of abdominal sonography in confirmed COVID-19 intensive care patients. *Egypt J Radiol Nucl Med* 2020; **51**: 198 [DOI: 10.1186/s43055-020-00317-9]

16 **Cheung S**, Quiwa JC, Pillai A, Onwu C, Tharayil ZJ, Gupta R. Superior Mesenteric Artery Thrombosis and Acute Intestinal Ischemia as a Consequence of COVID-19 Infection. *Am J Case Rep* 2020; **21**: e925753 [PMID: 32724028 DOI: 10.12659/AJCR.925753]

17 **Bhayana R**, Som A, Li MD, Carey DE, Anderson MA, Blake MA, Catalano O, Gee MS, Hahn PF, Harisinghani M, Kilcoyne A, Lee SI, Mojtahed A, Pandharipande PV, Pierce TT, Rosman DA, Saini S, Samir AE, Simeone JF, Gervais DA, Velmahos G, Misdraji J, Kambadakone A. Abdominal Imaging Findings in COVID-19: Preliminary Observations. *Radiology* 2020; **297**: E207-E215 [PMID: 32391742 DOI: 10.1148/radiol.2020201908]

18 **Ying M**, Lu B, Pan J, Lu G, Zhou S, Wang D, Li L, Shen J, Shu J; From the COVID-19 Investigating and Research Team. COVID-19 with acute cholecystitis: a case report. *BMC Infect Dis* 2020; **20**: 437 [PMID: 32571224 DOI: 10.1186/s12879-020-05164-7]

19 **Medeiros AK**, Barbisan CC, Cruz IR, de Araújo EM, Libânio BB, Albuquerque KS, Torres US. Higher frequency of hepatic steatosis at CT among COVID-19-positive patients. *Abdom Radiol (NY)* 2020; **45**: 2748-2754 [PMID: 32683613 DOI: 10.1007/s00261-020-02648-7]

20 **Jung EM**, Stroszczynski C, Jung F. Contrast enhanced ultrasonography (CEUS) to detect abdominal microcirculatory disorders in severe cases of COVID-19 infection: First experience. *Clin Hemorheol Microcirc* 2020; **74**: 353-361 [PMID: 32333581 DOI: 10.3233/CH-209003]

21 **Revzin MV**, Raza S, Srivastava NC, Warshawsky R, D'Agostino C, Malhotra A, Bader AS, Patel RD, Chen K, Kyriakakos C, Pellerito JS. Multisystem Imaging Manifestations of COVID-19, Part 2: From Cardiac Complications to Pediatric Manifestations. *Radiographics* 2020; **40**: 1866-1892 [PMID: 33136488 DOI: 10.1148/rg.2020200195]

22 **Lui K**, Wilson MP, Low G. Abdominal imaging findings in patients with SARS-CoV-2 infection: a scoping review. *Abdom Radiol (NY)* 2021; **46**: 1249-1255 [PMID: 32926211 DOI: 10.1007/s00261-020-02739-5]

23 **de-Madaria E**, Siau K, Cárdenas-Jaén K. Increased Amylase and Lipase in Patients With COVID-19 Pneumonia: Don't Blame the Pancreas Just Yet! *Gastroenterology* 2021; **160**: 1871 [PMID: 32330475 DOI: 10.1053/j.gastro.2020.04.044]

24 **de-Madaria E**, Capurso G. COVID-19 and acute pancreatitis: examining the causality. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 3-4 [PMID: 33203968 DOI: 10.1038/s41575-020-00389-y]

25 **Aloysius MM**, Thatti A, Gupta A, Sharma N, Bansal P, Goyal H. COVID-19 presenting as acute pancreatitis. *Pancreatology* 2020; **20**: 1026-1027 [PMID: 32444169 DOI: 10.1016/j.pan.2020.05.003]

26 **McNabb-Baltar J**, Jin DX, Grover AS, Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Shen L, Chan WW. Lipase Elevation in Patients With COVID-19. *Am J Gastroenterol* 2020; **115**: 1286-1288 [PMID: 32496339 DOI: 10.14309/ajg.0000000000000732]

27 **Szatmary P**, Arora A, Thomas Raraty MG, Joseph Dunne DF, Baron RD, Halloran CM. Emerging Phenotype of Severe Acute Respiratory Syndrome-Coronavirus 2-associated Pancreatitis. *Gastroenterology* 2020; **159**: 1551-1554 [PMID: 32497545 DOI: 10.1053/j.gastro.2020.05.069]

28 **Hadi A**, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, Gluud LL. Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family members. *Pancreatology* 2020; **20**: 665-667 [PMID: 32387082 DOI: 10.1016/j.pan.2020.04.021]

29 **Pinte L**, Baicus C. Pancreatic involvement in SARS-CoV-2: case report and living review. *J Gastrointestin Liver Dis* 2020; **29**: 275-276 [PMID: 32531002 DOI: 10.15403/jgld-2618]

30 **Juhász MF**, Ocskay K, Kiss S, Hegyi P, Párniczky A. Insufficient etiological workup of COVID-19-associated acute pancreatitis: A systematic review. *World J Gastroenterol* 2020; **26**: 6270-6278 [PMID: 3317779 DOI: 10.3748/wjg.v26.i40.6270]

31 **Shiralkar K**, Chinapuvvula N, Ocazionez D. Cross-Sectional Abdominal Imaging Findings in Patients With COVID-19. *Cureus* 2020; **12**: e9538 [PMID: 32905406 DOI: 10.7759/cureus.9538]

32 **Keshavarz P**, Rafiee F, Kavandi H, Goudarzi S, Heidari F, Gholamrezanezhad A. Ischemic gastrointestinal complications of COVID-19: a systematic review on imaging presentation. *Clin Imaging* 2021; **73**: 86-95 [PMID: 33341452 DOI: 10.1016/j.clinimag.2020.11.054]

33 **Horvat N**, Pinto PVA, Araujo-Filho JAB, Santos JMMM, Dias AB, Miranda JA, de Oliveira CV, Barbosa CS, Morais TC, N Assuncao-Jr A, Nomura CH, Viana PCC. Abdominal gastrointestinal imaging findings on computed tomography in patients with COVID-19 and correlation with clinical outcomes. *Eur J Radiol Open* 2021; **8**: 100326 [PMID: 33495735 DOI: 10.1016/j.ejro.2021.100326]

34 **Bruno G**, Fabrizio C, Santoro CR, Buccoliero GB. Pancreatic injury in the course of coronavirus disease 2019: A not-so-rare occurrence. *J Med Virol* 2021; **93**: 74-75 [PMID: 32497298 DOI: 10.1002/jmv.26134]

35 **Schaefer EAK**, Arvind A, Bloom PP, Chung RT. Interrelationship Between Coronavirus Infection and Liver Disease. *Clin Liver Dis (Hoboken)* 2020; **15**: 175-180 [PMID: 32489653 DOI: 10.1002/cld.967]

World Journal of Radiology

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

World J Radiol 2021 July 28; 13(7): 233-242

DOI: 10.4329/wjr.v13.i7.233

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Retrospective Study

"Pulmonary target sign" as a diagnostic feature in chest computed tomography of COVID-19

Ramezan Jafari, Nematollah Jonaidi-Jafari, Houshyar Maghsoudi, Fatemeh Dehghanpoor, U Joseph Schoepf, Kyle A Ulversoy, Amin Saburi

ORCID number: Ramezan Jafari 0000-0003-1099-4259; Nematollah Jonaidi-Jafari 0000-0002-6006-7771; Houshyar Maghsoudi 0000-0003-1099-4250; Fatemeh Dehghanpoor 0000-0003-1450-8748; U Joseph Schoepf 0000-0002-6164-5641; Kyle A Ulversoy 0000-0002-0757-4336; Amin Saburi 0000-0001-7743-8244.

Author contributions: Jafari R, Jonaidi-Jafari N and Saburi A deigned the study; Jafari R, Jonaidi-Jafari N, Maghsoudi H, Dehghanpoor F collected the data; Jafari R, Jonaidi-Jafari N, Schoepf UJ, Ulversoy KA, Saburi A interpreted the data; Schoepf UJ, Ulversoy KA and Saburi A prepared the initial draft; Saburi A, Ulversoy KA and Schoepf UJ edited the final draft; all authors proved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Baqiyatallah University of Medical sciences, Tehran, Iran.

Conflict-of-interest statement: Schoepf UJ receives institutional research support and / or personal fees for consulting and speaking from Bayer, Bracco, ElucidBioImagingGuerbet, Heart Flow, Inc., Keya Medical, and

Ramezan Jafari, Houshyar Maghsoudi, Fatemeh Dehghanpoor, Department of Radiology, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran 11151877, Iran

Ramezan Jafari, Nematollah Jonaidi-Jafari, Amin Saburi, Health Research Center, Baqiyatallah University of Medical Sciences, Tehran 11151877, Iran

U Joseph Schoepf, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC 29425, United States

Kyle A Ulversoy, Faculty of Medicine, Augusta University/University of Georgia Medical Partnership, Athens, GA 30606, United States

Amin Saburi, Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran 11151877, Iran

Corresponding author: Amin Saburi, MD, Doctor, Senior Researcher, Health Research Center, Baqiyatallah University of Medical Sciences, Mollasadra St, Vanak Sq, Tehran 11151877, Iran. aminsaburi@yahoo.com

Abstract

BACKGROUND

In chest computed tomography (CT) scan, bilateral peripheral multifocal ground-glass opacities, linear opacities, reversed halo sign, and crazy-paving pattern are suggestive for coronavirus disease 2019 (COVID-19) in clinically suspicious cases, but they are not specific for the diagnosis, as other viral pneumonias, like influenza and some viral pneumonia may show similar imaging findings.

AIM

To find a specific imaging feature of the disease would be a welcome guide in diagnosis and management of challenging cases.

METHODS

Chest CT imaging findings of 650 patients admitted to a university Hospital in Tehran, Iran between January 2020 and July 2020 with confirmed COVID-19 infection by RT-PCR were reviewed by two expert radiologists. In addition to common non-specific imaging findings of COVID-19 pneumonia, radiologic characteristics of "pulmonary target sign" (PTS) were assessed. PTS is defined as a

Siemens Healthineers. Other authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Iran

Peer-review report's scientific quality classification

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

Received: January 29, 2021
Peer-review started: January 29, 2021
First decision: March 17, 2021
Revised: March 30, 2021
Accepted: June 15, 2021
Article in press: June 15, 2021
Published online: July 28, 2021

P-Reviewer: Chen X
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Yuan YY

circular appearance of non-involved pulmonary parenchyma, which encompass a central hyperdense dot surrounded by ground-glass or alveolar opacities.

RESULTS

PTS were presented in 32 cases (frequency 4.9%). The location of the lesions in 31 of the 32 cases (96.8%) was peripheral, while 4 of the 31 cases had lesions both peripherally and centrally. In 25 cases, the lesions were located near the pleural surface and considered pleural based and half of the lesions (at least one lesion) were in the lower segments and lobes of the lungs. 22 cases had multiple lesions with a > 68% frequency. More than 87% of cases had an adjacent bronchovascular bundle. Ground-glass opacities were detectable adjacent or close to the lesions in 30 cases (93%) and only in 7 cases (21%) was consolidation adjacent to the lesions.

CONCLUSION

Although it is not frequent in COVID-19, familiarity with this feature may help radiologists and physicians distinguish the disease from other viral and non-infectious pneumonias in challenging cases.

Key Words: Chest computed tomography; Diagnosis; Viral pneumonia; COVID-19; Pulmonary target sign; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In this report, a new diagnostic imaging sign in chest computed tomography of coronavirus disease 2019 cases, the "pulmonary target sign", is reported and its characteristics are described. Previous reports are limited to a small number of case reports and this appearance is not fully described.

Citation: Jafari R, Jonaidi-Jafari N, Maghsoudi H, Dehghanpoor F, Schoepf UJ, Ulversoy KA, Saburi A. "Pulmonary target sign" as a diagnostic feature in chest computed tomography of COVID-19. *World J Radiol* 2021; 13(7): 233-242
URL: https://www.wjgnet.com/1949-8470/full/v13/i7/233.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i7.233

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the seventh member of the non-segmented, enveloped, and positive-sense-RNA Coronaviridae family, which causes acute respiratory illness. This new coronavirus was first detected in Wuhan, China, in December 2019. It has since rapidly spread throughout the world and was recognized as a global health emergency[1,2]. COVID-19 presents as a wide spectrum of clinical pictures, from asymptomatic or mild flu-like illness to severe respiratory infection and even death[3,4].

A definitive diagnosis of COVID-19 mainly relies on RT-PCR testing in suspected cases. Chest computed tomography (CT) also has an undeniable importance in the diagnostic management of COVID-19 due to its high sensitivity and widespread availability[5]. The most common radiologic findings of COVID-19 are bilateral, peripheral, multifocal ground-glass opacities (GGO) and consolidations, linear opacities, reversed halo sign, and crazy-paving pattern[4,6]. These findings are highly suggestive, but not specific, for the diagnosis of COVID-19 infection, as other viral pneumonias, like influenza, severe acute respiratory syndrome and middle east respiratory syndrome, may show similar imaging findings[7,8]. Therefore, finding a specific and unique imaging feature of the disease in chest CT of patients with COVID-19 could be extremely helpful in the diagnostic work-up of these patients by limiting the differential diagnosis.

Some relatively specific features of the disease in chest CT have been discussed in the literature, including the "parallel pleural sign", "rings of Saturn appearance" and, recently, the "pulmonary target sign (PTS)"[9,10]. The latter imaging finding seems to be more specific for the disease. It was initially reported by Jafari *et al*[11] and

Shaghaghi *et al*[12] as a hyperattenuating ring surrounding a dense central dot, mimicking a target sign. This was termed a "target-shaped combined halo and reversed-halo sign" and "rings of Saturn"[11,12]. One month later, a similar pattern, named "chest target sign", was reported by McLaren *et al*[13] called "Bulls eye sign". Subsequently, de Farias *et al*[14] and Müller *et al*[15] also reported this imaging feature and its variants. Recently, Jafari *et al*[16] reported four cases of "PTS". In this contribution, we review chest CT images of 32 cases of PTS.

MATERIALS AND METHODS

Study design

Chest CT imaging findings of 650 patients admitted to a university Hospital in Tehran, Iran with confirmed COVID-19 infection by RT-PCR between January 2020 and July 2020 were reviewed by two expert radiologists.

Imaging protocol

All chest CT scan were obtained using a 16-row detector CT scanner (GE, optima, United States). Based on protocol of COVID-19 low-dose thoracic CT scan, the following items were considered: Tube voltage, 120 kVp; mAs, 30; slice thickness, 2.5 mm; reconstruction interval, 1.25 mm; rotation time, 0.5 s; pitch, 0.984; beam collimation, 40.

Chest CT interpretation

In addition to common non-specific imaging findings of COVID-19 pneumonia, radiologic characteristics of PTS will be presented. This chest CT sign of the disease as a circular appearance of non-involved pulmonary parenchyma with a central hyperdense dot, which is surrounded by ground glass or alveolar opacities, resembling a shooting target.

RESULTS

Of the 650 patients reviewed, 32 cases of PTS were found (4.9% prevalence). The location of the lesions in 31 of the 32 cases was peripheral, while 4 of the 31 cases had lesions both peripherally and centrally. Only one case had an isolated central lesion mimicking a solitary pulmonary nodule (Figures 1 and 2A).

The typical shape of PTS was seen in 31 cases, while 1 case had a PTS variant with double peripheral dense rings, which was previously named "rings of Saturn" (see Figure 2).

In 25 cases, the lesions (at least one if there were multiple) were located near the pleural surface and considered pleural based (see Figure 3). Half of the lesions (at least one lesion) were in the lower segments and lobes of the lungs (see Figure 4).

More than 87% of cases had an adjacent bronchovascular bundle (BVB). This characteristic was reported when a dense branching linear structure was approaching the lesion (see Figure 5).

Of the 32 cases, 22 had multiple lesions with a > 68% frequency (see Figure 6). GGOs were detectable adjacent or close to the lesions in 30 cases (93%) and only in 7 cases (21%) was consolidation adjacent to the lesions, Figure 7.

8 cases showed pulmonary complications of COVID-19, including pneumothorax (1 case) and pleural effusion (7 cases/21%). Three cases (9%) showed parallel pleural sign and 6 cases (18%) showed fibrotic bands (see Figure 8). The characteristics are summarized in Table 1.

DISCUSSION

Regarding the descriptive findings and characteristics of PTS lesions, they tend to be multiple lesions, located in the periphery, and located adjacent to a BVB and GGOs. They are uncommonly seen centrally or basally or with adjoining consolidation. Due to a low frequency of fibrotic bands as a marker of healing and concomitant complications, such as pleural effusion, it seems that PTS appear at early phases.

Table 1 Cases characteristics

Characteristics of PTS	Number (32 cases)	Frequency (4.9%)
Only peripheral	31	96.8%
Both central and peripheral	4	12.5%
Age (mean ± SD)	53.1 ± 13.4	-
Gender (male)	28	87.5%
Along with BVB	28	87.5%
Pleura-based[1]	25	78.1%
Adjacent GGO	30	93.7%
Adjacent consolidation	7	21.8%
Basal lobes and segments[2]	16	50.0%
Multiple	22	68.7%

[1]Pleura based or close to pleural surface.
[2]If only one of multiple lesions present at lower segments and lobes, considered positive.
BVB: Bronchovascular bundle; GGO: Ground-glass opacities; PTS: Pulmonary target sign.

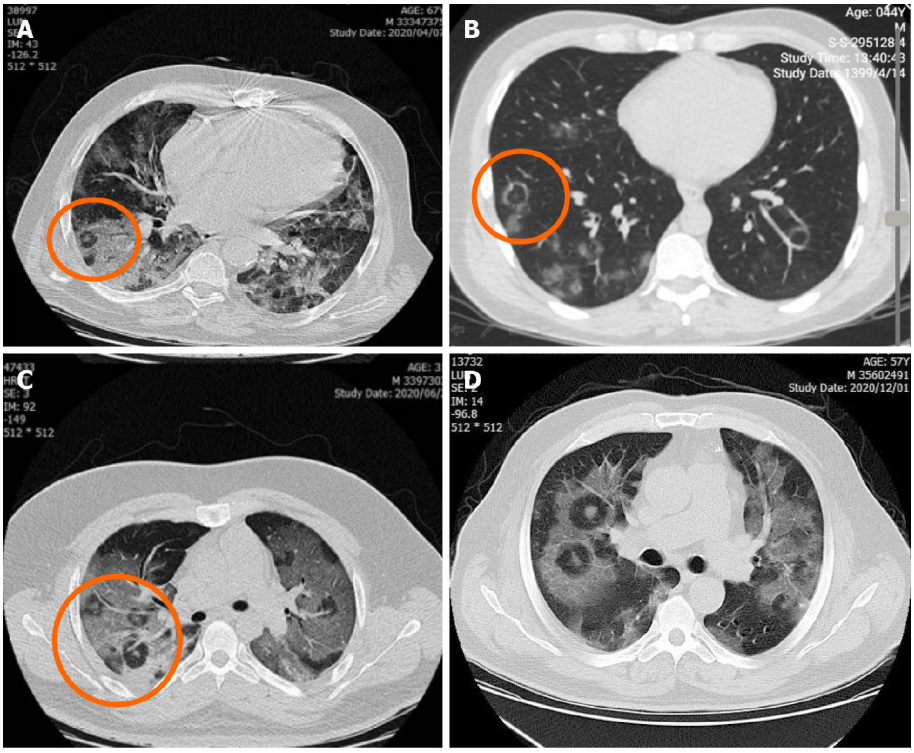


Figure 1 "Pulmonary target sign" in 4 different cases varies according to the location of the lesions. A and B: Peripheral location; C and D: Central location.

In such contagious and life-threatening infections as COVID-19, having a consistent and reliable diagnostic and screening tool is vital. Currently, CT, with its high sensitivity and specificity, is one of the most valuable screening and diagnostic tools [17,18]. Although commonly reported findings in COVID-19 CT scans are not specific for a diagnosis of COVID-19 *vs* other viral pneumonias, some recently reported specific features of the disease, like PTS, can be helpful for this aim.

It is important to know the difference between PTS and the Atoll sign. An Atoll sign has central opacities consisting of GGO, while PTS has a central dot which can represent a filled bronchiole or vessel. Moreover, it was previously noted that "the crescentic appearance of the reversed halo sign is typical on CT whereas the target sign has a polygonal appearance peripherally"[19]. This feature has been frequently re-

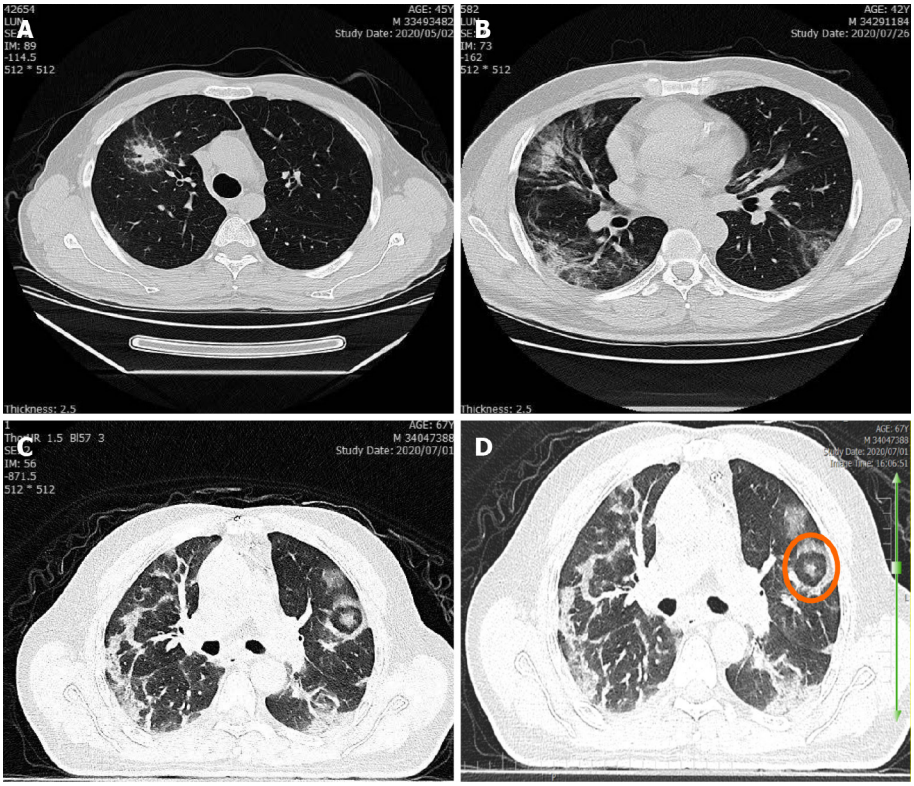


Figure 2 Variants of "pulmonary target sign" in 4 different cases. A: "Pulmonary target sign" (PTS) similar to a solitary pulmonary nodule; B: "Rings of Saturn" as a variant of PTS; C and D: PTS with parallel pleural sign.

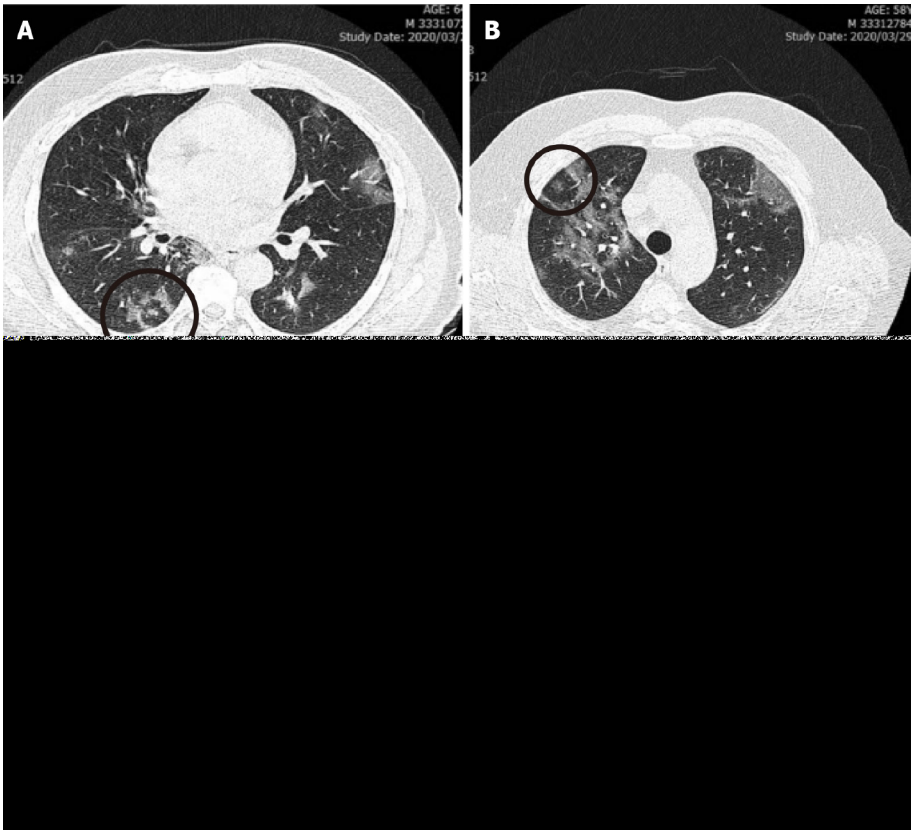


Figure 3 "Pulmonary target sign" in 4 different patients. A and B: "Pulmonary target sign" (PTS) as a pleural based lesion; C: PTS with incomplete peripheral ring; D: Complete peripheral ring.

ported as Atoll sign, which may be due to the unfamiliarity with this sign among

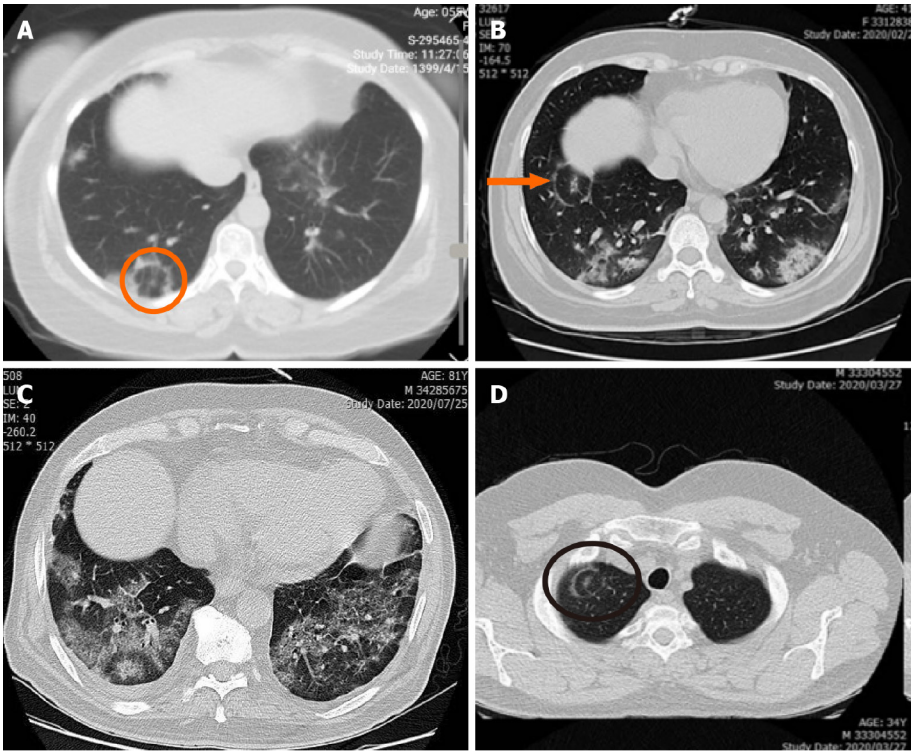


Figure 4 "Pulmonary target sign" in 4 different individuals. A, B and C: Basal location of "pulmonary target sign"; D: Apical location.

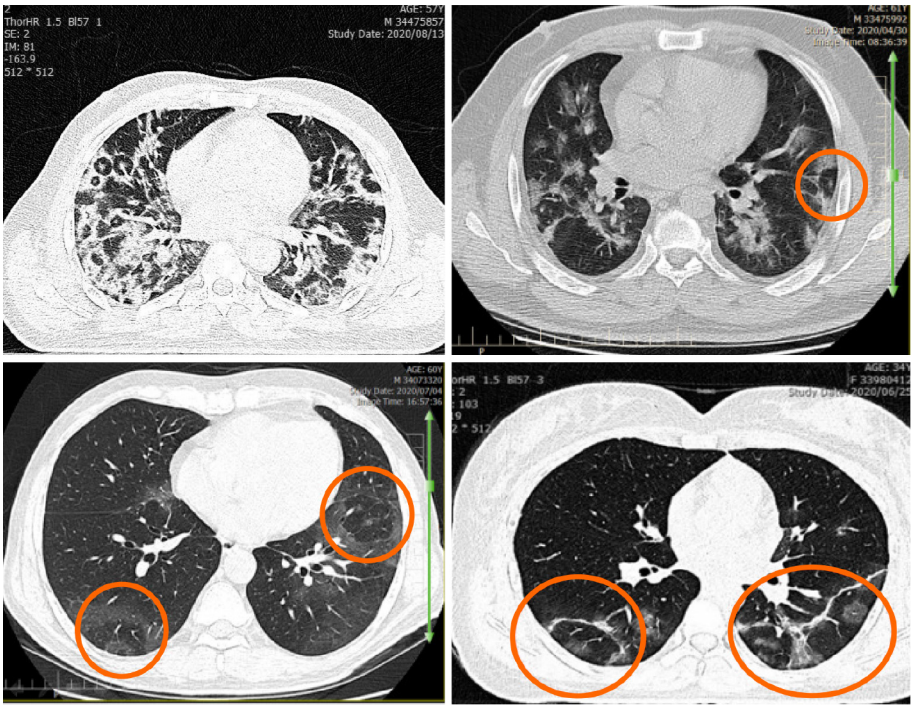


Figure 5 "Pulmonary target sign" in 4 different cases. "Pulmonary target sign" along with a broncho-vascular bundle.

physicians and radiologists[20-22]. For differentiation, it was described that "the peripheral wall of the CT target sign has a polygonal appearance in most patients", in contrast to the constellation of the reverse halo sign[19].

Generally, diffuse subpleural and peripheral ill-defined GGO with air-bronchograms, adjacent pleural thickening and septal or interlobular thickening were reported as the imaging hallmark of the novel coronavirus, while hilar or mediastinal lymphadenopathy, pleural effusion, pulmonary nodules and cavitations are unusual findings[2].

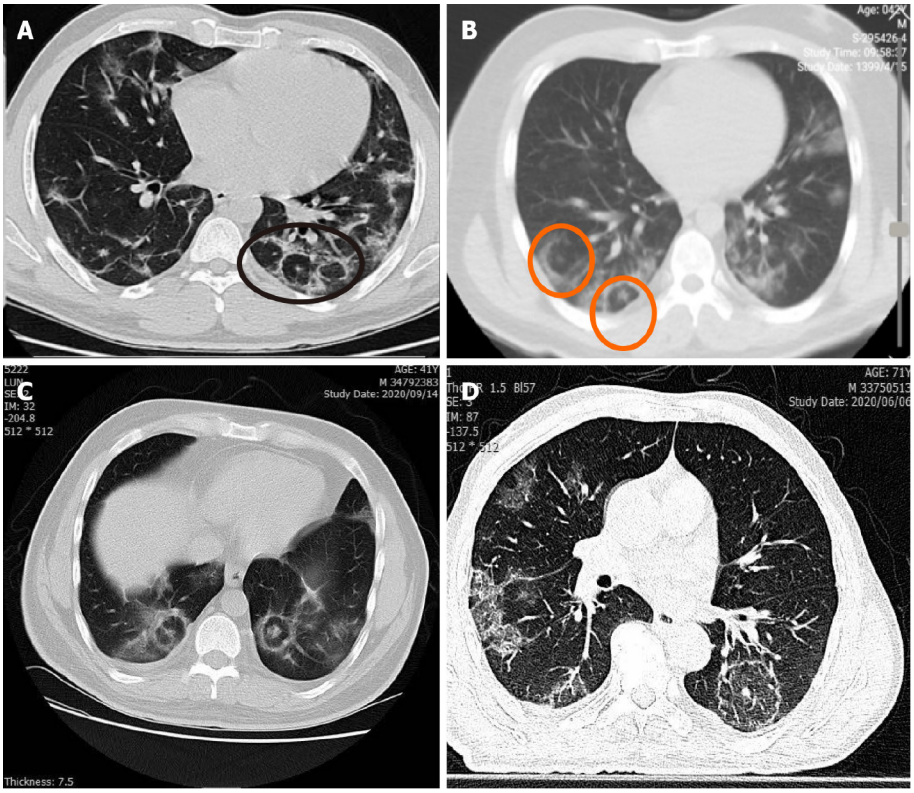


Figure 6 Laterality of "pulmonary target sign" in 4 different cases. A and B: Multiple unilateral "pulmonary target sign"; C: bilateral lesions; D: Solitary lesion.

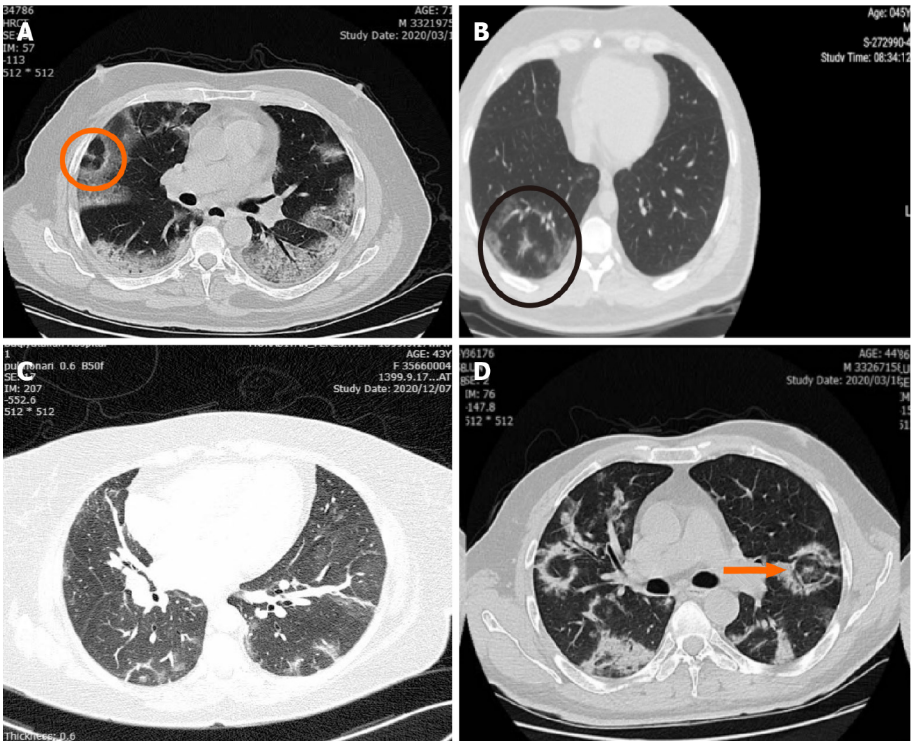


Figure 7 Correlation of "pulmonary target sign" with adjacent ground-glass opacities or consolidation. A: Circular adjacent ground-glass opacities (GGO); B and C: Patchy adjacent GGO; D: adjacent patchy consolidation.

In our contribution, we present 32 PCR confirmed cases of COVID-19 infection with specific findings on their chest CT. As mentioned previously, in addition to common findings of COVID-19 infection, their chest CT revealed a circular appearance of non-involved pulmonary parenchyma, which encompassed a central hyperdense dot

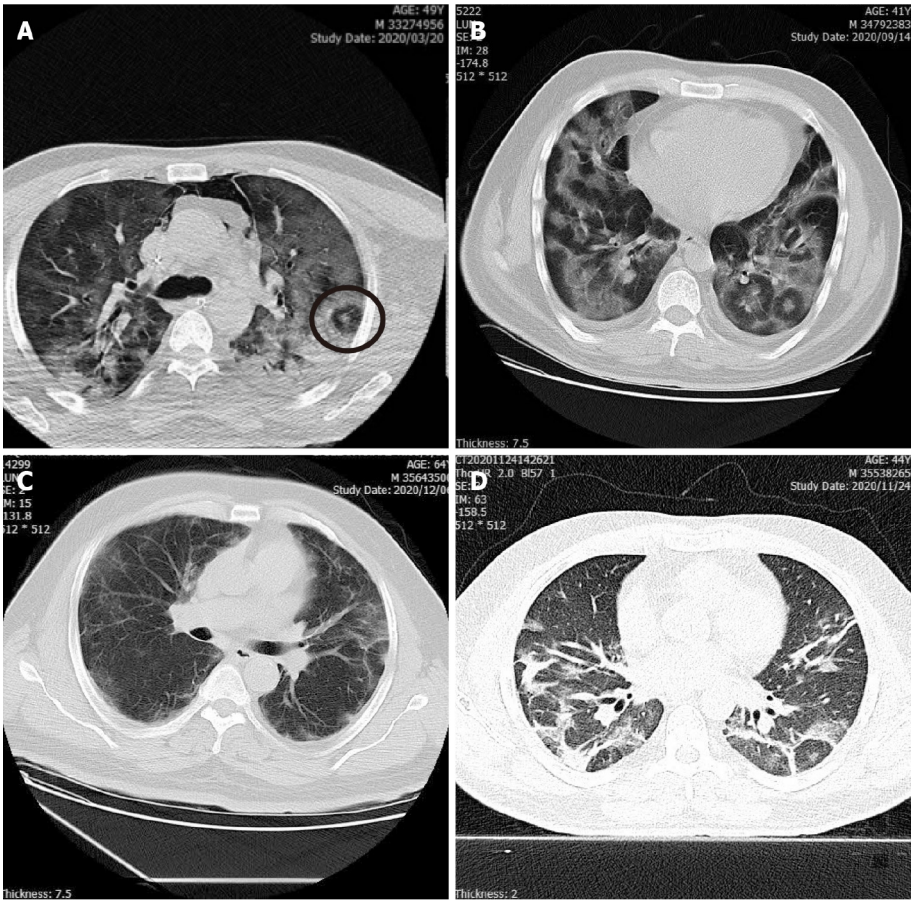


Figure 8 "Pulmonary target sign" with coronavirus disease 2019 complications. A: Pneumothorax and pneumomediastinum; B: Pleural effusion; C: Pleural thickening; D: Fibrotic band.

surrounded by ground-glass or alveolar opacities. This represents a unique finding that has never been reported in any other disease. We hypothesize that this appearance is due to a pattern of lobar involvement of COVID-19 *via* bronchiolar and venolymphaticdrainage[11,23]. Interstitial pneumonitis and subsequent organizing pneumonia with diffuse alveolar damage were reported in the advanced phase of the disease[19,24]. Therefore, the PTS feature will likely develop when the venolymphatic drainage system is subject to a considerable load of fluid entrapment, as in the case of alveolar wall injury and bronchial occlusion by this secretion (central dot) secondary to COVID-19.

CONCLUSION

We present specific, unique chest CT imaging features in 32 confirmed cases of COVID-19 infection. Although these findings are not observed in all patients with this disease and it is uncommon (about 5% frequency), we believe PTS to be a specific finding which can distinguish COVID-19 pneumonia from other similar viral pneumonias. However, due to the only recent recognition of this feature and the scarcity of reported cases, it is not yet clear whether PTS is seen only in COVID-19 or will also be observed in other viral pneumonias with similar pathophysiology.

ARTICLE HIGHLIGHTS

Research background

Chest computed tomography scan findings like bilateral ground glass opacities and consolidations are commonly used as distinguishing features in the differential diagnosis of coronavirus disease 2019 (COVID-19). However, a problem in diagnosis

arises when other viral or atypical pneumonia infections are suspected, as they may present similarly.

Research motivation

Pulmonary target sign (PTS) is a feature of COVID-19 that has been recently suggested as an atypical presentation of pulmonary involvement and may be used to distinguish COVID-19 from other similar pneumonia infections.

Research objectives

In this paper, the PTS and its characteristics were assessed among COVID-19 confirmed patients.

Research methods

Among all cases of COVID-19 that were referred to a tertiary medical center in Tehran, Iran, chest CT scan findings of 650 serologically positive cases of COVID-19 were evaluated for PTS and its characteristics.

Research results

32 individuals with at least one PTS in their CT scan were identified in which most of the PTSs were multiple in number, in a peripheral location, and near a bronchovascular bundle.

Research conclusions

The PTS has a frequency of about 5% and specific characteristics that may make it useful in the prompt diagnosis of COVID-19.

Research perspectives

The relationship between the presence of the PTS and the prognosis of COVID-19 still needs to be elucidated. Additionally, the mechanisms behind the pathogenesis and the timeline of PTS progression are suggested areas of research for future studies.

REFERENCES

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

2 **Shi H**, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]

3 **Kanne JP**, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for Radiologists on COVID-19: An Update-*Radiology* Scientific Expert Panel. *Radiology* 2020; **296**: E113-E114 [PMID: 32105562 DOI: 10.1148/radiol.2020200527]

4 **Saburi A**, Schoepf UJ, Ulversoy KA, Jafari R, Eghbal F, Ghanei M. From Radiological Manifestations to Pulmonary Pathogenesis of COVID-19: A Bench to Bedside Review. *Radiol Res Pract* 2020; **2020**: 8825761 [PMID: 33294226 DOI: 10.1155/2020/8825761]

5 **Li M**, Lei P, Zeng B, Li Z, Yu P, Fan B, Wang C, Zhou J, Hu S, Liu H. Coronavirus Disease (COVID-19): Spectrum of CT Findings and Temporal Progression of the Disease. *Acad Radiol* 2020; **27**: 603-608 [PMID: 32204987 DOI: 10.1016/j.acra.2020.03.003]

6 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]

7 **Hosseiny M**, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology Perspective of Coronavirus Disease 2019 (COVID-19): Lessons From Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome. *AJR Am J Roentgenol* 2020; **214**: 1078-1082 [PMID: 32108495 DOI: 10.2214/AJR.20.22969]

8 **Hanfi SH**, Lalani TK, Saghir A, McIntosh LJ, Lo HS, Kotecha HM. COVID-19 and its Mimics: What the Radiologist Needs to Know. *J Thorac Imaging* 2021; **36**: W1-W10 [PMID: 32852419 DOI: 10.1097/RTI.0000000000000554]

9 **Wang C**, Shi B, Wei C, Ding H, Gu J, Dong J. Initial CT features and dynamic evolution of early-stage patients with COVID-19. *Radiol Infect Dis* 2020; **7**: 195-203 [PMID: 32864406 DOI: 10.1016/j.jrid.2020.08.002]

10 **Wu J**, Pan J, Teng D, Xu X, Feng J, Chen YC. Interpretation of CT signs of 2019 novel coronavirus

(COVID-19) pneumonia. *Eur Radiol* 2020; **30**: 5455-5462 [PMID: 32367422 DOI: 10.1007/s00330-020-06915-5]

11 **Jafari R**, M Colletti P, Saburi A. "Rings of Saturn" appearance: a unique finding in a case of COVID-19 pneumonitis. *Diagn Interv Radiol* 2021; **27**: 154 [PMID: 32673208 DOI: 10.5152/dir.2020.20266]

12 **Shaghaghi S**, Daskareh M, Irannejad M, Shaghaghi M, Kamel IR. Target-shaped combined halo and reversed-halo sign, an atypical chest CT finding in COVID-19. *Clin Imaging* 2021; **69**: 72-74 [PMID: 32682246 DOI: 10.1016/j.clinimag.2020.06.038]

13 **McLaren TA**, Gruden JF, Green DB. The bullseye sign: A variant of the reverse halo sign in COVID-19 pneumonia. *Clin Imaging* 2020; **68**: 191-196 [PMID: 32853842 DOI: 10.1016/j.clinimag.2020.07.024]

14 **Gomes de Farias LP**, Caixeta Souza FH, da Silva Teles GB. The Target Sign and Its Variant in COVID-19 Pneumonia. *Radiol Cardiothorac Imaging* 2020; **2**: e200435 [PMID: 33778617 DOI: 10.1148/ryct.2020200435]

15 **Müller CIS**, Müller NL. Chest CT target sign in a couple with COVID-19 pneumonia. *Radiol Bras* 2020; **53**: 252-254 [PMID: 32904794 DOI: 10.1590/0100-3984.2020.0089]

16 **Jafari R**, Maghsoudi H, Saburi A. A Unique Feature of COVID-19 Infection in Chest CT; "Pulmonary Target" Appearance. *Acad Radiol* 2021; **28**: 146-147 [PMID: 33246787 DOI: 10.1016/j.acra.2020.11.004]

17 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

18 **Goyal N**, Chung M, Bernheim A, Keir G, Mei X, Huang M, Li S, Kanne JP. Computed Tomography Features of Coronavirus Disease 2019 (COVID-19): A Review for Radiologists. *J Thorac Imaging* 2020; **35**: 211-218 [PMID: 32427651 DOI: 10.1097/RTI.0000000000000527]

19 **Marchiori E**, Nobre LF, Hochhegger B, Zanetti G. CT characteristics of COVID-19: reversed halo sign or target sign? *Diagn Interv Radiol* 2021; **27**: 306-307 [PMID: 33290240 DOI: 10.5152/dir.2020.20734]

20 **Hoda A**, Arash S. The Role of Chest CT Scan in Diagnosis of COVID-19. *Adv J Emerg Med* 2020; **4**: e64 [DOI: 10.22114/ajem.v4i2s.451]

21 **hao L**, Chen B, Huang Y, Yang M, Yang J, Zhao Z. A Dynamic Follow-Up of Pneumonia Caused by Coronavirus Disease 2019 (COVID-19) on CT Scan. *Iran J Radiol* 2020; **17**: e102847 [DOI: 10.5812/iranjradiol.102847]

22 **Zhang FY**, Qiao Y, Zhang H. CT imaging of the COVID-19. *J Formos Med Assoc* 2020; **119**: 990-992 [PMID: 32307320 DOI: 10.1016/j.jfma.2020.04.006]

23 **Kambouchner M**, Bernaudin JF. Intralobular pulmonary lymphatic distribution in normal human lung using D2-40 antipodoplanin immunostaining. *J Histochem Cytochem* 2009; **57**: 643-648 [PMID: 19289553 DOI: 10.1369/jhc.2009.953067]

24 **Elsoukkary SS**, Mostyka M, Dillard A, Berman DR, Ma LX, Chadburn A, Yantiss RK, Jessurun J, Seshan SV, Borczuk AC, Salvatore SP. Autopsy Findings in 32 Patients with COVID-19: A Single-Institution Experience. *Pathobiology* 2021; **88**: 56-68 [PMID: 32942274 DOI: 10.1159/000511325]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 August 28; 13(8): 243-257

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 8 August 28, 2021

SYSTEMATIC REVIEWS

World Journal of Radiology

Monthly Volume 13 Number 8 August 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Francesco Lassandro, MD, Doctor, Medical Assistant, Radiology Section, Department of Services, Azienda Ospedali dei Colli, Monaldi Hospital, Naples 80131, Italy. francesco.lassandro@ospedalideicolli.it

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJR* as 0.51.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Jie Ma*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
August 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 August 28; 13(8): 243-257

DOI: 10.4329/wjr.v13.i8.243

ISSN 1949-8470 (online)

SYSTEMATIC REVIEWS

Differential diagnosis of COVID-19 at the chest computed tomography scan: A review with special focus on cancer patients

Fabiana Perrone, Maurizio Balbi, Chiara Casartelli, Sebastiano Buti, Gianluca Milanese, Nicola Sverzellati, Melissa Bersanelli

ORCID number: Fabiana Perrone 0000-0001-8090-770X; Maurizio Balbi 0000-0002-8436-3655; Chiara Casartelli 0000-0002-7638-5299; Sebastiano Buti 0000-0003-0876-0226; Gianluca Milanese 0000-0003-1974-4854; Nicola Sverzellati 0000-0002-4820-3785; Melissa Bersanelli 0000-0002-6527-6281.

Author contributions: Bersanelli M, Perrone F, and Casartelli C designed the work, planned the literature review according to PRISMA methods, and identified the areas of interest to discuss; Perrone F and Casartelli C collected the data; Balbi M prepared the figures; Perrone F and Balbi M wrote the first draft of the manuscript; Bersanelli M revised the manuscript for relevant scientific content and copyediting; Buti S, Milanese G, and Sverzellati N revised the manuscript for relevant scientific content; All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: Melissa Bersanelli received honoraria as a speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, Astra Zeneca, Pierre Fabre, and Pfizer and as a consultant for advisory role by Novartis, BMS, IPSEN, and Pfizer; she also received fees for copyright

Fabiana Perrone, Chiara Casartelli, Sebastiano Buti, Melissa Bersanelli, Medical Oncology Unit, University Hospital of Parma, Parma 43126, Italy

Fabiana Perrone, Chiara Casartelli, Melissa Bersanelli, Department of Medicine and Surgery, University of Parma, Parma 43126, Italy

Maurizio Balbi, Gianluca Milanese, Nicola Sverzellati, Department of Surgical Sciences, Institute of Diagnostic and Interventional Radiology, University of Parma, Parma 43126, Italy

Corresponding author: Melissa Bersanelli, MD, Adjunct Professor, Chief Doctor, Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, Parma 43126, Italy. bersamel@libero.it

Abstract

BACKGROUND

Given the several radiological features shared by coronavirus disease 2019 pneumonia and other infective or non-infective diseases with lung involvement, the differential diagnosis is often tricky, and no unequivocal tool exists to help the radiologist in the proper diagnosis. Computed tomography is considered the gold standard in detecting pulmonary illness caused by severe acute respiratory syndrome coronavirus 2.

AIM

To conduct a systematic review including the available studies evaluating computed tomography similarities and discrepancies between coronavirus disease 2019 pneumonia and other pulmonary illness, then providing a discussion focus on cancer patients.

METHODS

Using pertinent keywords, we performed a systematic review using PubMed to select relevant studies published until October 30, 2020.

RESULTS

Of the identified 133 studies, 18 were eligible and included in this review.

CONCLUSION

Ground-glass opacity and consolidations are the most common computed tomography lesions in coronavirus disease 2019 pneumonia and other respiratory

transfer by Sciclone Pharmaceuticals and research funding by Roche S.p.A., Seqirus UK, Pfizer, Novartis, BMS, Astra Zeneca, and Sanofi Genzyme. Sebastiano Buti received honoraria as a speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca and Novartis; he also received research funding from Novartis. All the other authors declare they have no conflicts of interest to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

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

Received: January 28, 2021
Peer-review started: January 28, 2021
First decision: May 6, 2021
Revised: May 18, 2021
Accepted: August 2, 2021

diseases. Only two studies included cancer patients, and the differential diagnosis with early lung cancer and radiation pneumonitis was performed. A single lesion associated with pleural effusion and lymphadenopathies in lung cancer and the onset of the lesions in the radiation field in the case of radiation pneumonitis allowed the differential diagnosis. Nevertheless, the studies were heterogeneous, and the type and prevalence of lesions, distributions, morphology, evolution, and additional signs, together with epidemiological, clinical, and laboratory findings, are crucial to help in the differential diagnosis.

Key Words: COVID-19; Computed tomography; Differential diagnosis; Cancer; Pneumonia; Radiological findings

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In the coronavirus disease 2019 era, the differential diagnosis of pneumonitis, already challenging in patients with multiple comorbidities and polypharmacological therapy, has become even more challenging. The gold-standard technique for diagnosing coronavirus disease 2019-related pneumonia is still not established. Still, a computed tomography scan is essential for the differential diagnosis of drug-induced pneumonitis, infectious pneumonia, and other conditions such as cancer progression. With this review, we have dealt with frequent radiological diatribes in the radiological diagnosis of coronavirus disease 2019 pneumonitis, with a special focus on cancer patients, for whom clinical elements can be more confounding than helpful as a compendium to the correct diagnostic conclusion.

Citation: Perrone F, Balbi M, Casartelli C, Buti S, Milanese G, Sverzellati N, Bersanelli M. Differential diagnosis of COVID-19 at the chest computed tomography scan: A review with special focus on cancer patients. *World J Radiol* 2021; 13(8): 243-257
URL: https://www.wjgnet.com/1949-8470/full/v13/i8/243.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i8.243

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak began in Wuhan, China, in late 2019 and rapidly spread worldwide at the beginning of 2020, when it was declared a global pandemic by the World Health Organization[1,2]. Many jurisdictions in several states carried out public health interventions to contain the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3]. Europe is now experiencing a second wave of contagion[4].

The virus has a specific tropism for the lower respiratory tract, and it is the cause of mild to severe respiratory infection[5].

Imaging has been widely employed to triage the massive load of acute respiratory referral due to COVID-19 by complementing the nucleic acid testing (*i.e.*, the diagnostic reference standard). Typical manifestations of COVID-19 pneumonia on computed tomography (CT) have become known since the early phase of the pandemic: bilateral peripheral opacities with a lower lung distribution, usually consisting of nodular or mass-like ground-glass opacities (GGO) variably associated with areas of consoli-dation[6,7]. CT abnormalities may be absent in the earliest disease phases and become more extensive in the peak stage (*i.e.*, around day 9 to 13) before resolve or evolve to a more organized phase, possibly leading to fibrotic-like changes[8,9].

Many of the hallmark CT findings are apparent on chest X-ray, which is prone to miss subtle GGO, even if relatively diffuse in extent. Nevertheless, chest X-ray has shown the potential to predict outcomes in relatively advanced disease stages, assess supervening complications, and monitor the disease course[10]. Lung ultrasound was suggested as a fast and feasible approach for triaging COVID-19 patients by identifying peripheral lung abnormalities such as confluent artifactual signs, small hyperechoic lung regions, thickened pleural lines, and consolidation[11,12]. Though highly sensitive, lung ultrasound is operator-dependent, challenging to perform in obese patients, and has lower specificity than CT[13].

Article in press: August 2, 2021
Published online: August 28, 2021

P-Reviewer: Fei C, Patel L
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Yuan YY

It is worth emphasizing that the imaging appearance of COVID-19 is non-specific, and the performance of different modalities dramatically relies on the disease prevalence. The typical manifestations may mimic or overlap with other infective and non-in-fectious diseases, including influenza and acute lung injuries from drug reactions and connective tissue diseases[14]. Identifying findings uncommonly seen in COVID-19 pneumonia such as cavitation, tree-in-bud, and pleural effusion may help suggest an alternative diagnosis, which cannot be prescinded from clinical evaluation.

In the present article, we performed a systematic review of the literature focusing on differential radiological diagnosis between COVID-19 pneumonia and other infective and non-infective lung diseases, then discussing possibly helpful clinical elements and finally focusing on this issue in cancer patients.

MATERIALS AND METHODS

We conducted this systematic review according to the Preferred Reporting Items guidelines for Systematic Reviews and Meta-Analysis (PRISMA) Statement[15]. The primary aim was to collect, describe, and discuss all the clinical studies evaluating the different CT findings between COVID-19 infection and other infective or non-infective lung diseases.

Search strategy

Two authors (CC and FP) carried out a comprehensive systematic search for published articles on the MEDLINE/PubMed library until October 31, 2020. Given the absence of articles on this topic before December 2019, when the first COVID-19 outbreak started, no upper limit for the search was chosen.

The following search keywords were used: "COVID-19" AND "computed tomography" AND "differential diagnosis." The reference lists of the included articles and reviews/meta-analyses on our research topic were also reviewed to identify additional relevant papers.

Study selection and eligibility criteria

Retrospective studies, prospective studies, and case reports describing the difference between CT signs caused by SARS-CoV2 infection and other respiratory and non-respiratory diseases were included. Only English-language articles were considered eligible. Studies with insufficient radiological data or focused on non-CT radiological findings (*i.e.*, ultrasound or radiography) were excluded. We planned qualitative analysis only, forecasting a high heterogeneity between the eligible studies, likely preventing quantitative analyses.

Narrative papers, such as commentaries and editorials, were excluded from the formal qualitative analysis, but the most relevant articles discussing the issue were considered in the discussion.

Data extraction and synthesis

The study characteristics (first author, year of publication, type of study, number of patients included, disease of comparison assessed, and main radiological similarities and discrepancies, laboratory findings) were extracted from the included articles by a single author (FP). Two reviewers (FP and CC) initially performed the data extraction, and then it was independently reviewed by an additional reviewer (MB).

Any doubt or disagreement was discussed with a fourth investigator (SB) and resolved with all investigators' consensus.

RESULTS

Literature search

Of the 133 studies found in the search, 104 were initially excluded by title and abstract reading. After reading the full text of the remaining 29 articles, 11 were excluded because they missed relevant radiological information or comparison between different imaging patterns. Overall, 18 studies satisfied the prespecified criteria and were selected for the qualitative analysis. The outline of the search is reported in Figure 1.

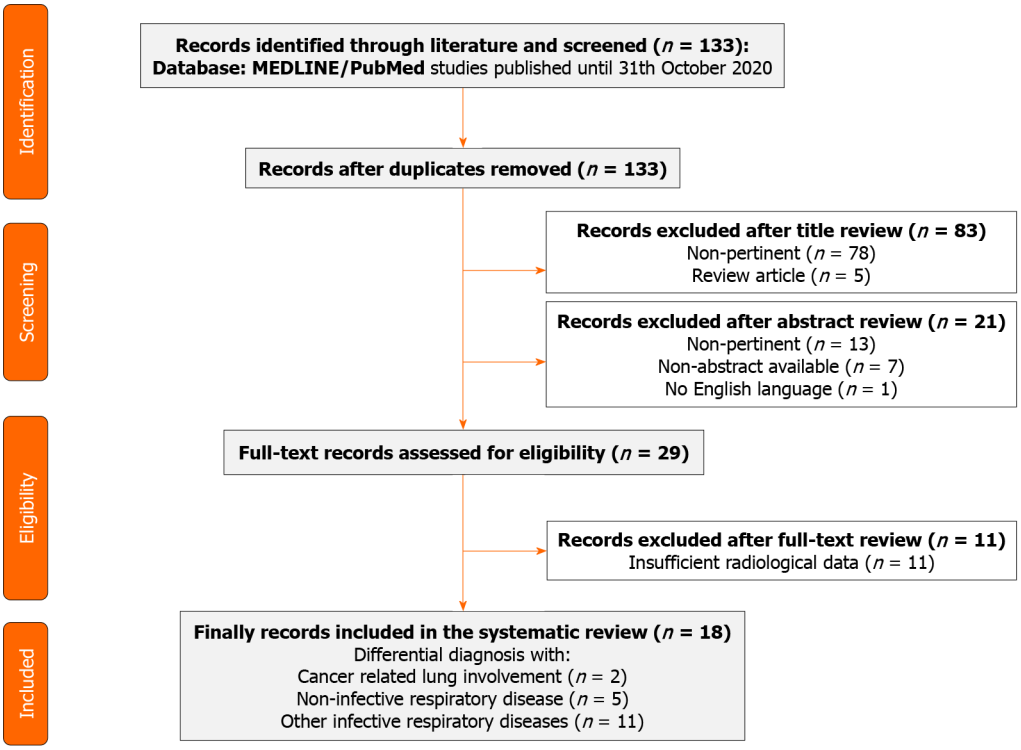


Figure 1 PRISMA flow diagram.

Characteristics of the included studies

Trial characteristics and the main results of the studies included are reported in Table 1. Among the 18 studies included, 5 were case report/case series[16-20], and 13 were retrospective[21-33]. All the studies described the typical radiological characteristics of COVID-19 pneumonia and addressed the radiological differential diagnosis issue. The difference between COVID-19 and non-infective respiratory diseases, namely: Systemic sclerosis and granulomatosis with polyangiitis (n = 2)[30,31], fat embolism (n = 1)[32], pulmonary contusion (n = 1)[33] were evaluated in 5 out of 18 studies. One study evaluated both heart failure-induced pulmonary edema and rheumatic pneumonia (n = 1)[16].

On the other hand, 11 studies explored the CT imaging differences between COVID-19 disease and other infective pneumonia. In particular, the differential diagnosis was performed with influenza pneumonia (n = 3)[23,30,33], community-acquired pneumonia (CAP) (n = 3)[24,25,31], and other non- specified viral or bacterial pneumonia (n = 5)[21,22,26,27,32].

Only two studies included cancer patients. One assessed the radiological discrepancies between COVID-19 disease with lung involvement and radiation pneumonitis [28]. In the other study, the differential diagnosis regarded early lung cancer[29].

In the majority of studies, detection of SARS-CoV-2 was performed by RT-PCR on throat/nasopharyngeal swab. The laboratory test was lacking in only one study, in which the final diagnosis was carried out based on clinical and epidemiological findings[20].

In the following paragraphs, the findings of the included studies are reported by topic.

Differential diagnosis between COVID-19 pneumonia and other non-infective respiratory diseases

The radiological difference between COVID-19 pneumonia and heart failure-induced pulmonary edema was evaluated by Dai *et al*[16].

Although GGOs and interlobular septal thickening were CT manifestations shared by both diseases, butterfly signs (patchy high attenuation patterns and large patchy high attenuation patterns in both lungs), peribronchial cuffing, and redistribution of blood flow in both lungs were typical in heart failure pulmonary edema.

Three rheumatologic diseases, namely systemic sclerosis, granulomatosis with polyangiitis, and rheumatic disease, often caused lung involvement with GGOs. Predominant lower lobe distribution associated with reticulations and honeycombing in

Table 1 Summary of the studies included in the systematic review

Ref.	Yr	Type of study	Patients, *n*	Disease in differential diagnosis	Radiological similarities with COVID-19 disease	Radiological discrepancy with COVID-19 disease	Laboratory findings
Dai *et al*[16]	2020	Case series	4 pts COVID-19 positive. 1 pts heart failure induced pulmonary edema. 1 pts rheumatic pneumonia.	Heart failure induced pulmonary edema. Rheumatic pneumonia.	Local or multiple GGOs. Patchy high-attenuation patterns. Sporadic or local interlobular septal thickening. Patchy GGOs and consolidations; interlobular septal thickening.	Butterfly sign. Peribronchial cuffing. Redistribution of blood flow in both lungs.	Normal WBC count, D-dimer, hs-CRP. RT-PCR for SARS-CoV-2 negative. Normal WBC and lymphocyte count, high hs-CRP, D-dimer, rheumatoid factor. RT-PCR for SARS-CoV-2 negative.
Orlandi *et al* [17]	2020	Case report	-	Systemic sclerosis ILD	Bilateral GGOs with or without consolidations. Reticulations.	Limited to lower lobes. Honeycombing pattern.	RT-PCR for SARS-CoV-2 negative
Shenavandeh *et al*[18]	2020	Case report	1	Granulomatosis with polyangiitis	GGOs and consolidation	Nodules and mass lesions	-
Chen *et al*[20]	2020	Case report	1	Pulmonary contusion	GGOs and consolidation	More consolidations. Less combined with pleural effusion and subpleural atelectasis. Different time evolution of lesions.	High WBC count and mild decreased of lymphocyte count
Mazouz *et al* [19]	2020	Case report	1	Fat embolism	Bilateral GGOs	Central and peripherical involvement	High CRP, alkalosis with hypoxemia, normal lymphocyte count. RT-PCR for SARS-CoV-2 negative.
Zhang *et al* [29]	2020	Retrospective	157 pts COVID-19. 374 pts with early lung cancer.	Early lung cancer	Air bronchogram. Cystic change.	Less lobes and segments involved. Unilateral oval lesions. Pure or mixed GGOs. Lobulated sign, pleural retraction and vessel convergence sign. Less lymphadenopathies and pleural effusion.	Higher WBC and lymphocyte count, lower D-dimer level.
Zeng *et al*[28]	2020	Retrospective	112 pts COVID-19 positive or suspected. 4 pts with radiation pneumonitis.	Radiation pneumonitis	GGOs with consolidation. Air bronchogram. Irregular intralobular or interlobular septal thickening. Fibrosis in late stage.	Onset within 6 mo after radiation. Slow evolution. Lesions confined to radiation fields.	High WBC count, D-Dimer, CRP and PCT, marked lymphopenia. RT-PCR for SARS-CoV-2 negative.
Himoto *et al* [27]	2020	Retrospective	21 pts COVID-19 positive. 15 pts with viral or bacterial pneumonia.	Pneumococcal pneumonia, Moraxella pneumonia, Legionella pneumonia, not-specified bacterial or viral pneumonia. Pneumocystis pneumonia and interstitial pneumonia.	Bilateral peripherical GGOs. No cavitation, airway abnormalities, pleural effusion, and mediastinal lymphadenopathy.	Less lobes involved. No rounded morphology lesions.	RT-PCR for SARS-CoV-2 negative
Luo *et al*[22]	2020	Retrospective	30 pts COVID-19 positive. 43 pts with viral or bacterial pneumonia.	Influenza pneumonia, Pneumocystis carinii pneumonia, Mycoplasma pneumonia and CAP.	GGOs with or without consolidation	Less lobes involved. Peribronchovascular distribution. Centrilobular nodules. Bronchial wall thickening.	WBC and lymphocyte count normal, but lower in COVID-19 positive patients. RT-PCR.

Xie *et al*[26]	2020	Retrospective	12 pts COVID-19 positive. 16 pts COVID-19 negative.	COVID-19 negative	Bilateral multiple lung involvement, large irregular/patchy opacities, rounded opacities and linear opacities, crazy-paving patterns, interlobular septal, pleural and peribronchovascular interstitial thickening, air bronchograms, tree-in-bud patterns.	More central distribution of lesions. Less frequent rounded opacities.	Higher level of neutrophil count in COVID-19 negative. RT-PCR.
Bai *et al*[21]	2020	Retrospective	219 pts COVID-19 positive. 205 pts with viral pneumonia.	Viral pneumonia	Bilateral, multiple GGOs, consolidation, nodules. Septal thickening.	More central + peripheral distribution. More air bronchogram, pleural thickening, pleural effusion and lymphadenopathy.	Higher WBC and lymphocyte count in patients with viral pneumonia. RT-PCR.
Chi *et al*[32]	2020	Retrospective	17 pts COVID-19 positive. 51 pts with viral or bacterial pneumonia.	Influenza A and B. Adenovirus. Chlamydia pneumonia. Mycoplasma pneumonia.	-	INFLUENZA A: scattered and patchy shadows and nodular shadows in both lungs. INFLUENZA B: subpleural patchy shadows. ADENOVIRUS: consolidation near the pleura. CHLAMYDIA PNEUMONIAE: multiple GGOs and consolidations in both lungs. MYCOPLASMA PNEUMONIAE: bronchial wall thickening, centrilobular nodules, GGOs and consolidation.	Higher WBC count, RT-PCR
Li *et al*[24]	2020	Retrospective	43 pts COVID-19 positive. 49 pts with CAP.	CAP	-	More nodular or consolidation shadows with or without patchy GGOs. Less fine mesh changes, small vessels dilatated, bronchiectasis and lesion with long axis parallel to the pleura.	RT-PCR
Liu *et al*[25]	2020	Retrospective	165 pts COVID-19 positive. 118 pts with CAP.	CAP	-	More central distribution. More frequent single lesion. GGOs rapid changes in consolidation. Fibrous cord and bronchial wall thickening.	Normal WBC count, higher lymphocyte count and CRP. RT-PCR.
Zhou *et al*[31]	2020	Retrospective	149 pts COVID-19 positive. 97 pts with CAP.	CAP (*Streptococcus. pneumoniae*)	-	More consolidation lesions, bronchial wall thickening, centrolobular nodules and pleural effusion. Less GGOs, crazy paving sign and abnormally thickened interlobular septa.	High WBC count, neutrophils count and CRP. Rt-PCR.
Liu *et al*[23]	2020	Retrospective	122 pts COVID-19 positive. 48 pts with influenza pneumonia.	Influenza pneumonia	GGOs with consolidation. Nodules. Linear opacities. Interlobular septal thickening tree-in-bud sign.	More nodules, pleural effusions and tree-in-bud sign. Central + peripheral distribution.	RT-PCR for influenza or SARS-CoV-2.
Zhao *et al*[33]	2020	Retrospective	31 pts COVID-19 positive. 18 pts with influenza pneumonia.	Influenza pneumonia	-	More consolidations and pleural effusions.	RT-PCR
Wang *et al* [30]	2020	Retrospective	13 pts COVID-19 positive. 92 pts with influenza pneumonia.	Influenza pneumonia	GGOs and GGOs with consolidation	Inferior lobe involved. Cluster-like GGOs. Lesion with vague margin. Bronchial wall thickening.	Normal WBC count. Low lymphocyte count in Influenza B. No significative difference between two groups. RT-PCR.

pts: Patients; GGO: Ground-glass opacity; ILD: Interstitial lung disease; CAP: Community acquired pneumonia; WBC: White blood count; hs-CRP: High

sensitivity C-reactive protein; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PCT: Procalcitonin; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein.

advanced cases distinguished systemic sclerosis-related interstitial lung disease from interstitial pneumonia, as reported by Orlandi *et al*[17].

According to Shenavandeh *et al*[18], pulmonary nodules, mass lesions, and consolidation caused by lung hemorrhage and infarction due to small vessel vasculitis were typical for granulomatosis with polyangiitis.

Finally, extensive patchy exudates and consolidations in both lungs, faint GGOs on edge, and interlobular septal thickening were characteristic features for rheumatic pneumonia observed by Dai *et al*[16].

Although GGOs and consolidation characterized pulmonary contusion (usually caused by traffic accidents, falls, bumps, and crashes), a higher proportion of consolidations often associated with bilateral pleural effusion and subpleural atelectasis was observed when compared to COVID-19 disease. In addition, the radiological evolution was different in the two illnesses. No signs or few sheet shadows may be observed in pulmonary contusion 4-6 h after injury. The lung returned to normal after 7-10 d. Otherwise, in the case of COVID-19, the radiological pattern was long-lasting[20].

As in COVID-19 disease, bilateral GGOs with multilobe central and peripheral involvement were observed by Mazouz *et al*[19] in the case of fat embolism.

Differential diagnosis between COVID-19 pneumonia and cancer-related lung lesions

One out of two studies including cancer patients investigated the difference between COVID-19 disease and pulmonary toxicities caused by radiotherapy. GGOs with partial consolidation, lung fibrosis characterized by linear scarring, air bronchograms, irregular intralobular or interlobular septal thickening were typical radiation pneumonitis features. With the onset within 6 mo after completing radiotherapy and limited distribution to the irradiation field, CT lesions were distinguished from COVID-19 pneumonia by Zeng *et al*[28].

The study on cancer patients conducted by Zhang *et al*[29] focused on the similarities and discrepancies between COVID-19 pneumonia and early lung cancer. Although GGOs, air bronchogram, and cystic changes were present in both diseases, some differences were observed. Pure and mixed GGOs were most frequent in lung cancer, while COVID-19 patients tended to have more than one type of lung lesion. Contrary to COVID-19 pneumonia, characterized by patchy and bilateral lesions, unilateral and oval lesions were predominant in lung cancer patients. Air bronchogram was prevalent in COVID-19 patients, in contrast with cystic changes in lung cancer patients. Some radiological features were present only in COVID-19 pneumonia, such as reticular pattern, subpleural linear opacity, bronchial dilatation, centrilobular nodu-le, and the tree-in-bud sign. On the other hand, lobulated signs, pleural retraction, and vessel convergence signs were present in lung cancer patients but absent in those with COVID-19. More lobes and segments were involved in COVID-19 pneumonia compa-red to early lung cancer.

Differential diagnosis between COVID-19 pneumonia and another infective pneumonitis

In a retrospective study, Himoto *et al*[27] used five chest CT criteria to distinguish COVID-19 pneumonia from other infective respiratory diseases, such as Pneumococcal pneumonia, Moraxella pneumonia, Legionella pneumonia, not-specified bacterial or viral pneumonia, Pneumocystis pneumonia, and non-specific interstitial pneumonia. The differential patterns evaluated were: (1) GGO-predominant lesions; (2) GGO- and peripheral-predominant lesions; (3) bilateral GGO-predominant lesions; (4) bilateral GGO- and peripheral-predominant lesions; and (5) bilateral GGO- and predominant peripheral lesions without nodules, airway abnormalities, pleural effusion, and mediastinal lymphadenopathy. Compared to other infective respiratory diseases analyzed, COVID-19 pneumonia had bilateral GGO- and peripheral-predominant lesions without airway abnormalities, mediastinal lymphadenopathy, and pleural effusion [27].

Luo *et al*[22] developed an imaging score to distinguish COVID-19 pneumonia and non-COVID-19 pneumonia (Influenza pneumonia, Pneumocystis carinii pneumonia, Mycoplasma pneumonia, and CAP). Seven positive signs were identified: posterior part/lower lobe predilection, bilateral involvement, rounded GGO, subpleural band-

like GGO, crazy-paving pattern, peripheral distribution, and GGO with or without consolidation. Only one-lobe involvement, only central distribution, the tree-in-bud sign, and bronchial wall thickening were considered negative signs. The score ranged from -4 to 7 and was significantly higher in the COVID-19 group than in the non-COVID-19 group. Both diseases shared GGOs with or without consolidation. The tree-in-bud sign was observed in non-COVID-19 patients only. Rounded and subpleural bandlike GGO were more common in COVID-19 patients.

Similarly, other authors found that pure/mixed GGOs, interlobular septal thickening, crazy-paving patterns, halo signs, and consolidation were common both in COVID-19-positive and negative patients. The unique CT finding, potentially typical of COVID-19 disease, was a peripheral distribution of the pulmonary lesions[26] and a high proportion of rounded opacities. Bronchial wall thickening was a characteristic sign of Mycoplasma pneumonia[32].

Although GGOs and consolidations were present in both other viral pneumonia (adenovirus, influenza, parainfluenza, rhinovirus, and others) and COVID-19, central plus peripherical distribution, air bronchogram, pleural thickening, pleural effusion, and lymphadenopathy were more frequent in viral pneumonia[21].

Two studies investigated the differential radiological manifestations of COVID-19 lung disease and CAP. By using a new radiological model, Li *et al*[24] observed that CAP was characterized more often by nodular or consolidation shadows with or without patchy GGOs and more rarely by subtle mesh changes, dilatated small vessels, bronchiectasis, and lesion with the long axis parallel to the pleura compared to COVID-19 pneumonia. Moreover, lymphadenopathy, pleural effusion, pleural and bronchial wall thickening, fibrous tissue, lung cavity, and bullae were detected by other authors in CT scans of CAP affected patients, while these findings were absent or more rarely in COVID-19 patients[25]. Similar radiological signs were observed by Zhou *et al*[31] in *Streptococcus pneumoniae* CAP.

Consolidation, nodules, pleural effusion, and tree-in-bud signs were the radiological manifestation in influenza pneumonia in the analysis by Liu *et al*[23] and Zhao *et al*[33]. The distribution of the lesions (bilateral lobe *vs* inferior lobe), their margin (clear *vs* vague), and the GGO lesion involvement pattern (patchy or GGO associated with consolidation *vs* cluster-like involvement) distinguished COVID-19 from influenza pneumonia, according to Wang *et al*[30].

DISCUSSION

The current review focuses on the differential diagnosis between COVID-19 disease and other respiratory and non-respiratory disorders.

Since the early phase of the pandemic, radiological imaging has been employed to assess the suspicion of COVID-19 pneumonia in patients selected by clinical triage, demonstrating the potential for a standardized assessment of the degree of pulmonary involvement and prognostication purposes. Moreover, it has been used as a tool capable of complementing the limited sensitivity and time-consuming laboratory testing process for the SARS-CoV-2 infection detection[34-37].

Such a practical approach has found application in an unprecedented pandemic scenario, where the prevalence of the disease was extraordinarily high, with the awareness that the imaging findings of COVID-19 pneumonia were non-specific as reflecting the diffuse alveolar damage and organizing pneumonia with features shared by a broad spectrum of disorders[38,39]. Despite the increasing knowledge about radiological imaging's role in the pandemic, the actual diagnostic performance of different imaging modalities is still unclear, with reported specificities and sensitivities depending on several factors, from the duration of symptoms to the pre-test probability of the disease. Without articulating the relative merit of X-ray or lung ultrasound *vs* CT, the latter is generally recognized as more sensitive for early parenchymal disease, disease progression, and differential diagnoses, including acute heart failure and pneumonia caused by other pathogens[40]. Remarkably, caution is warranted when analyzing data about the specificity and sensitivity of CT in detecting COVID-19 pneumonia, as some of the most cited studies from the radiology literature seem to suffer from limitations that may lead to overreaching conclusions[16,41-43]. Among the studies included in the present analysis, Bai *et al*[21] recruited the most extensive study population in which differences between COVID-19 and viral pneumonia were evaluated[21]. Though these authors concluded that radiologists are likely to distinguish COVID-19 from viral pneumonia on chest CT with high specificity (*i.e.*, up to 94%), the lack of training information or specific diagnostic criteria in

their study suggests that such results could have been overestimated.

Similarly, other studies included in the present analyses should be interpreted with caution due to limitations such as selection bias or the relatively limited number of patients. Given this awareness, it is noticeable how some CT imaging findings, namely mucoid impactions, centrilobular nodules, lobar consolidation, and significant pleural effusion, have been consistently found to be less frequent in COVID-19 than in other types of pneumonia (Figures 2-4). Thus, they are potentially helpful in everyday practice to complement clinical data in triaging acute respiratory patients[22,23,25,31,44]. Notably, radiologists need to have consciousness of ancillary findings that can be encountered in association with typical pulmonary features of COVID-19 pneumonia, possibly mimicking diseases other than COVID-19 (*e.g.*, centrilobular solid nodules: polyhedral in shape and close to enlarged vessels within ground-glass opacities in COVID-19 pneumonia, while rounded or branching in minor airway diseases)[45].

Imaging findings typical of interstitial pneumonia may be found in asymptomatic COVID-19 patients[46]. Interestingly, incidental GGO showing accumulation of fluorine-18 fluorodeoxyglucose at the positron-emission tomography scan has been described in cancer patients with SARS-CoV-2 infection, raising the suspicion of tumor progression in cases of a false-negative RT-PCR result[47-49]. In those situations, an approach that includes a comparison with recent chest CT findings, as well as a close follow-up, would be appropriate.

When dealing with cancer patients, COVID-19 needs to be considered among diseases that may confound staging or treatment response assessment[50]. For obvious reasons, special attention will need to be given to patients being screened or treated for lung cancer. In our experience, different etiopathogenetic factors can coexist, and their respective inflammatory phenomena can be overlapped in the same patient, as shown in Figure 5, collecting the different CT patterns of five cancer patients who underwent differential diagnosis for pneumonitis.

Besides cancer progression, COVID-19 pneumonia has been investigated as a mimicker of early lung cancer, both potentially displaying as single or multifocal GGOs [29]. Unsurprisingly, in their retrospective study, Zhang *et al*[29] found a single location and nodular morphology as significantly more frequent in lung cancer than in COVID-19[29]. Although the authors are alert about the consequences of an inappropriate surgical approach in these patients, it is reasonable to assume that evaluating the temporal evolution of CT findings, symptoms, and molecular test results would allow avoiding such a diagnostic and therapeutic pitfall in most cases.

Radiotherapy and oncologic treatment, such as target therapy and immunotherapy, may induce lung toxicity, mimicking COVID-19 illness. Zeng *et al*[28] recruited suspected COVID-19 patients diagnosed with cancer and treated with radiation to explore the differential diagnosis between COVID-19 pneumonia and radiation pneumonitis. The location, extent, and distribution of the lung CT abnormalities were considered useful to differentiate these two entities, with acute radiation-induced pneumonitis usually displaying GGOs or consolidation in the irradiated lung in contrast to the predominantly peripheral, subpleural opacities described in COVID-19 pneumonia. Otherwise, the differential diagnosis between COVID-19 and immuno-related pneumonia is likely to be less straightforward. The issue is highly relevant, especially considering the expanding immune checkpoint inhibitor indications and their potential to induce unique pulmonary toxicities[51,52]. Pneumonitis is a rare but potentially severe side effect of immune checkpoint inhibitors, involving 2.7% of the patients treated with anti-programmed cell death 1 and anti-programmed death-ligand 1 monotherapy and 6.6% of the patients receiving the combination of anti-programmed cell death 1 and anti-cytotoxic T-lymphocyte antigen 4[53]. Several clinical and radiological presentations have been described. Dyspnea and cough are the most frequent symptoms, while fever occurs in 12% of cases[54]. These clinical manifestations could be further confounding for the differential diagnosis. From a radiology perspective, COVID-19 and immune-related pneumonia have a range of imaging manifestations that can substantially overlap, particularly in cases of organizing pneumonia pattern (*i.e.*, the most common pattern seen across all tumor treatments and regimens) and when leading to diffuse GGO and consolidation as a result of diffuse alveolar damage[51,52]. The varying sensitivity of molecular confirmation of SARS-CoV-2 infection and the low specificity of both entities' clinical manifestation renders even more complicated the correct diagnosis, mostly requiring a multidisciplinary discussion before deciding on patient management[55]. However, the simultaneous presence of other immune-related adverse events, such as diarrhea, skin toxicities, and thyroid alterations, with or without a high level of inflammatory factors (*i.e.*, interleukin-6, C-reactive protein) involved in the cytokine storm (the latter also shared with COVID-19), could lead to the hypothesis of pneumonitis most likely

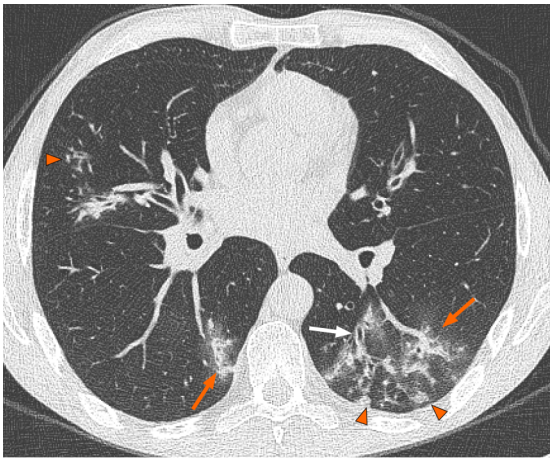


Figure 2 Axial computed tomography image of a 36-year-old man shows nodular (arrowheads) and peribronchovascular branching (orange arrows) opacities along with bronchial wall thickening (white arrow), which suggest a diagnosis other than coronavirus disease 2019 pneumonia. The patient was diagnosed with *Mycoplasma pneumoniae* pneumonia.

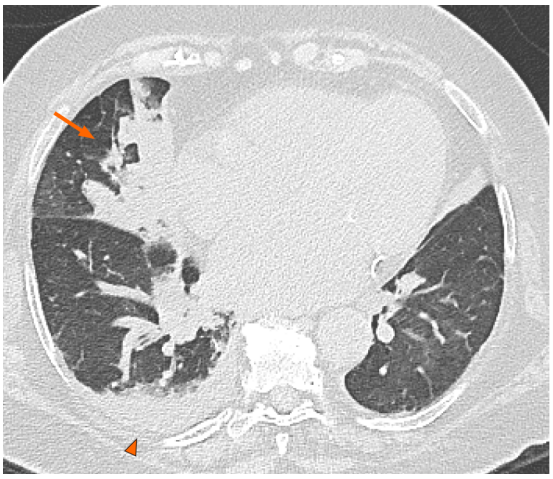


Figure 3 Axial computed tomography image shows right lung consolidation (arrow) and unilateral pleural effusion (arrowhead) in a 64-year-old man with bacterial pneumonia.

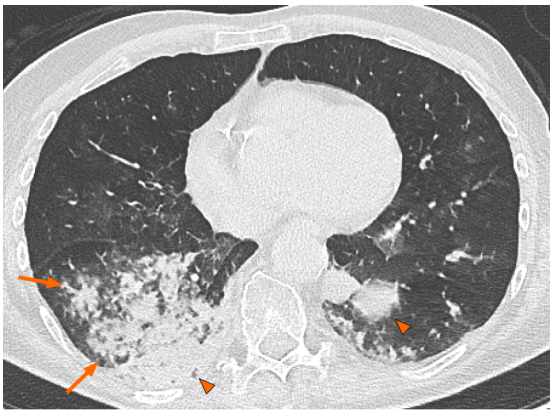


Figure 4 Axial computed tomography image in a 50-year-old woman diagnosed with bronchopneumonia shows confluent centrilobular nodules (arrows) and consolidation (arrowheads) mostly located in the lower lobes.

due to immunotherapy.

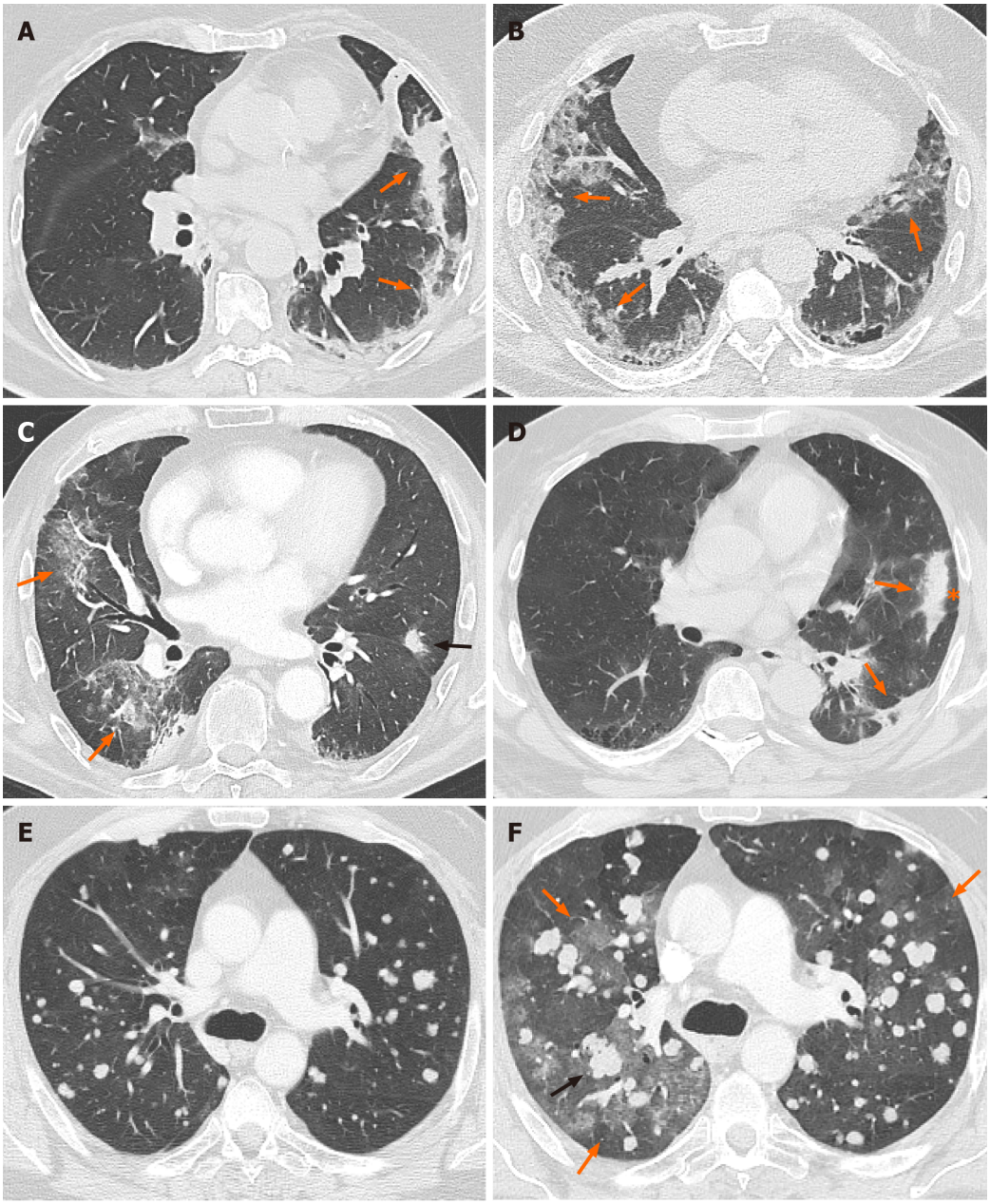


Figure 5 Axial computed tomography image. A: Axial computed tomography (CT) image of a 45-year-old patient with coronavirus disease 2019 showing left peripheral consolidation with perilobular distribution (arrows) suggesting organizing pneumonia; B: Axial CT image showing bilateral ground-glass opacities distributed in the subpleural regions (arrows) in a renal cancer patient confirmed with coronavirus disease 2019 pneumonia; C: Axial CT image showing multifocal ground-glass opacities in the right lung (orange arrows) and nodular consolidation (black arrow) in a renal cancer patient diagnosed with immune-related pneumonitis after treatment with nivolumab; D: Axial CT image of a patient suffering from immune-related pneumonitis showing multifocal, bandlike consolidation in the left lower lobe (arrows) with peripheral sparing (asterisk) suggesting organizing pneumonia; E and F: The last is a case of immune-related pneumonitis in a patient undergoing ipilimumab plus nivolumab for metastatic soft tissue sarcoma, whose baseline axial CT image (E) shows bilateral solid metastatic nodules; the axial CT image obtained after starting immunotherapy (F) shows new multifocal ground-glass opacities (orange arrows) with interval enlargement and an increasing number of pulmonary nodules (black arrow).

In addition to immune checkpoint inhibitors, other anticancer drugs such as tyrosine kinase inhibitors (*i.e.*, gefitinib, erlotinib, crizotinib, osimertinib, panitumumab, cetuximab, and others), mTOR inhibitors (everolimus, temsirolimus), and chemotherapy (topotecan, bleomycin, gemcitabine, and others) can induce an interstitial pneumonitis[56]. To date, neither radiological nor clinical features can help the physician in the differential diagnosis. The rapid development of cardiovascular complications, such as acute pericarditis, left ventricular dysfunction, acute myocardial injury, embolic complications due to coagulopathy, such as disseminated intravascular coagulation, venous thromboembolism, or massive pulmonary embolism, with or without detection of the virus, can address the diagnosis of COVID-19[57].

Although lymphopenia and a high level of D-dimer and C-reactive protein are often identified in COVID-19 patients, these laboratory findings are not unique and are inadequate to address the proper diagnosis, especially in cancer patients.

Our systematic review has several limitations, including the mostly retrospective nature and the heterogeneity of the included studies.

CONCLUSION

The patient's global view of epidemiological, clinical, radiological, and laboratory elements could help the physician overcome the diagnostic difficulties in the COVID-19 era.

ARTICLE HIGHLIGHTS

Research background

Several radiological features are shared by coronavirus disease 19 (COVID-19) pneumonia and other infective or non-infective pulmonary diseases.

Research motivation

The differential diagnosis of COVID-19 pneumonia is a radiological challenge.

Research objectives

To identify crucial radiological features of COVID-19 pneumonia reported by the literature and their differential diagnosis.

Research methods

We performed a systematic review with a descriptive aim.

Research results

Ground-glass opacity and consolidations are the most common computed tomography lesions in COVID-19 pneumonia and other respiratory diseases. Of the identified 133 studies, 18 were eligible and included in this review. Single lesion associated with pleural effusion and lymphadenopathies distinguishes COVID-19 pneumonia from early lung cancer. Only two studies included cancer patients, and the differential diagnosis with early lung cancer and radiation pneumonitis was performed. The onset of the lesions in the radiation fields only allows the differential diagnosis between COVID-19 pneumonia and radiation pneumonitis.

Research conclusions

Computed tomography scan is essential for the differential diagnosis of drug-induced pneumonitis, infectious pneumonia, and other conditions such as cancer progression.

Research perspectives

The focus on patients with cancer evidenced a wide lack of data in this field, suggesting at least retrospective collection of data in this population.

REFERENCES

1 **Xu S**, Li Y. Beware of the second wave of COVID-19. *Lancet* 2020; **395**: 1321-1322 [PMID: 32277876 DOI: 10.1016/S0140-6736(20)30845-X]

2 **World Health Organization**. Rolling updates on coronavirus disease (COVID-19): WHO characterizes COVID-19 as a pandemic. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen

3 **Sebhatu A**, Wennberg K, Arora-Jonsson S, Lindberg SI. Explaining the homogeneous diffusion of COVID-19 nonpharmaceutical interventions across heterogeneous countries. *Proc Natl Acad Sci USA* 2020; **117**: 21201-21208 [PMID: 32788356 DOI: 10.1073/pnas.2010625117]

4 **Looi MK**. Covid-19: Is a second wave hitting Europe? *BMJ* 2020; **371**: m4113 [PMID: 33115704 DOI: 10.1136/bmj.m4113]

5 **Ragnoli B**, Malerba M. Focus on the Potential Role of Lung Ultrasound in COVID-19 Pandemic: What More to Do? *Int J Environ Res Public Health* 2020; **17** [PMID: 33202769 DOI:

10.3390/ijerph17228398]
6 **Chung M**, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A, Li K, Li S, Shan H. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020; **295**: 202-207 [PMID: 32017661 DOI: 10.1148/radiol.2020200230]
7 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]
8 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]
9 **Han X**, Fan Y, Alwalid O, Li N, Jia X, Yuan M, Li Y, Cao Y, Gu J, Wu H, Shi H. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology* 2021; **299**: E177-E186 [PMID: 33497317 DOI: 10.1148/radiol.2021203153]
10 **Toussie D**, Voutsinas N, Finkelstein M, Cedillo MA, Manna S, Maron SZ, Jacobi A, Chung M, Bernheim A, Eber C, Concepcion J, Fayad ZA, Gupta YS. Clinical and Chest Radiography Features Determine Patient Outcomes in Young and Middle-aged Adults with COVID-19. *Radiology* 2020; **297**: E197-E206 [PMID: 32407255 DOI: 10.1148/radiol.2020201754]
11 **Peng QY**, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; **46**: 849-850 [PMID: 32166346 DOI: 10.1007/s00134-020-05996-6]
12 **Poggiali E**, Dacrema A, Bastoni D, Tinelli V, Demichele E, Mateo Ramos P, Marcianò T, Silva M, Vercelli A, Magnacavallo A. Can Lung US Help Critical Care Clinicians in the Early Diagnosis of Novel Coronavirus (COVID-19) Pneumonia? *Radiology* 2020; **295**: E6 [PMID: 32167853 DOI: 10.1148/radiol.2020200847]
13 **Colombi D**, Petrini M, Maffi G, Villani GD, Bodini FC, Morelli N, Milanese G, Silva M, Sverzellati N, Michieletti E. Comparison of admission chest computed tomography and lung ultrasound performance for diagnosis of COVID-19 pneumonia in populations with different disease prevalence. *Eur J Radiol* 2020; **133**: 109344 [PMID: 33091835 DOI: 10.1016/j.ejrad.2020.109344]
14 **Goyal N**, Chung M, Bernheim A, Keir G, Mei X, Huang M, Li S, Kanne JP. Computed Tomography Features of Coronavirus Disease 2019 (COVID-19): A Review for Radiologists. *J Thorac Imaging* 2020; **35**: 211-218 [PMID: 32427651 DOI: 10.1097/RTI.0000000000000527]
15 **Kristjansson M**, Bieluch VM, Byeff PD. Mycobacterium haemophilum infection in immunocompromised patients: case report and review of the literature. *Rev Infect Dis* 1991; **13**: 906-910 [PMID: 1962107 DOI: 10.1371/journal.pmed.1000097]
16 **Dai WC**, Zhang HW, Yu J, Xu HJ, Chen H, Luo SP, Zhang H, Liang LH, Wu XL, Lei Y, Lin F. CT Imaging and Differential Diagnosis of COVID-19. *Can Assoc Radiol J* 2020; **71**: 195-200 [PMID: 32129670 DOI: 10.1177/0846537120913033]
17 **Orlandi M**, Lepri G, Bruni C, Wang Y, Bartoloni A, Zammarchi L, Cometi L, Guiducci S, Matucci-Cerinic M, Bellando-Randone S. The systemic sclerosis patient in the COVID-19 era: the challenging crossroad between immunosuppression, differential diagnosis and long-term psychological distress. *Clin Rheumatol* 2020; **39**: 2043-2047 [PMID: 32514674 DOI: 10.1007/s10067-020-05193-2]
18 **Shenavandeh S**, Sefidbakht S, Iranpour P, Teimouri A, Hooshmandi S, Hooshmandi E, Athari M. COVID-19 and granulomatosis with polyangiitis (GPA): a diagnostic challenge. *Rheumatology (Oxford)* 2020; **59**: 2170-2171 [PMID: 32556292 DOI: 10.1093/rheumatology/keaa326]
19 **Mazouz S**, Aissaoui O, Fehdi MA, Nsiri A, AlHarrar R. COVID-19 suspicion revealed to be fat embolism syndrome. *Pan Afr Med J* 2020; **36**: 104 [PMID: 32821315 DOI: 10.11604/pamj.2020.36.104.23631]
20 **Chen LR**, Chen ZX, Liu YC, Peng L, Zhang Y, Xu Q, Lin Q, Tao YM, Wu H, Yin S, Hu YJ. Pulmonary contusion mimicking COVID-19: A case report. *World J Clin Cases* 2020; **8**: 1554-1560 [PMID: 32368550 DOI: 10.12998/wjcc.v8.i8.1554]
21 **Bai HX**, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, Pan I, Shi LB, Wang DC, Mei J, Jiang XL, Zeng QH, Egglin TK, Hu PF, Agarwal S, Xie FF, Li S, Healey T, Atalay MK, Liao WH. Performance of Radiologists in Differentiating COVID-19 from Non-COVID-19 Viral Pneumonia at Chest CT. *Radiology* 2020; **296**: E46-E54 [PMID: 32155105 DOI: 10.1148/radiol.2020200823]
22 **Luo L**, Luo Z, Jia Y, Zhou C, He J, Lyu J, Shen X. CT differential diagnosis of COVID-19 and non-COVID-19 in symptomatic suspects: a practical scoring method. *BMC Pulm Med* 2020; **20**: 129 [PMID: 32381057 DOI: 10.1186/s12890-020-1170-6]
23 **Liu M**, Zeng W, Wen Y, Zheng Y, Lv F, Xiao K. COVID-19 pneumonia: CT findings of 122 patients and differentiation from influenza pneumonia. *Eur Radiol* 2020; **30**: 5463-5469 [PMID: 32399710 DOI: 10.1007/s00330-020-06928-0]
24 **Li Z**, Zeng B, Lei P, Liu J, Fan B, Shen Q, Pang P, Xu R. Differentiating pneumonia with and without COVID-19 using chest CT images: from qualitative to quantitative. *J Xray Sci Technol* 2020; **28**: 583-589 [PMID: 32568167 DOI: 10.3233/XST-200689]
25 **Liu KC**, Xu P, Lv WF, Chen L, Qiu XH, Yao JL, Gu JF, Hu B, Wei W. Differential diagnosis of coronavirus disease 2019 from community-acquired-pneumonia by computed tomography scan and follow-up. *Infect Dis Poverty* 2020; **9**: 118 [PMID: 32843064 DOI: 10.1186/s40249-020-00737-9]
26 **Xie S**, Lei Z, Chen X, Liu W, Wang X, Dong Y, Guo Y, Duan Y, Cao H, Qin J, Lin B. Chest CT-

based differential diagnosis of 28 patients with suspected corona virus disease 2019 (COVID-19). *Br J Radiol* 2020; **93**: 20200243 [PMID: 32450727 DOI: 10.1259/bjr.20200243]

27 **Himoto Y**, Sakata A, Kirita M, Hiroi T, Kobayashi KI, Kubo K, Kim H, Nishimoto A, Maeda C, Kawamura A, Komiya N, Umeoka S. Diagnostic performance of chest CT to differentiate COVID-19 pneumonia in non-high-epidemic area in Japan. *Jpn J Radiol* 2020; **38**: 400-406 [PMID: 32232648 DOI: 10.1007/s11604-020-00958-w]

28 **Zeng Q**, Tang C, Deng L, Li S, Liu J, Wang S, Shan H. Differential Diagnosis of COVID-19 Pneumonia in Cancer Patients Received Radiotherapy. *Int J Med Sci* 2020; **17**: 2561-2569 [PMID: 33029098 DOI: 10.7150/ijms.46133]

29 **Zhang YJ**, Yang WJ, Liu D, Cao YQ, Zheng YY, Han YC, Jin RS, Han Y, Wang XY, Pan AS, Dai JY, Sun QF, Zhao FQ, Yang QY, Zhang JH, Liu SJ, Da Q, Guo W, Li CQ, Zhang WT, Wu H, Chen XS, Ji AQ, Xiang J, Chen K, Feng XJ, Zhang XF, Cao QQ, Qin L, Li J, Zhou M, Lu Y, Wang CF, Yan FH, Li HC, Qu JM. COVID-19 and early-stage lung cancer both featuring ground-glass opacities: a propensity score-matched study. *Transl Lung Cancer Res* 2020; **9**: 1516-1527 [PMID: 32953523 DOI: 10.21037/tlcr-20-892]

30 **Wang H**, Wei R, Rao G, Zhu J, Song B. Characteristic CT findings distinguishing 2019 novel coronavirus disease (COVID-19) from influenza pneumonia. *Eur Radiol* 2020; **30**: 4910-4917 [PMID: 32323011 DOI: 10.1007/s00330-020-06880-z]

31 **Zhou J**, Liao X, Cao J, Ling G, Ding X, Long Q. Differential diagnosis between the coronavirus disease 2019 and Streptococcus pneumoniae pneumonia by thin-slice CT features. *Clin Imaging* 2021; **69**: 318-323 [PMID: 33045476 DOI: 10.1016/j.clinimag.2020.09.012]

32 **Chi Q**, Dai X, Jiang X, Zhu L, Du J, Chen Y, Zheng J, Huang J. Differential diagnosis for suspected cases of coronavirus disease 2019: a retrospective study. *BMC Infect Dis* 2020; **20**: 679 [PMID: 32948121 DOI: 10.1186/s12879-020-05383-y]

33 **Zhao W**, Xie X, Liu J. The importance of distinguishing COVID-19 from more common respiratory illnesses. *Epidemiol Infect* 2020; **148**: e195 [PMID: 32873360 DOI: 10.1017/S0950268820001971]

34 **Sverzellati N**, Milanese G, Milone F, Balbi M, Ledda RE, Silva M. Integrated Radiologic Algorithm for COVID-19 Pandemic. *J Thorac Imaging* 2020; **35**: 228-233 [PMID: 32271278 DOI: 10.1097/RTI.0000000000000516]

35 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin O, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. *Radiology* 2020; **296**: 172-180 [PMID: 32255413 DOI: 10.1148/radiol.2020201365]

36 **Prokop M**, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**: E97-E104 [PMID: 32339082 DOI: 10.1148/radiol.2020201473]

37 **Feng Z**, Yu Q, Yao S, Luo L, Zhou W, Mao X, Li J, Duan J, Yan Z, Yang M, Tan H, Ma M, Li T, Yi D, Mi Z, Zhao H, Jiang Y, He Z, Li H, Nie W, Liu Y, Zhao J, Luo M, Liu X, Rong P, Wang W. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. *Nat Commun* 2020; **11**: 4968 [PMID: 33009413 DOI: 10.1038/s41467-020-18786-x]

38 **Tian S**, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol* 2020; **15**: 700-704 [PMID: 32114094 DOI: 10.1016/j.jtho.2020.02.010]

39 **Carsana L**, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, Rech R, Colombo R, Antinori S, Corbellino M, Galli M, Catena E, Tosoni A, Gianatti A, Nebuloni M. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020; **20**: 1135-1140 [PMID: 32526193 DOI: 10.1016/S1473-3099(20)30434-5]

40 **Driggin E**, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, Brown TS, Der Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol* 2020; **75**: 2352-2371 [PMID: 32201335 DOI: 10.1016/j.jacc.2020.03.031]

41 **Fang Y**, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296**: E115-E117 [PMID: 32073353 DOI: 10.1148/radiol.2020200432]

42 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]

43 **Raptis CA**, Hammer MM, Short RG, Shah A, Bhalla S, Bierhals AJ, Filev PD, Hope MD, Jeudy J, Kligerman SJ, Henry TS. Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date. *AJR Am J Roentgenol* 2020; **215**: 839-842 [PMID: 32298149 DOI: 10.2214/AJR.20.23202]

44 **Revel MP**, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A; European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European

Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; **30**: 4903-4909 [PMID: 32314058 DOI: 10.1007/s00330-020-06865-y]

45 **Silva M**, Ledda RE, Schiebler M, Balbi M, Sironi S, Milone F, Affanni P, Milanese G, Sverzellati N. Frequency and characterization of ancillary chest CT findings in COVID-19 pneumonia. *Br J Radiol* 2021; **94**: 20200716 [PMID: 33471553 DOI: 10.1259/bjr.20200716]

46 **Varble N**, Blain M, Kassin M, Xu S, Turkbey EB, Amalou A, Long D, Harmon S, Sanford T, Yang D, Xu Z, Xu D, Flores M, An P, Carrafiello G, Obinata H, Mori H, Tamura K, Malayeri AA, Holland SM, Palmore T, Sun K, Turkbey B, Wood BJ. CT and clinical assessment in asymptomatic and pre-symptomatic patients with early SARS-CoV-2 in outbreak settings. *Eur Radiol* 2021; **31**: 3165-3176 [PMID: 33146796 DOI: 10.1007/s00330-020-07401-8]

47 **Polverari G**, Arena V, Ceci F, Pelosi E, Ianniello A, Poli E, Sandri A, Penna D. ^{18}F-Fluorodeoxyglucose Uptake in Patient With Asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus Disease 2019) Referred to Positron Emission Tomography/Computed Tomography for NSCLC Restaging. *J Thorac Oncol* 2020; **15**: 1078-1080 [PMID: 32243920 DOI: 10.1016/j.jtho.2020.03.022]

48 **Zou S**, Zhu X. FDG PET/CT of COVID-19. *Radiology* 2020; **296**: E118 [PMID: 32142399 DOI: 10.1148/radiol.2020200770]

49 **Liu C**, Zhou J, Xia L, Cheng X, Lu D. 18F-FDG PET/CT and Serial Chest CT Findings in a COVID-19 Patient With Dynamic Clinical Characteristics in Different Period. *Clin Nucl Med* 2020; **45**: 495-496 [PMID: 32332319 DOI: 10.1097/RLU.0000000000003068]

50 **Boettcher AN**, Hammoud DA, Weinberg JB, Agarwal P, Mendiratta-Lala M, Luker GD. Cancer Imaging and Patient Care during the COVID-19 Pandemic. *Radiol Imaging Cancer* 2020; **2**: e200058 [PMID: 33778750 DOI: 10.1148/rycan.2020200058]

51 **Nishino M**, Hatabu H, Hodi FS. Imaging of Cancer Immunotherapy: Current Approaches and Future Directions. *Radiology* 2019; **290**: 9-22 [PMID: 30457485 DOI: 10.1148/radiol.2018181349]

52 **Kalisz KR**, Ramaiya NH, Laukamp KR, Gupta A. Immune Checkpoint Inhibitor Therapy-related Pneumonitis: Patterns and Management. *Radiographics* 2019; **39**: 1923-1937 [PMID: 31584861 DOI: 10.1148/rg.2019190036]

53 **Nishino M**, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2016; **2**: 1607-1616 [PMID: 27540850 DOI: 10.1001/jamaoncol.2016.2453]

54 **Naidoo J**, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J, Voss MH, Rudin CM, Rizvi H, Hou X, Rodriguez K, Albano M, Gordon RA, Leduc C, Rekhtman N, Harris B, Menzies AM, Guminski AD, Carlino MS, Kong BY, Wolchok JD, Postow MA, Long GV, Hellmann MD. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* 2017; **35**: 709-717 [PMID: 27646942 DOI: 10.1200/JCO.2016.68.2005]

55 **Naidoo J**, Reuss JE, Suresh K, Feller-Kopman D, Forde PM, Mehta Steinke S, Rock C, Johnson DB, Nishino M, Brahmer JR. Immune-related (IR)-pneumonitis during the COVID-19 pandemic: multidisciplinary recommendations for diagnosis and management. *J Immunother Cancer* 2020; **8** [PMID: 32554619 DOI: 10.1136/jitc-2020-000984]

56 **Sakai F**, Johkoh T, Kusumoto M, Arakawa H, Takahashi M. Drug-induced interstitial lung disease in molecular targeted therapies: high-resolution CT findings. *Int J Clin Oncol* 2012; **17**: 542-550 [PMID: 23138271 DOI: 10.1007/s10147-012-0489-2]

57 **Azer SA**. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New Microbes New Infect* 2020; **37**: 100738 [PMID: 32834902 DOI: 10.1016/j.nmni.2020.100738]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 September 28; 13(9): 258-313

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 9 September 28, 2021

REVIEW

MINIREVIEWS

SYSTEMATIC REVIEWS

CASE REPORT

World Journal of Radiology

Monthly Volume 13 Number 9 September 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Alberto S Tagliafico, MD, Associate Professor, Department of Health Sciences, University of Genova, Italy. alberto.tagliafico@unige.it

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJR* as 0.51.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
September 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 September 28; 13(9): 258-282

DOI: 10.4329/wjr.v13.i9.258

ISSN 1949-8470 (online)

REVIEW

Comprehensive literature review on the radiographic findings, imaging modalities, and the role of radiology in the COVID-19 pandemic

Aman Pal, Abulhassan Ali, Timothy R Young, Juan Oostenbrink, Akul Prabhakar, Amogh Prabhakar, Nina Deacon, Amar Arnold, Ahmed Eltayeb, Charles Yap, David M Young, Alan Tang, Subramanian Lakshmanan, Ying Yi Lim, Martha Pokarowski, Pramath Kakodkar

ORCID number: Aman Pal 0000-0001-7834-918X; Abulhassan Ali 0000-0001-7246-8444; Timothy R Young 0000-0001-8444-8571; Juan Oostenbrink 0000-0003-0103-4678; Akul Prabhakar 0000-0002-5451-8425; Amogh Prabhakar 0000-0001-9664-1520; Nina Deacon 0000-0002-8580-9081; Amar Arnold 0000-0002-8624-2996; Ahmed Eltayeb 0000-0002-3772-3179; Charles Yap 0000-0001-9477-6827; David M Young 0000-0001-6551-7527; Alan Tang 0000-0001-5744-3628; Subramanian Lakshmanan 0000-0002-2070-3657; Ying Yi Lim 0000-0003-1528-0191; Martha Pokarowski 0000-0001-6647-7029; Pramath Kakodkar 0000-0002-5288-1247.

Author contributions: Pal A, Ali A, Young TR, Oostenbrink J, Prabhakar A, Prabhakar A, Deacon N, Arnold A, Yap C, Young DM, Tang A, Lakshmanan S, and Kakodkar P performed acquisition and curation of the data; Pal A, Ali A, Young TR and Kakodkar P analyzed the data; Pal A, Ali A, Oostenbrink J, Prabhakar A, Prabhakar A, Deacon N, Arnold A, Eltayeb A, Eltayeb A, Yap C, Young DM, Tang A, and Kakodkar P performed interpretation of the data; Pal A, Ali A, Young TR, Oostenbrink J, Prabhakar A,

Aman Pal, Abulhassan Ali, Timothy R Young, Juan Oostenbrink, Akul Prabhakar, Amogh Prabhakar, Nina Deacon, Amar Arnold, Ahmed Eltayeb, Charles Yap, Subramanian Lakshmanan, Ying Yi Lim, Pramath Kakodkar, School of Medicine, National University of Ireland Galway, Galway H91 TK33, Galway, Ireland

David M Young, Department of Computer Science, Yale University, New Haven, CO 06520, United States

Alan Tang, Department of Health Science, Duke University, Durham, NC 27708, United States

Martha Pokarowski, The Hospital for Sick Kids, University of Toronto, Toronto M5S, Ontario, Canada

Corresponding author: Pramath Kakodkar, MD, Doctor, School of Medicine, National University of Ireland Galway, University Road, Galway H91 TK33, Galway, Ireland.
p.kakodkar1@nuigalway.ie

Abstract

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, over 103214008 cases have been reported, with more than 2231158 deaths as of January 31, 2021. Although the gold standard for diagnosis of this disease remains the reverse-transcription polymerase chain reaction of nasopharyngeal and oropharyngeal swabs, its false-negative rates have ignited the use of medical imaging as an important adjunct or alternative. Medical imaging assists in identifying the pathogenesis, the degree of pulmonary damage, and the characteristic features in each imaging modality. This literature review collates the characteristic radiographic findings of COVID-19 in various imaging modalities while keeping the preliminary focus on chest radiography, computed tomography (CT), and ultrasound scans. Given the higher sensitivity and greater proficiency in detecting characteristic findings during the early stages, CT scans are more reliable in diagnosis and serve as a practical method in following up the disease time course. As research rapidly expands, we have emphasized the CO-RADS classification system as a tool to aid in communicating the likelihood of COVID-19 suspicion among healthcare workers. Additionally, the utilization of other scoring

Prabhakar A, Deacon N, Arnold A, Eltayeb A, Yap C, Young DM, Tang A, Lakshmanan S, Lim YY, Pokarowski M, and Kakodkar P wrote the original draft; Pal A, Lim YY, Pokarowski M, and Kakodkar P performed the critical revision; All authors have read and approved the final manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Ireland

Peer-review report's scientific quality classification

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

Received: February 6, 2021
Peer-review started: February 6, 2021
First decision: March 17, 2021
Revised: March 28, 2021
Accepted: August 4, 2021
Article in press: August 4, 2021
Published online: September 28, 2021

P-Reviewer: Kashyap MK
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Liu JH

systems such as MuLBSTA, Radiological Assessment of Lung Edema, and Brixia in this pandemic are reviewed as they integrate the radiographic findings into an objective scoring system to risk stratify the patients and predict the severity of disease. Furthermore, current progress in the utilization of artificial intelligence *via* radiomics is evaluated. Lastly, the lesson from the first wave and preparation for the second wave from the point of view of radiology are summarized.

Key Words: Coronavirus; COVID-19; Computed tomography; Ultrasound; MuLBSTA Scoring system; Radiological Assessment of Lung Edema classification; Brixia score

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Since there is a rapid expansion and knowledge regarding the radiological findings in coronavirus disease 2019 (COVID-19), it is important to condense and collate the most important findings into a one-stop guide. We tried to undertake the same and provide digital images with markings that would be helpful for anyone interested in understanding the typical radiological features alongside the evidence-based findings of COVID-19 pneumonia. Additionally, we highlight and provide evidence-based findings regarding the predominantly utilized clinical scoring systems that integrate radiology.

Citation: Pal A, Ali A, Young TR, Oostenbrink J, Prabhakar A, Prabhakar A, Deacon N, Arnold A, Eltayeb A, Yap C, Young DM, Tang A, Lakshmanan S, Lim YY, Pokarowski M, Kakodkar P. Comprehensive literature review on the radiographic findings, imaging modalities, and the role of radiology in the COVID-19 pandemic. *World J Radiol* 2021; 13(9): 258-282
URL: https://www.wjgnet.com/1949-8470/full/v13/i9/258.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i9.258

INTRODUCTION

The current standard for the definitive diagnosis of coronavirus disease 2019 (COVID-19) is reverse-transcription polymerase chain reaction (RT-PCR) from the upper respiratory tract *via* nasopharyngeal and oropharyngeal swabs[1]. The diagnostic accuracy of real-time RT-PCR is as high as 95%[2]. However, the limitations of RT-PCR lies in its much lower diagnostic accuracy; it has high specificity but variable sensitivity ranging from 60%-70% to 95%-97%, respectively[3-5].

Medical imaging plays a key role in assisting the clinical decisions made towards the diagnosis, management, and follow-up of COVID-19 patients. This review presents the current literature related to the characteristics and key findings of COVID-19 in common radiological imaging modalities such as chest x-rays (CXRs), computed tomography (CT), and lung ultrasonography (LUS). To objectively stratify the severity of COVID-19, CXRs and CT scans are used in conjunction with various classifications systems such as CO-RADS, MuLBSTA, and the Radiological Assessment of Lung Edema (RALE) to facilitate the appropriate evaluation and treatment for infected cases. These are also explored within this review. Other imaging modalities such as magnetic resonance imaging (MRI), positron emission tomography (PET), and echocardiography are less commonly used but can be ordered to assess certain complications and treatment responses. Prior to reviewing these topics, the fundamental basics of COVID-19 pathophysiology are highlighted in the following section.

Pathophysiology of COVID-19

Aerosolization of respiratory droplets containing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the primary mode of transmission of COVID-19. The SARS-CoV-2 virion can further inoculate the mucous membranes *via* the facial T-zone (eyes, nose, and mouth). The current suggested model of pathogenesis for SARS-CoV-2 infection is composed of three phases: Viral replication, hyperactive immune system, and pulmonary destruction[6]. These phases are discussed in the following subsections.

Viral replication

Viral particles manifest their infectivity through replication within the host cell in the following five steps: Attachment, penetration, biosynthesis, maturation, and release [7]. SARS-CoV-2 binds with high affinity to angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2) receptors. Interestingly the ACE2 receptors are predominantly expressed with high density within the type II pneumocytes of the lung[8]. These receptors are also found in the heart (pericytes), ileum (enterocytes), kidney (podocytes), and bladder (urothelial cells)[8]. Once SARS-CoV-2 attaches to host receptors (ACE2 and TMPRSS2), the virion fuses with the membrane and enters the cell *via* endocytosis. Subsequently, inside the cell, the viral RNA enters the nucleus and alters the replication machinery to biosynthesize viral proteins. Upon maturation of the new viral particles, they are released to infect and continue their vicious cycle in other nearby cells[7].

Hyperactive immune system

Immune hyperactivity is a result of the stress-induced apoptosis of the affected cells and the viral RNA being recognized as a foreign genome by Toll-like receptors[9]. This leads to a cytokine storm (release of tumor necrosis factor, interleukin 6 [IL-6], IL-1β,

C-C motif chemokine ligand 2), which is stimulated by macrophages and dendritic cells and causes the infiltration of several inflammatory mediators in the alveolar-capillary interface[9]. Since there is a high density of ACE2 receptors along the peripheries of the lung parenchyma, the majority of damage early on is seen at these sites as a characteristic pulmonary ground-glass opacity (GGO) detected by a CT scan.

Pulmonary destruction

Although the purpose of inflammatory mediators is to fight against the virus until development of the adaptive immune system, their excessive infiltration damages this membrane, causing a build-up of fluid within the alveolar sacs and lung injury that further reduces ventilation[10]. The migration of fluid into the alveolar sacs is governed by the imbalance in Starling forces; $F = k([P_c - P_a] - s[\pi_c - \pi_a])$[11]. The diffuse alveolar damage caused by the viral particles results in an increased capillary wall permeability (high k value), thereby increasing the force at which fluid migrates from the capillaries to the alveolar space. Figure 1 summarizes the findings of Gralinski *et al* [12] as an illustration of the progressive development within an infected alveolus, both pathologically and radiologically[12]. The normal alveolar wall is comprised of type I and II pneumocytes, while the alveolar macrophages and surfactant reside in the alveolar space. In an acute setting of infection, the pneumocytes secrete inflammatory cytokines and exhibit cytopathic effects, while surfactant levels decrease. As the disease progresses, ventilation is impeded as pulmonary edema and airway debris coincide within the alveolar spaces, alongside the formation of hyaline membrane. Radiologically, the initial features of localized pulmonary edema is seen as GGOs (highly attenuated patches on CXR/CT) and as the severity of tissue damage increases, the pulmonary edema becomes more diffuse and is seen as wide areas of consolidation on the chest imaging modalities[13].

The radiodensities vary between each material and can be quantified using the Hounsfield scale, measured as Hounsfield units. Air, lung, ground glass, water, consolidation, and metal have radiodensities of -1000, -900, -800 to -100, 0, 30, and > 100, respectively[14]. The varying radiodensity of ground glass is associated with the severity of tissue damage and pulmonary edema as a more severe alveolar damage would elicit a higher radiodensity due to a greater fluid accumulation. Extreme tissue damage with complete alveolar consolidation presents as increased attenuation with anomalous opacities on chest imaging.

CHEST RADIOGRAPHY AND CT IMAGING

The role of imaging during the COVID-19 pandemic has yet to be fully explored. CXR and chest CT scans are not an official primary component of diagnosis but rather a supporting feature for diagnosis specifically to determine severity and the appropriate treatment response required. The high rate of false-negative results and fear of viral spread during sample transfers in RT-PCRs show the need for a systematic approach in the diagnosis of COVID-19 through a combination of clinical signs and radiological findings on CXR and CT, which are important in determining the severity of disease and guiding treatment responses[15]. It is important to note that chest CTs have the additional advantage of detecting changes of COVID-19 pneumonia in asymptomatic

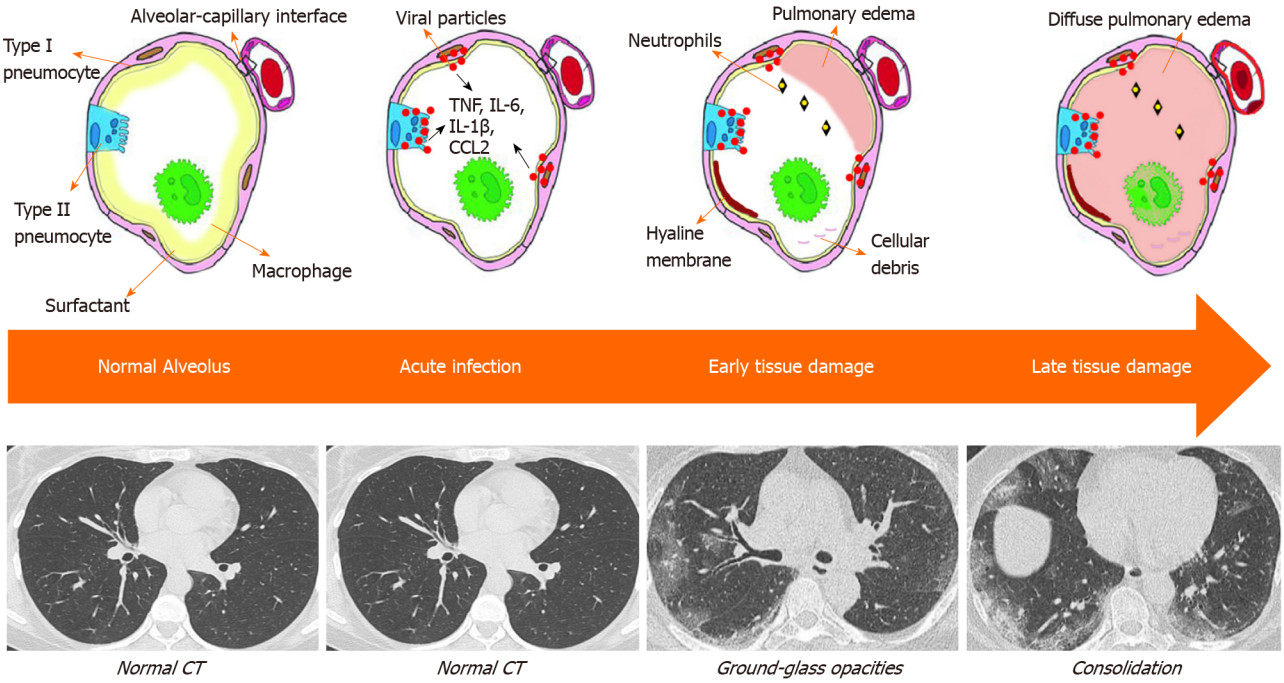


Figure 1 Model of infected lung through pathological and radiological perspectives.

patients[16].

CLASSICAL FINDINGS IN CHEST RADIOGRAPHY

Admitted in-patients presenting with COVID-19 provide a large repository of radiological images due to the ease of evaluations *via* solitary portable CXR. Findings of COVID-19 on CXR include hazy opacification, which is the radiographic equivalent to GGO found on a chest CT scan. These hazy opacifications have a predilection for the basal lung and its peripheries. These opacifications may be unilateral or bilateral. In severe cases, the middle to upper fields of the lung may become affected. In the penultimate disease stage (days 10-12), the areas of opacity coalesce and become denser. This presents as patchy consolidates similar to the pattern of acute respiratory distress syndrome (ARDS)[13]. The compilation of diagnostic factors such as signs, symptoms, oxygen saturation, and CXR appearance can offer a faster and inexpensive method for severity assessment. Most notable CXR findings included bilateral chest involvement 76.8% (95% confidence interval [CI]: 62.5%-87%), consolidation 75.5% (95%CI: 50.5%-91%), GGO 71% (95%CI: 40%-90%), and unilateral chest involvement in 16.5% (95%CI: 8.5%-29.5%)[17]. Some less common CXR findings include reticular interstitial thickening in 39.9% (n = 107/268), nodules 9.3% (n = 25/268), and pneumothorax, or pleural effusion (1%-3%)[18]. These findings could be a consequence of COVID-19 or pre-existing comorbidities, or just coincidental. Figure 2 shows a collection of chest radiographs with abnormal findings with a background of a positive SARS-CoV-2 PCR test. Examples of bilateral patchiness (Figure 2A), unilateral GGO (Figure 2B), pneumothorax (Figure 2C), and linear patchiness (Figure 2D) are modified from Singh *et al*[15], Martini *et al*[19], Rampa *et al*[20], and Kaufman *et al*[21]. Examples of nodular (Figure 2E) and reticular consolidations (Figure 2F) are modified from Yasin *et al*[22].

One large study (n = 1198) showed that the sensitivity and specificity of CXR for detecting features of COVID-19 pneumonia were 56% (95%CI: 51%-60%) and 60% (95%CI: 54%-65%), respectively[23]. In comparison, the chest CT provides an increase in sensitivity by 29% (95%CI: 19%-38%) in comparison to CXR[23]. This variable explains the limited usage of CXR in the screening, diagnosis, or follow-up of COVID-19 patients.

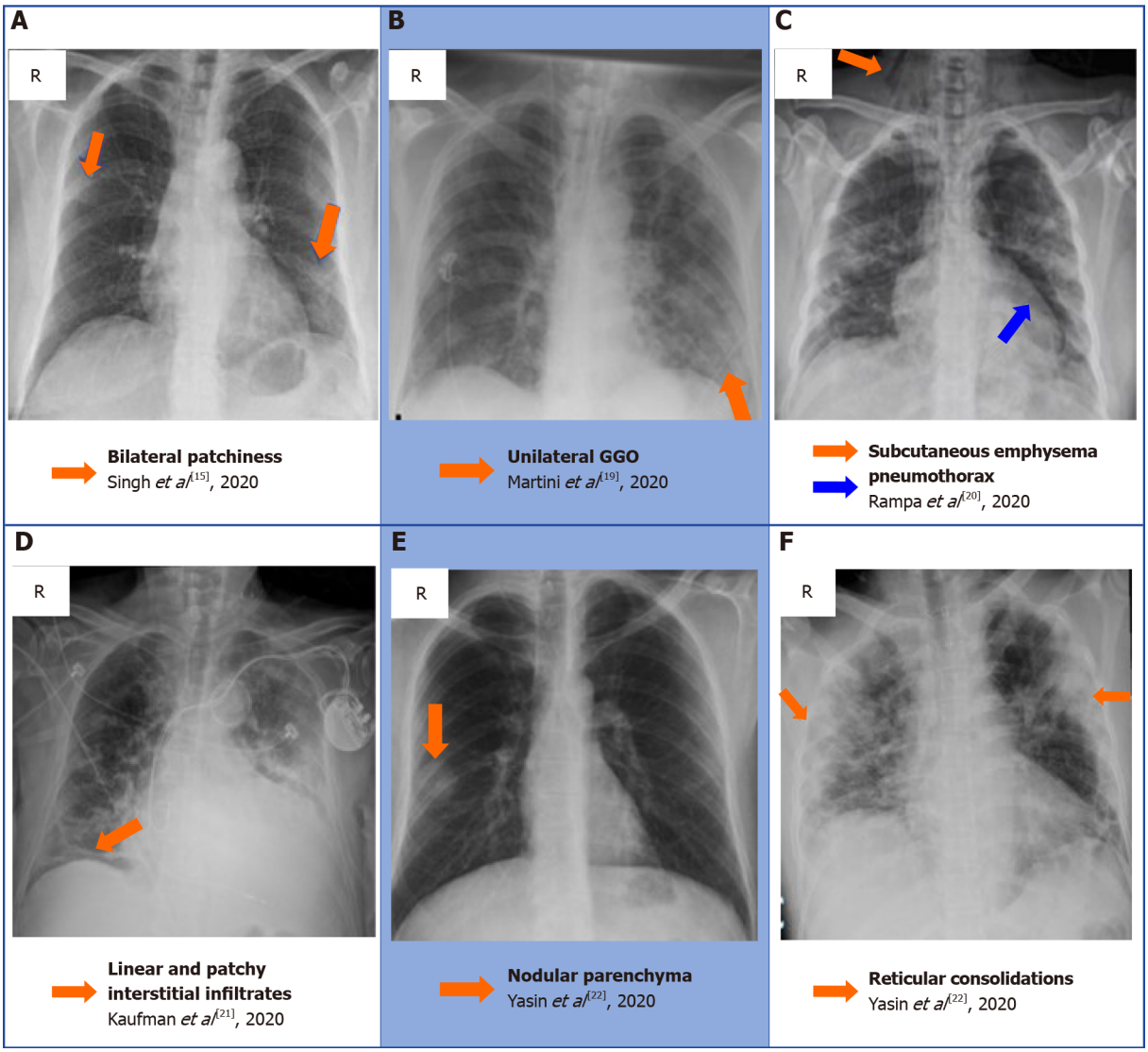


Figure 2 A collection of chest radiographs that displays some of the common and rare findings of coronavirus disease 2019 pneumonia [15,19-22]. A: Bilateral patchiness; B: Unilateral ground glass opacification; C: Subcutaneous emphysema secondary to a pneumothorax; D: Linear and patchy interstitial infiltrate in the right basal zone; E: Nodular appearance of the right lobe parenchyma; F: reticular appearance of the consolidation bilaterally. A: Citation: Singh B, Kaur P, Reid RJ, Shamoon F, Bikkina M. COVID-19 and Influenza Co-Infection: Report of Three Cases. *Cureus* 2020; 12: e9852. Copyright ©The Author(s) 2020. Published by Cureus; B: Citation: Martini K, Blüthgen C, Walter JE, Messerli M, Nguyen-Kim TD, Frauenfelder T. Accuracy of Conventional and Machine Learning Enhanced Chest Radiography for the Assessment of COVID-19 Pneumonia: Intra-Individual Comparison with CT. *Journal of Clinical Medicine* 2020;.9: 3576 Copyright ©The Author(s) 2020. Published by MDPI, Basel, Switzerland; C: Citation: Rampa L, Miceli A, Casilli F, Biraghi T, Barbara B, Donatelli F. Lung complication in COVID-19 convalescence: A spontaneous pneumothorax and pneumatocele case report. *Journal of Respiratory Diseases and Medicine* 2020; 2. Copyright ©The Author(s) 2020. Published by Open-access article; D: Citation: Kaufman A, Naidu S, Ramachandran S, Kaufman D, Fayad Z, Mani V. Review of radiographic findings in COVID-19. *World Journal of Radiology* 2020; 12: 142-55. Copyright ©The Author(s) 2020. Published by Baishideng Publishing Group Inc; E and F: Citation: Yasin R, Gouda W. Chest X-ray findings monitoring COVID-19 disease course and severity. *The Egyptian Journal of Radiology and Nuclear Medicine* 2020; 51: 193. Copyright ©The Author(s) 2020. Published by BMJ.

CLASSICAL CT FINDINGS OF COVID-19 PNEUMONIA

While CXR is a practical method of screening, a recent meta-analysis showed that chest CTs are superior in the screening and assessment of COVID-19 pneumonia due to its increased sensitivity of 91.9% (95%CI: 89.8%-93.7%)[2]. CT is proficient in detecting early signs of COVID-19 pneumonia in comparison to CXR. This is evident by the detection of early-stage GGOs and consolidative opacities, which are often not visible on CXR or may appear normal with minimal interstitial markings[24]. In similar patients where CXR detects minimal interstitial markings, subtle opacities, or occult signs, CT would display identifiable GGO. Figure 3 shows a summary of the meta-analysis of classical and ancillary CT imaging findings by Bao *et al*[25].

Ancillary late-stage CT finding of COVID-19 pneumonia includes crazy-paving, which is defined by the Fleischner Society as diffuse GGO with superimposed

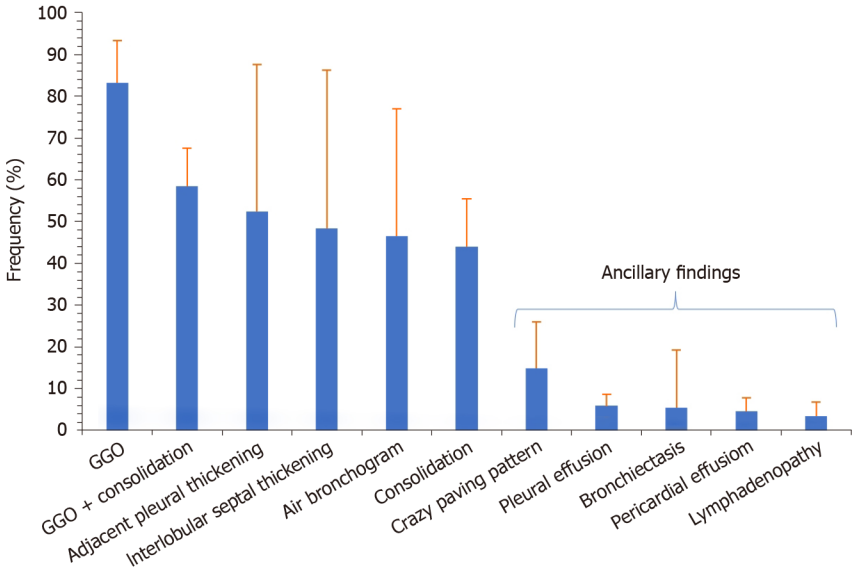


Figure 3 Summary of the frequency distribution of classical and ancillary computed tomography imaging findings in coronavirus disease 2019 pneumonia. The whiskers indicate the 95% confidence interval. GGO: Ground-glass opacity.

thickened intralobular lines and interlobular septa. The discovery of crazy-paving on a CT image is radiographic evidence of progressive COVID-19[26]. Additionally, diffuse patchy consolidation with reticular configuration becomes more predominant later in the disease course. Other classical chest CT findings that rule-in COVID-19 are lateralization of GGO early in the disease course, with multifocal, bilateral, and basilar lobe predominance, peripheral GGO with a rounded or oval morphology[18]. Figure 4 shows a collection of some notable classical chest CT findings in the axial plane of COVID-19 patients. Examples of classical findings such as GGOs (Figure 4A), air bronchograms (Figure 4B), bronchial thickening (Figure 4E), and pleural adhesions (Figure 4F) are all modified from Fu *et al*[27]. Additionally, examples of GGO superimposed with consolidation (Figure 4D) and crazy paving sign (Figure 4C) are modified from Gillespie *et al*[26] and Ali *et al*[28].

Additionally, Figure 5 shows the common lobes wherein classical CT findings of COVID-19 are distributed based on the findings of a meta-analysis by Bao *et al*[25]. Although the exact mechanism is unidentified, the increased incidence of findings in the lower lobes may be related to the anatomical structure of the trachea and bronchi, alongside the gravitational force that allows the virion particles to settle at the base more readily. Furthermore, since the right main bronchus bifurcates at a smaller angle and is wider than the left main bronchus, the virion particles can travel more easily towards the right lower lobe.

NON-CLASSICAL CT FINDINGS OF COVID-19 PNEUMONIA

Less commonly reported imaging findings that may help to rule-in COVID-19 is subsegmental vascular engorgement[29]. Furthermore, another uncommon but positive feature that rules in COVID-19 is the atoll sign on CT, also referred to as the reverse halo sign[18]. This is defined as a focal rounded area of GGO which is surrounded by a complete or nearly complete ring of denser consolidation which is observed on CT[30]. Other causes of the reverse-halo sign may be chronic lung injury, and notably, may raise the concern of pulmonary infarction. Interestingly, one meta-analysis indicates that these non-classical CT findings might be more common than previously predicted. Figure 6 shows the summary of results from a meta-analysis conducted by Ojha *et al*[31] to tabulate the incidence of non-classical CT findings in COVID-19 patients.

Figure 7 displays a collection of chest CTs in the axial plane that are examples of the ancillary findings in COVID-19. Examples of vascular enlargement (Figure 7A) are modified from Kwee *et al*[32]. Examples of subpleural curvilinear opacities (Figure 7B) and reverse halo sign (Figure 7F) are modified from Kong *et al*[33]. Additionally, examples of reticular pattern (Figure 7C), pulmonary nodules (Figure 7D), and

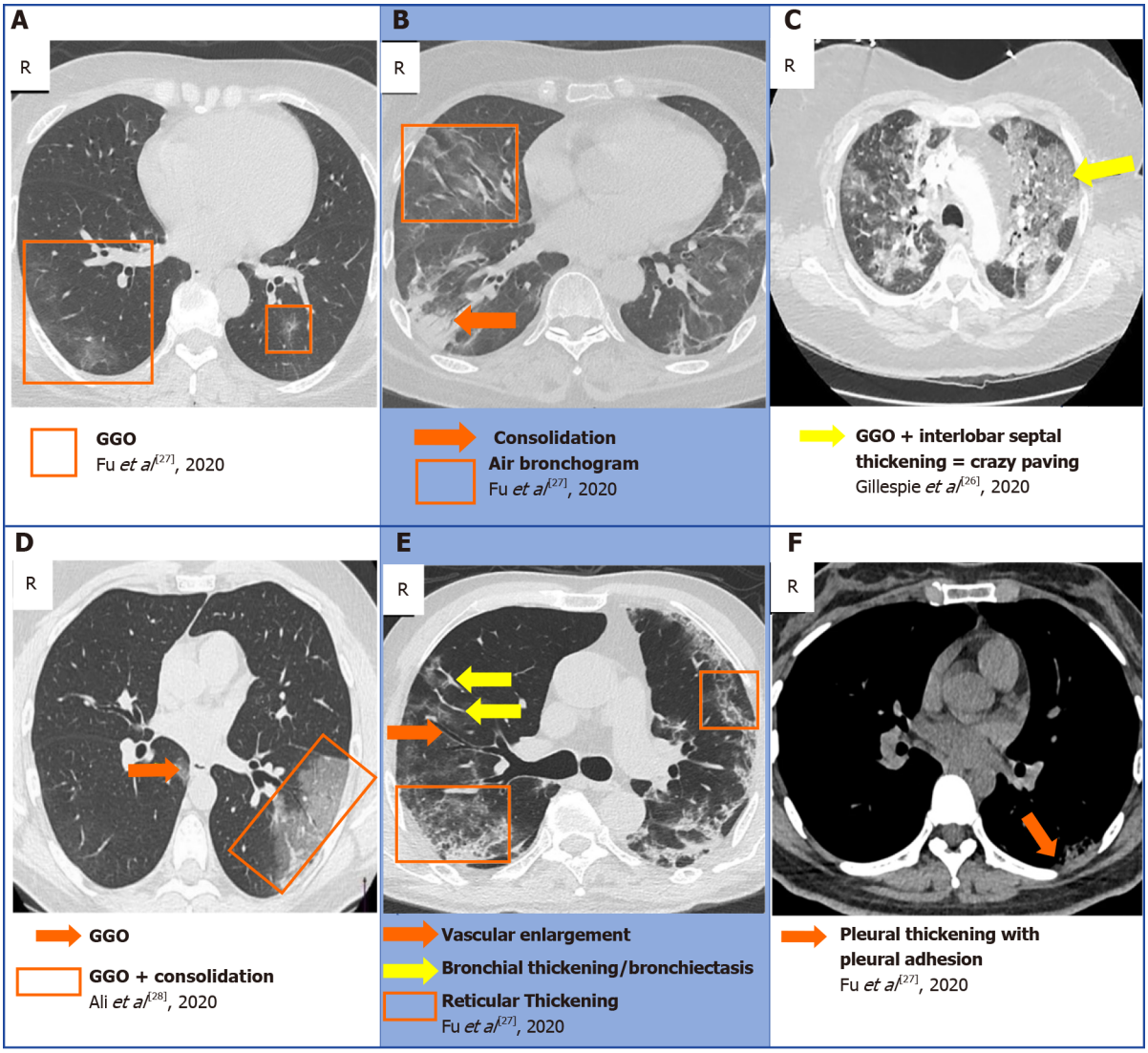


Figure 4 A collection of chest computed tomography that displays some of the classical findings of coronavirus disease 2019 pneumonia[26-28]. A: Ground-glass opacity (GGO); B: Consolidation and air bronchogram; C: Crazy paving; D: GGO superimposed with consolidation; E: Bronchiectasis, reticular thickening, with vascular enlargement; F: Pleural adhesion. A, B, E and F: Citation: Fu Z, Tang N, Chen Y, Ma L, Wei Y, Lu Y, Ye K, Liu H, Tang F, Huang G, Yang Y, Xu F. CT features of COVID-19 patients with two consecutive negative RT-PCR tests after treatment. *Science Report* 2020; 10: 11548. Copyright ©The Author(s) 2020. Published by Springer Nature; C: Citation: Gillespie M, Flannery P, Schumann JA, Dincher N, Mills R, Can A. Crazy-Paving: A Computed Tomographic Finding of Coronavirus Disease 2019. *Clinical Practice and Cases in Emergency Medicine* 2020; 4: 461-463. Copyright ©The Author(s) 2020. Published by UC Irvine; D: Citation: Ali TF, Tawab MA, ElHariri MA. CT chest of COVID-19 patients: what should a radiologist know? *Egyptian Journal of Radiology and Nuclear Medicine* 2020; 51: 120. Copyright ©The Author(s) 2020. Published by Springer Nature.

bilateral hilar lymphadenopathy (Figure 7E) are modified from Meirelles *et al*[34], Zhang *et al*[35], Mughal *et al*[36], respectively.

Negative features that rule-out COVID-19 include lobar consolidation, which is more commonly seen in bacterial pneumonia rather than COVID-19 pneumonia, along with lack of GGO. Moreover, in early disease, there is a notable absence of features such as pleural effusion, mediastinal lymphadenopathy, lung cavitation and discrete pulmonary nodules such as the tree-in-bud sign in centrilobular nodules[24]. Ultimately, CT has an extremely high sensitivity of 94% in the detection of COVID-19; however, due to multiple pathologies which may be causative for the features seen in CT; CT has a particularly poor, and varying specificity of 25%-80%[37].

NON-COVID-19 CAUSES OF GGO

There are many causative pathologies unrelated to COVID-19, which may present as GGO on imaging, and this is the reason for the low specificity of CT imaging (25.1%, [95%CI: 21.0%-29.5%]) in diagnosing COVID-19 pneumonia[2]. Acute causes have

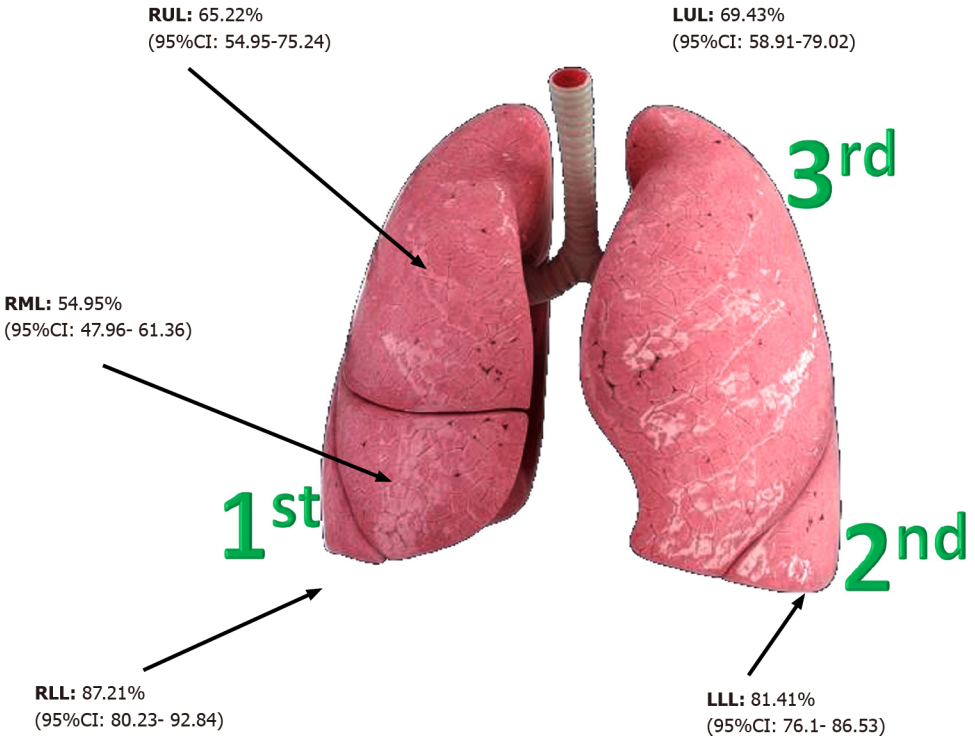


Figure 5 Summary of the frequency distribution of lesions in the lung lobes on computed tomography imaging of coronavirus disease 2019 patients. CI: Confidence interval; LLL: Left lower lobe; LUL: Left upper lobe (LUL); RLL: Right lower lobe; RML: Right middle lobe; RUL: Right upper lobe.

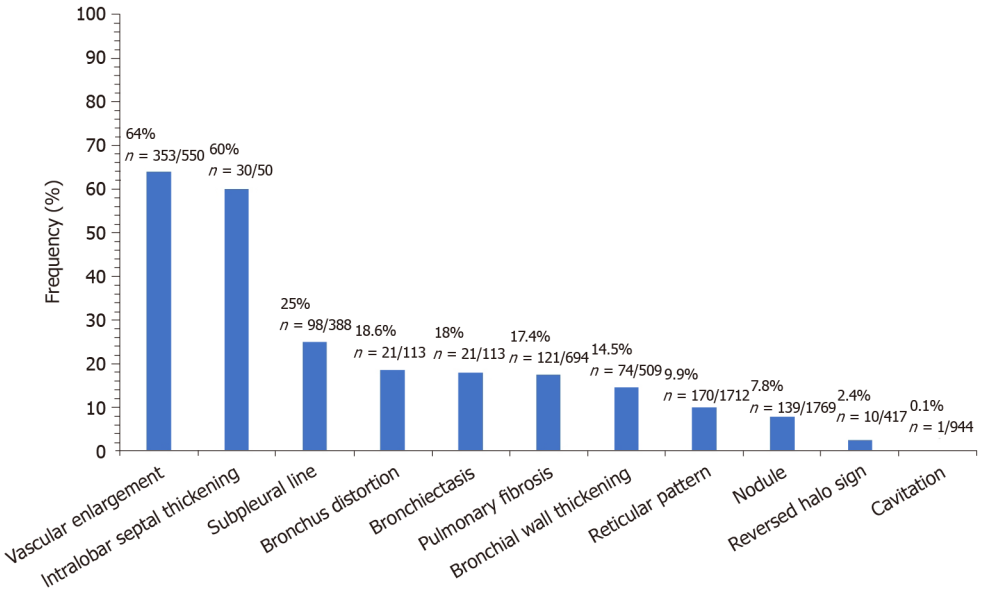


Figure 6 Summary of the frequency distribution of classical and ancillary computed tomography imaging findings in coronavirus disease 2019 pneumonia. The whiskers indicate the 95% confidence interval. The data are adapted from the meta-analysis conducted by Ojha *et al*[31].

abrupt signs on imaging arising in less than 4 wk. This may be pneumonia caused by a myriad of viruses such as influenza A or B, herpes simplex virus type 1, and cytomegalovirus[10]. In addition, acute eosinophilic pneumonia (AEP) may present as bilateral patchy GGO areas with interlobular septal thickening[38]. Drug toxicity due to cytotoxic drugs such as cyclophosphamide or bleomycin may manifest as scattered or diffuse areas of GGO[39]. Additional presentations may be due to chronic diseases lasting greater than 4 wk. Chronic eosinophilic pneumonia may also give rise to similar signs as AEP. Moreover, early lung cancer such as lung adenocarcinoma may be detected early by the appearance of GGO, improving surgical outcomes[40]. Ultimately, the varying causes of GGO on imaging demonstrates why CT alone is not

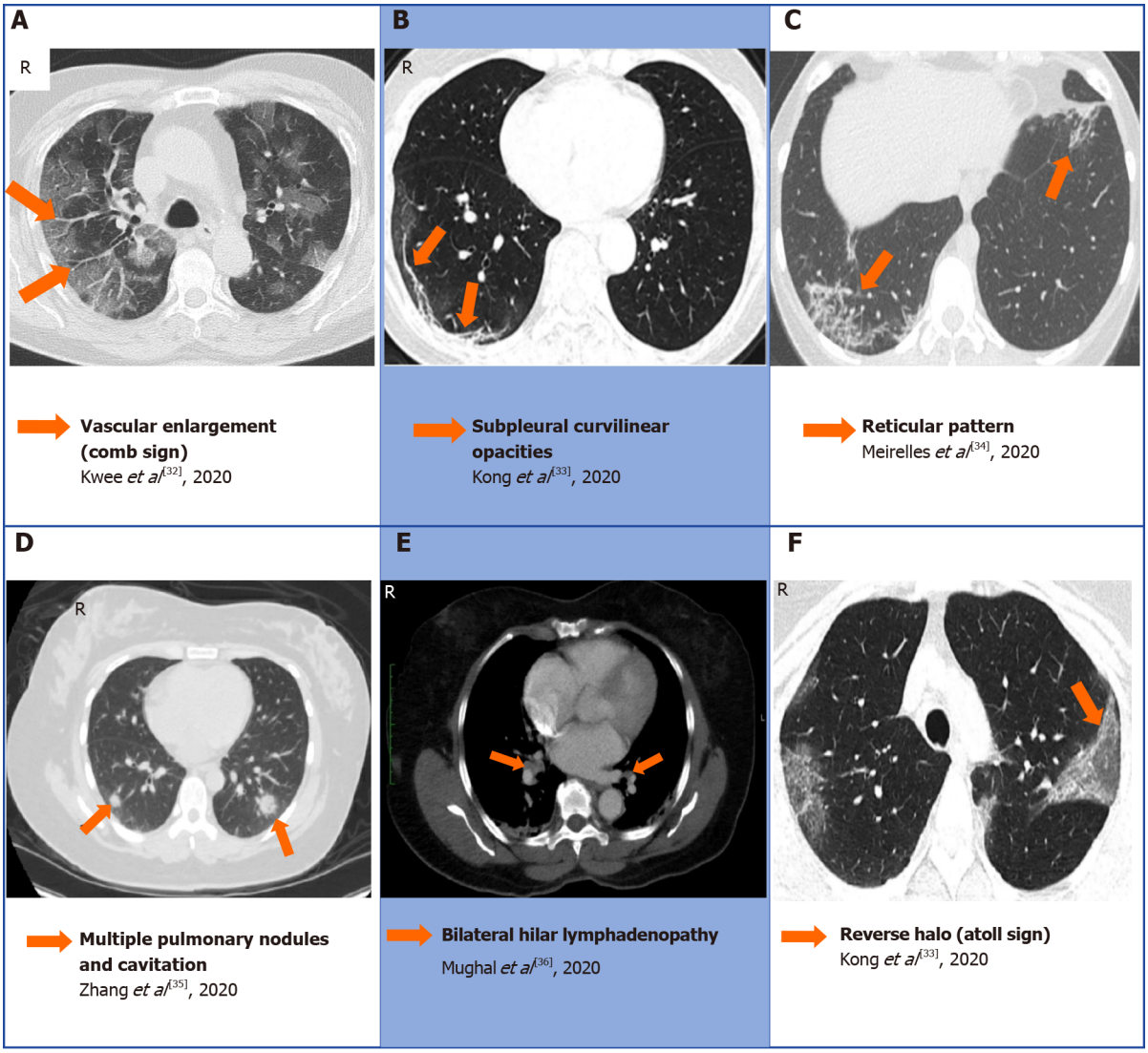


Figure 7 A collection of chest computed tomography that displays some of the atypical findings of coronavirus disease 2019 pneumonia [32-36]. A: Comb sign in the right lobe characterized by vascular enlargement; B: Curvilinear opacities in the subpleural area; C: Reticular pattern bilaterally; D: Multiple nodules and cavitation; E: Bilateral hilar lymphadenopathy; F: Atoll sign also known as reverse halo. A: Citation: Kwee TC, Kwee RM. Chest CT in COVID-19: What the radiologist needs to know. *Radiographics* 2020; 40: 1848-1865. Copyright ©The Author(s) 2021. Published by Radiographics; B and F: Citation: Kong W, Agarwal PP. Chest imaging appearance of COVID-19 infection. *Radiology: Cardiothoracic Imaging* 2020; 2: e200028. Copyright ©The Author(s) 2020. Published by the Radiological Society of North America, Inc; C: Citation: Meirelles GSP. COVID-19: A brief update for radiologists. *Radiologia Brasileira* 2020; 53: 320-328. Copyright ©The Author(s) 2020. Published by Radiology brasil; D: Citation: Zhang Q, Douglas A, Abideen ZU, Khanal S, Tzarnas S. Novel coronavirus (2019-nCoV) in disguise. *Cureus* 2020; 12: e7521. Copyright ©The Author(s) 2020. Published by Cureus; E: Citation: Mughal MS, Rehman R, Osman R, Kan N, Mirza H, Eng MH. Hilar lymphadenopathy, a novel finding in the setting of coronavirus disease (COVID-19): A case report. *Journal of Medical Case Reports* 2020; 14: 124. Copyright ©The Author(s) 2020. Published by BMC.

enough to accurately diagnose a patient with COVID-19 without clinical context, medication history, and RT-PCR/serology COVID-19 testing.

TIME COURSE: LAGGING OF COVID-19 FEATURES ON RADIOLOGICAL IMAGING

Although the preliminary imaging modality for patients presenting with COVID-19 is a solitary portable anteroposterior chest radiograph, many patients will have an early negative CXR/CT result. This can be due to a lack of macroscopic lung involvement at the time of presentation or minute findings on CXR/CT. During the early stages of disease (0-3 d), the viral particles take over host cell machinery, replicating and inducing a cytokine storm in the form of an acute infection. Gu *et al*[41] reported that nearly 13% of CT scans depict a normal finding in this early phase, while 63.2% of the cases exhibit a classical GGO appearance. A proposed hypothesis suggests that the

SARS-CoV-2 virion has not accumulated at an adequate density to induce pulmonary parenchymal damage. Therefore, the chest CT appears as a minimally hazy opacification with normal-appearing underlying vessels and bronchial structures. As the disease course progresses to the intermediate stage (4-7 d), there will be diffuse alveolar damage and GGO evolves into consolidation. The majority of the structures on chest CT will appear obscured in comparison to the primary GGO feature seen in the early stages. In the final stage (8-14 d), fibrotic lesions are significantly increased due to scarring of the lung tissue secondary to the resolution of organizing pneumonia [42]. Consolidation is also markedly enhanced in over 78% of the cases; however, the fibrotic lesions help distinguish the case presentation of late-stage from intermediate-stage disease in the majority of patients. Figure 8 summarizes the frequencies of typical CT findings (GGO, consolidation, fibrosis) based on the temporal stages of disease according to data from Gu *et al*[41].

ULTRASOUND IMAGING

LUS

LUS is an established imaging test for detecting various lung abnormalities, and in the context of COVID-19, may help clinicians with the diagnosis and evaluation of disease severity. Furthermore, it is useful for prognostic stratification and assessing the development of disease, and has assisted with the management of associated respiratory complications[43-46]. In comparison to CXR or CT, bedside LUS is faster, non-invasive, and radiation-free[47,48]. Point-of-care ultrasound (POCUS) machines are portable, allowing clinicians to assess patients at their bedside. This mitigates the need for patient mobilization to the radiology unit, thereby decreasing the risk of exposure to other patients[49,50]. POCUS is also economical, easy to learn, repeatable, and can obtain results of high reproducibility[51,52]. Moreover, POCUS offers an alternative imaging modality to triage patients' COVID risk levels and to streamline the pathway to warrant a requisition for second-level imaging or interventional management[51]. Heightened transmission of COVID-19 in healthcare workers has highlighted the importance of LUS in providing the option of concomitant execution of clinical examination and lung imaging at the bedside by the same physician[53,54].

CLASSICAL ULTRASOUND SIGNS: A AND B LINES

A- and B-lines are ultrasonographic artifacts that can be seen during the ultrasonography of an aerated lung. A-lines are typically horizontal artifacts that represent a normal lung surface[55]. B-lines are vertical, comet tail-like artifact indicating subpleural interstitial edema, likely representing reverberations generated by thickened interlobular septa and other subpleural structures[56]. In a normal lung ultrasound, the A-lines are horizontal to pleura and typical B-line patterns include a single cone-shaped line, single thin or thick line, or subpleural consolidation without air bronchogram[57].

ULTRASONOGRAPHIC PATTERNS IN COVID-19

Clear ultrasonographic patterns can be found in patients with COVID-19. Large numbers of B-lines, irregularity of the pleural line, and small clusters of subpleural pulmonary consolidations also frequently occur in the posterior and inferior areas[54,58]. Poggiali *et al*[44] concluded a strong correlation between LUS findings and concurrent CT scans in patients (n = 12) with COVID-19. These results also revealed diffuse B patterns and bilateral lung involvement with GGO in all of these patients [58]. Additionally, both imaging modalities also detected organizing pneumonia in four patients[59]. A summary of results from Norbedo *et al*[59] and McDermott *et al* [60] showed typical LUS findings in pediatric and adult patients with COVID-19. The literature review conducted by Norbedo *et al*[59] in pediatric patients (n = 18) with COVID-19 revealed LUS findings of B-line vertical artifacts, pleural irregularities, and small subpleural consolidations, as well as white patchy lung areas. A similar review conducted by Norbedo *et al*[59] on adult patients (n = 43) with COVID-19 revealed consistent LUS findings; irregular B-lines (focal), multifocal and confluent; thickening of pleural line with pleural line subpleural consolidations; and a variety of patterns

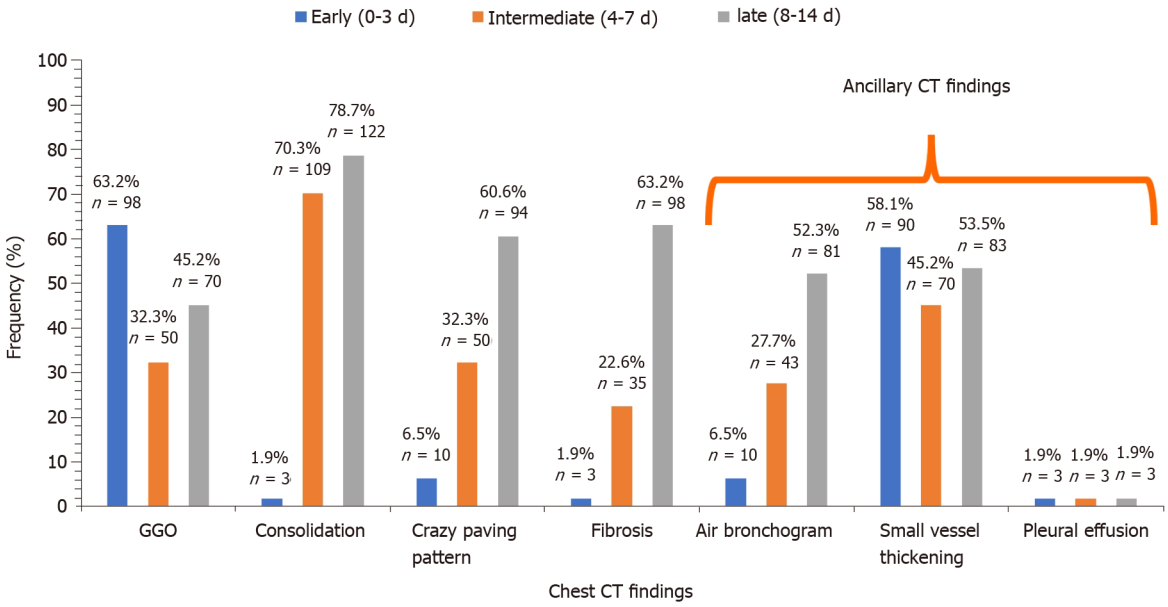


Figure 8 Summarizes the frequencies of chest classical and ancillary computed tomography findings at different stages of disease progression (early [*n* = 155], intermediate [*n* = 155], and late [*n* = 155]). Data acquired from Gu *et al*[41].

including multifocal small, non-translobar, and translobar with occasional mobile air bronchograms. The authors also concluded that pleural effusion in COVID-19 patients is uncommon[59].

LUS is able to detect dynamic changes associated with COVID-19. The main early-stage ultrasound finding was focal B-lines, which becomes multifocal and confluent as the disease progresses with further development of consolidations. During convalescence, B-lines and consolidations gradually disappear and are replaced by A-lines[57,61,62].

Interestingly, one study showed that LUS findings in patients with COVID-19 pneumonia exhibited typical patterns consistent with COVID-19 in 38.5% of cases (*n* = 52) and atypical patterns in 61.5% of cases (*n* = 83)[63]. The ability of LUS to diagnose COVID-19 can be inferred from its sensitivity of 76.9%, specificity of 77.1%, positive predictive value of 57.7%, and negative predictive value of 89.2%[63]. Additionally, when comparing LUS to chest CT, the results suggest a sensitivity and specificity of 65% and 72.7%, respectively[63]. Figure 9 shows a simplified flowchart for triaging patients presenting with respiratory symptoms during the COVID-19 pandemic in the emergency department as suggested by Schmid *et al*[63].

12-ZONE SCORING SYSTEM

In clinical practice, there are various scoring systems to quantify the extent of lung involvement, and in the context of COVID-19, we observed the most prominent one to be the 12-zone scoring system, used as a tool to assess regional and global lung aeration in ARDS as well as COVID-19 pneumonitis[61,64-66]. A total of 12 areas in the right and left lung are examined, namely the anterosuperior, anteroinferior, laterosuperior, lateroinferior, posterosuperior, and posteroinferior lung regions on each side of the lung. Scoring of each area is performed in accordance with the most severe lung ultrasound finding detected in the corresponding intercostal spaces and is given a score from 0-3, tallying up to a maximum of 36. Figure 10 outlines the assessed zone and the criteria for each of the values. The Australasian College of Emergency Medicine proposed a severity classification of patients based on this score as normal (0), mild (1-5), moderate (> 5-15), and severe (≥ 15)[65].

One study by Speidel *et al*[67] showed that the lung ultrasound scoring system (LUSS) had promising diagnostic efficacy with an odds ratio (OR) of 1.30, a 95%CI between 1.09 to 1.54 (P = 0.003), and an area under the curve (AUC) of 0.85 (95%CI: 0.71 to 0.99)[67]. Utilization of a cutoff of 8 of 36 points in participants (*n* = 10/11) with a primary diagnosis of COVID-19 were correctly predicted with a sensitivity of 91% (95%CI: 59% to 100%)[67]. In the cohort without a primary diagnosis of COVID-19

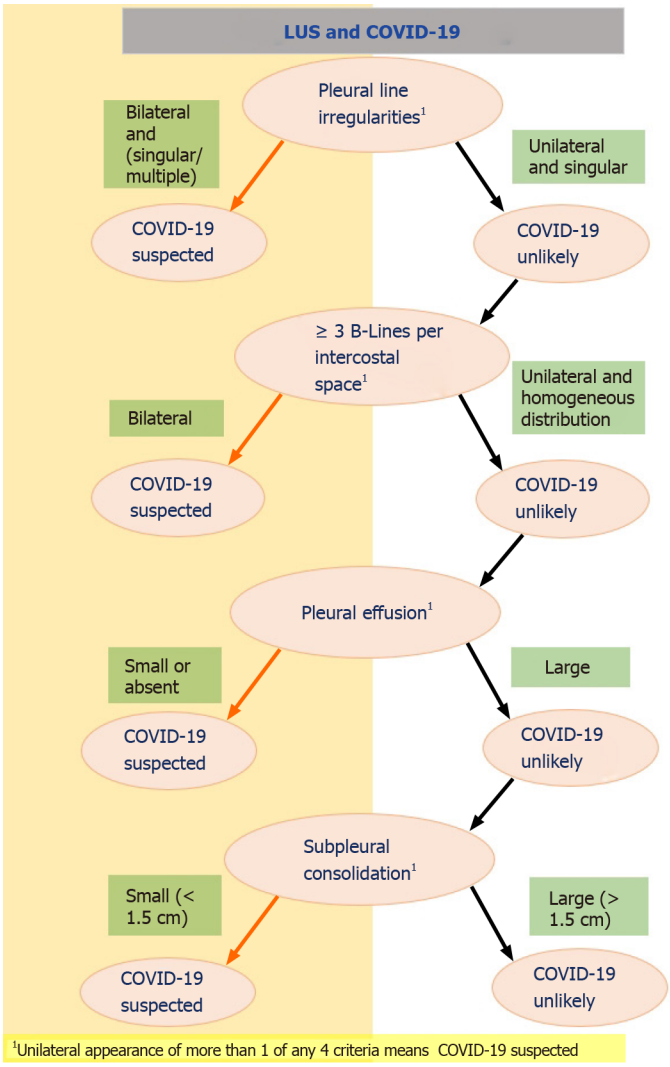


Figure 9 Shows a simplified flowchart guiding the triage in patients presenting with respiratory symptoms during the coronavirus disease 2019 pandemic using lung ultrasonography in the emergency department. [1]Unilateral appearance of more than 1 of any 4 criteria means coronavirus disease 2019 suspected. COVID-19: Coronavirus disease 2019; LUS: Lung ultrasonography.

(others, n = 38), COVID-19 was correctly ruled out in 29 of these 38 patients (specificity = 76%, 95%CI: 60% to 89%)[67]. LUSS, therefore, is a promising screening tool in hospitalized patients suspected of COVID-19. A summary of the results by Speidel *et al* [67] are shown in Figure 11 of typical LUS findings (B-line, and subpleural consolidations) and LUSS scores at varying lung zones in patients with and without a primary diagnosis of COVID-19.

LUS appears to have a promising role in screening clinically suspected or diagnosed COVID-19, only when it is implemented as an adjunct with other diagnostic modalities. An amalgamation of LUS findings with clinical history, physical examination, and knowledge of pretest probability will supplement increasing efficacy. POCUS may facilitate the physician in undertaking the appropriate management pathway or rule in an alternative diagnosis. The practicality of utilization of LUS will remain dependent on resource availability, personnel expertise, and flexibility of LUS configuration for each situation.

DISADVANTAGES OF LUS

LUS has been criticized for its low specificity in the diagnosis of COVID-19. This is because described features including confluent B-lines, consolidations, and irregular pleural lines simply refer to the lung surface density state and are not pathognomonic for COVID-19[68]. Additionally, LUS cannot detect deep lesions as the aerated parenchyma blocks the transmission of ultrasonography. In order for the lesion to

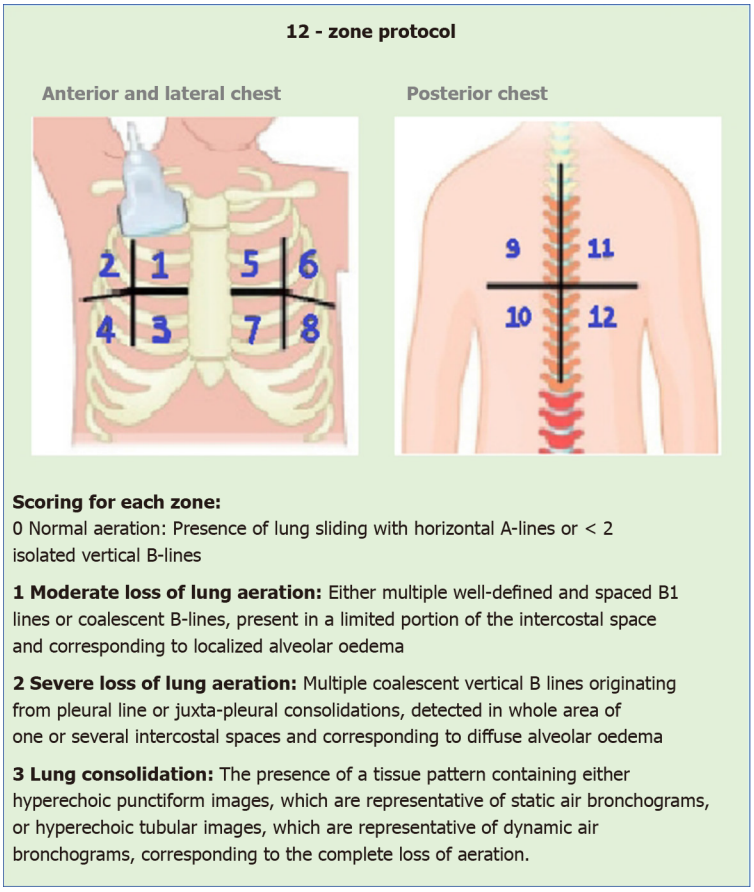


Figure 10 Schematic diagram describing the 12-zone assessed using the lung ultrasonography 12-zone scoring method. The criteria for each score value (0-3) is described and tabulated.

detected, it must extend to the pleural surface. Furthermore, LUS does not exclude COVID-19 in subjects with no pulmonary complications, and therefore cannot be used as a diagnostic tool by itself to stratify patients who may or may not be infected with COVID-19[47].

ROLE OF MRI, PET, AND ECHO IMAGING

There is no documented role of pulmonary MRI in the diagnosis of COVID-19 pneumonia. Cardiac MRIs may be helpful in the future to detect complications such as myocarditis and cardiomyopathy. Fluorodeoxyglucose PET (FDG-PET) scans are not used in emergencies, but some studies explain its utilization in describing the subtleties of typical pulmonary findings in COVID-19 pneumonia. The FDG-PET avidity corresponds to the GGOs in CTs, and this is because of the increased glucose requirement by the neutrophils at the site to fight the infection. There is a theoretical possibility of utilizing FDG-PET in the future to monitor treatment response, predict recovery and survey the long-term consequences of COVID-19.

Deep vein thrombosis and peripheral thrombosis are common in areas with high COVID-19 prevalence due to an increased risk of hypercoagulability; therefore, the use of compression ultrasonography is expected to increase. CT pulmonary angiography is mainly used to confirm the prognosis of pulmonary embolism (PE) and stratify patients with acute PE. Point of care echocardiography might be useful as the sensitivity of right ventricular dilation in detecting PE using POC echocardiography can be as high as 90%. Echocardiography can also be used to evaluate COVID-19-related acute cardiac injuries as abnormalities in echocardiography are linked to a worse prognosis and more severe disease[13].

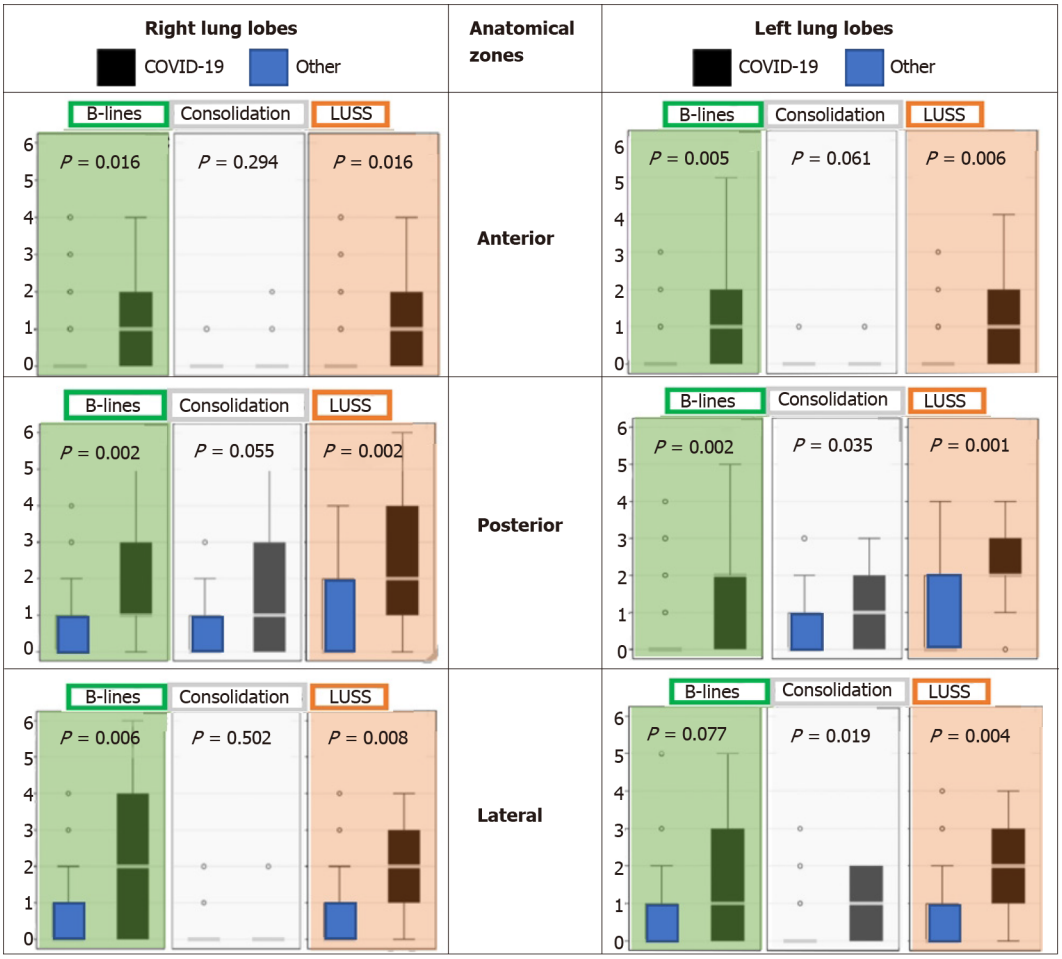


Figure 11 Lung ultrasonography presentation of B-lines (green panel), subpleural consolidations (white panel), and lung ultrasound scores (orange panel) at different lung zones (anterior, lateral, posterior) in patients with a primary diagnosis of coronavirus disease 2019 (*n* = 11) and without coronavirus disease 2019 (other, *n* = 38). Boxplots around median and interquartile range (IQR), with outliers within 1.5 IQR of the nearest quartile. Other (extrapulmonary infection/inflammation (*n* = 10), pneumonia of other etiology (*n* = 8), exacerbated asthma/ chronic obstructive pulmonary disease (*n* = 7), pulmonary neoplasia (*n* = 4), pulmonary embolism (*n* = 2), congestive heart failure (*n* = 2), and not documented (*n* = 5)). Statistically significant outcomes with $P < 0.05$. Data utilized from Speidel *et al*[67]. COVID-19: Coronavirus disease 2019; LUSS: Lung ultrasound score.

CLASSIFICATION SYSTEMS

CO-RADS classification system

In March 2020, a classification system by the Dutch Association for Radiology was implemented to aid with making the diagnosis of COVID-19. This system was called CO-RADS which stands for COVID-19 reporting and data system and was developed to report CT findings with ease and replicability among other physicians, as prior to this, no system had been developed directly for COVID-19. The system assigns the CT scan a CO-RAD score between 1 to 5 depending on the radiological findings of the chest, and in some cases, a score of 0 and 6 can be used. A score of 0 and 6 is used when the CT is uninterpretable, and a positive RT-PCR test must be present, respectively. Level 1 classification indicates a very low level of suspicion for COVID-19 as these cases do not have any nodules bilaterally and only have normal/benign findings[69]. Infections that can be considered level 1 for COVID-19 include mild or severe emphysema, perifissural nodules, lung tumor indications, and fibrosis[69]. This category is also known as negative for pneumonia. Level 2 is as having a low likelihood of COVID-19, but encompasses infectious diseases such as bronchitis, infectious bronchiolitis, bronchopneumonia, lobar pneumonia, and pulmonary abscesses[69]. CT features include those similar to an atypical pulmonary appearance like tree-in-bud sign, a centrilobular nodular pattern, lobar or segmental consolidation, and lung cavitation. Level 3 is the "middle ground" where the viewer can be unsure of the diagnosis as the features seen are those consistent with COVID-19 but also with viral pneumonia or non-infectious causes[69]. Findings in this level consist of perihilar GGO, homogenous extensive GGO with or without sparing of some secondary

pulmonary lobules, or GGO together with smooth interlobular septal thickening with or without pleural. GGO can also be seen on CT, which is characteristic of COVID-19, but the opacities seen are also compatible with organizing pneumonia. Although levels 4 and 5 have similar findings, the presence of GGO with or without consolidations in lung areas close to the visceral pleura indicates a CO-RADS score of level 5 [69]. A summary of the CO-RADS categories and its criteria outlined by Prokop *et al* are outlined in Table 1.

A study by Bellini *et al*[70] analyzed the diagnostic yield of CO-RADS in identifying lung involvement in patients suspected of COVID-19 (n = 572, COVID-19 (n = 142), not COVID-19 (n = 430)) by multiple radiologist and physicians at different levels of expertise. Overall, CO-RADS showed promising accuracy for lung involvement with a mean AUC of 72% (95%CI: 67% to 75%)[70]. The receiver operating characteristic (ROC) curve revealed that application of a threshold ≥ 4 resulted in a moderate specificity of 81% (95%CI: 76% to 84%) and a low sensitivity of 61% (95%CI: 52% to 69%)[70]. The CO-RADS rating among all readers was moderate as shown by Fleiss' Kappa statistic of 0.43 (95%CI: 0.42 to 0.44) and with a substantial agreement for categories; CO-RADS 1 (Fleiss' K = 0.61 (95%CI: 0.60 to 0.62) and for CO-RADS 5 (Fleiss' K = 0.60 (95%CI: 0.58 to 0.61))[70].

MULBSTA SCORING SYSTEM

Another scoring system used for COVID-19 is known as the MuLBSTA score, which looks at key components such as multi-lobar infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hypertension, and age. Five points are assigned for multi-lobar infiltration, 4 points if the lymphocyte count is less than or equal to 0.8 × 10^9/L, 4 points for bacterial infiltration that is confirmed by lab results or on CT, 3 points for those who are currently smoking (2 for those who have previously been smokers), 2 points for hypertension, and 1 point for age above 60-years-old. A total score of 12 was used as the cut-off; those with scores between 0 and 11 were considered low risk while those with a score of ≥ 12 are considered high-risk patients. Those who are in the high-risk category are more likely to require intensive care unit treatment or were more likely to die due to the infection. This scoring system became useful as it helps to predict the prognosis of patients based on other clinical features and co-morbidities[66]. A retrospective study by Ma *et al*[71] (n = 330), showed that the ROC curve analysis on the MuLBSTA early warning scoring system for severe COVID-19 patients has an accuracy of 92.7% (95%CI: 89.2% to 96.3%), sensitivity of 65.1%, and specificity of 95.4%. These outcomes indicate that MuLBSTA is a good early warning system for severe COVID-19 patients.

RALE CLASSIFICATION

This system aims to associate the course and severity of CXR in COVID-19 with the diagnostic RT-PCR result. The RALE score involves individually assessing each lung and depending on how much of the lung is involved, a score is assigned to it. With no involvement, the score is 0, less than 25% lung involvement is 1, 25% lung involvement is 2, 50% of the lung is 3, and a level 4 classification is given when the lung is involved more than 75%. The overall score is calculated by adding the two scores, indicating the involvement of each lung[66]. The RALE score can be used to predict the outcomes of patients with COVID-19 pneumonia and their need for mechanical ventilation (MV). Interestingly, this scoring system is practical and only one of the few ones that incorporate a prognostic value. This makes it a valuable proxy system to compare against an artificial intelligence (AI) model.

One study by Ebrahimian *et al*[72] evaluated the implementation of AI such as the commercially available AI algorithm (qXR v2.1 c2; Qure.ai Technologies, Mumbai, Maharashtra) has been on the rise. This model was trained on patient data with a positive SARS-CoV-2 RT-PCR assay. The AI score had a strong positive correlation with RALE score for each site of the patient CXR (r^2 = 0.79 to 0.86; P < 0.0001)[72]. It also revealed that patients that received MV or deceased had a significantly higher AI or RALE score when compared to those not requiring MV or attained convalescence [72]. This study concluded that instead of comparing the RALE and AI score to the baseline CXRs, combining the RALE and AI score over progressive serial CXRs with clinical and lab data would drastically improve the predictability of both the AI score and the subjective RALE score.

Table 1 Association between CO-RADS categories and level of suspicion for pulmonary involvement of coronavirus disease 2019

CO-RADS category	Suspicion level for pulmonary involvement of COVID-19	Summary
0	Not interpretable	Scan insufficient for assigning score
1	Very low	Normal or non-infectious scan
2	Low	Typical for other infection but not COVID-19
3	Ambiguous	Non-specific features of COVID-19
4	High	Increased suspicion of COVID-19
5	Very high	Typical features of COVID-19
6	Proven	Positive RT-PCR test for COVID-19

Table modified from Prokop *et al*[69]. COVID-19: Coronavirus disease 2019.

BRIXIA SCORE

This score was designed and implemented for serial monitoring by the 'Radiology Unit 2 of ASST Spedali Civili di Brescia' and was later validated for risk stratification on a greater population by Borghesi *et al*[73]. According to this scoring system, the lung is divided into six different zones, three on each of the lungs, in either anteroposterior or posteroanterior views. With regards to the scoring of the zones, the score given can be between and including 0-3 based on the involvement of the lung. A score of 0 is given if there are no abnormalities seen on X-ray, a score of 1 is given when there are interstitial infiltrates. Two is given if there are interstitial and alveolar infiltrates, with the interstitial markings being more prominent. A score of 3 is assigned when there are both interstitial and alveolar infiltrates present, with the latter being more prominent. These scores are given to each of the 6 zones and are then aggregated to get a final score. This type of semiquantitative scoring makes CXR interpreting faster and more streamlined for evaluation[73]. The Brixia score becomes more useful when serial CXRs are performed as this enables documentation of additional sub-scores. The H-score is the highest Brixia score documented during the serial CXRs. Contrastingly, the L-score is the lowest Brixia score documented during the serial CXRs. Additionally, the Brixia score is documented at admission (A-score) and discharge/death (E-score).

One study by Maroldi *et al*[74] retrospectively assessed the clinical value of the Brixia score in 953 COVID-19 patients. In this study, the H-score was significantly higher with a median of 12 and interquartile range (IQR) between 9 to 14 in the deceased cohort compared to the discharged cohort (median: 8, IQR 5 to 11). Similarly, the L-score (7 *vs* 5; $P < 0.0003$), A-score (9 *vs* 8; $P < 0.039$), and E-score (12 *vs* 7; $P < 0.0001$) were all higher in the deceased cohort than the discharged cohort[74]. Overall, logistic regression showed a significant predictive value for H-score of OR 1.25. The ROC curve revealed an AUC of 0.863[74]. Additional Cox proportional hazards regression revealed age has a hazard ratio (HR) of 4.17 ($P = 0.0001$), H-score of < 9 has a HR 0.36 ($P = 0.0012$) and worsening of H-score compared to a score below 3, which has a HR of 1.57 ($P = 0.0227$) and is associated with a worse outcome[74]. These outcomes demonstrate the importance of the Brixia score in the monitoring and assessment of COVID-19 pneumonia and its strong correlation with a patient's prognosis.

PERMANENT LUNG SCARRING POST COVID-19

Research into the evolution of COVID-19 pneumonia imaging during the follow-up in the later stages of the disease is an interesting area. Zhao *et al*[75] demonstrated that at 3 mo, typical lung features (GGO, interstitial thickening. and crazy paving) were almost resolved, with some fibrosis. High-resolution CT scans of patients ($n = 55$) revealed that 67.27% had GGO ($n = 37$), 27.27% had interstitial thickening ($n = 15$), and 5.45% had crazy-paving patterns ($n = 3$)[75]. However, the study only included 55 patients who had non-critical COVID-19 pneumonia. Long-term follow-up studies with a larger sample size are crucial to better understand the trends in recovery. The available literature reports consistent findings of partial healing of GGO and consol-

idation from approximately day 14. In some patients, CT findings also demonstrated signs of fibrosis. In February to March 2020, a case series provided the earliest reports of follow-up CT findings. Partial healing of a mixed pattern of GGO and consolidation occurred from the day 14 onwards according to Duan and Qin[76], and Shi *et al*[77]. Wei *et al*[79], reported lung fibrosis in COVID-19 patients on day 12 which was corroborated by a case presented by Li *et al*[78] which described similar findings on day 14. Pan *et al*[80] presented a retrospective study (n = 63) following up COVID-19 patients. These patients were re-examined in intervals of 3-14 d wherein enlarged fibrous stripes and solid white nodules were documented. Pan *et al*[42] reported that after 14 d, 65% had GGO (n = 13/20) and 75% had consolidation (n = 15/20), but crazing-paving pattern was absent in all 20 patients. Bernheim *et al*[81] found that in 25 patients, after 6-12 d, 88% had GGO (n = 22/25) and 60% had consolidation (n = 15/25). Crazy-paving pattern was present in 20% of patients (n = 5), and 24% had bronchial wall thickening (n = 6) but no patients had underlying pulmonary fibrosis [81]. Wang *et al*[82] reported that during days 12-17 there was a notable increase in the mixed pattern, although GGO were still predominant. Xiong *et al*[83] observed that after an average of 11.6 d the follow-up CT showed progressive GGO, consolidation, interstitial thickening, fibrous stripes, and air bronchograms. These findings aid our understanding of the recovery patterns in infected patients. Furthermore, follow-up and management plans will need high-quality evidence to guide clinical decision-making and monitor treatment efficacy with supplemental oxygen and antifibrotic agents.

AI INTERVENTIONAL SYSTEMS

AI is a broad concept that refers to a set of advanced computational algorithms that utilizes heuristic pattern recognition for a given training dataset and therefore makes predictions on unseen testing datasets. Radiomics utilizes data-characterization algorithms for extracting and evaluating features from radiological medical images and further uses them to creating statistical models with the intent to provide support for diagnosis and management[84]. Radiologic parameters considered for analysis include size, shape and textural features that have useful spatial information on pixel or voxel distribution and patterns[85]. Integration of AI into radiomic datasets has the potential to streamline COVID-19 diagnosis. In early February 2020, Beijing-based AI company *Infervision* launched the "Coronavirus artificial intelligence solution," an algorithm that utilizes CT imaging data to diagnose COVID-19 on CT[86]. The reports revealed an increased ability to read images in 10 s, drastically improving clinical workflow efficiency, and reducing variable human error, while continuously improving diagnostic accuracy[87].

Another study developed a deep-learning COVID-19 diagnosis system from a dataset including 11356 CT volumes from COVID-19, influenza-A/B, non-viral community-acquired pneumonia and non-pneumonia subjects from China[88]. The basic workflow of the deep-learning-based diagnosis model contains utilization of CT data as the input, the lung is then segmented, COVID-19 diagnosis is made based on the location of infectious slices (Figure 12). This study found that the AI system outperformed very experienced radiologists based on speed. Another study by Harmon *et al*[89] showed that the use of the AI system that can detect COVID-19 pneumonia with 90.8% accuracy, 84% sensitivity, and 93% specificity. A total of 1280 patients from China, Italy, and Japan were used to train the deep-learning algorithms, and the system was tested independently on 1337 patients, with normal controls from oncology, emergency, and pneumonia-related indications. There was a 10% false-positive rate of incorrectly diagnosed COVID-19 related patients. This indicates potential for overlapped diagnosis with other pneumonia etiologies. Another limiting factor in using AI is the need for thousands of high-quality CT studies to train the AI. Overall, AI systems could be trained to be extremely accurate, sensitive, and specific for COVID-19 diagnosis. However, it may be more useful in specific assessment of imaging findings of COVID-19[88,89].

A subsequent study conducted by Yu *et al*[90] investigated various pre-trained deep learning AI models against 246 severe cases and 483 non-severe COVID-19 cases and found that DenseNet-201 with cubic SVM model achieved a high severity classification accuracy of 95.20% and 95.34% for ten-fold cross-validation and leave-one-out validation, respectively. These effective results show that the utility of the proposed pipeline model was able to achieve a rapid and accurate identification of the severity of COVID-19, indicating its potential for use by clinicians in not just diagnosis but also

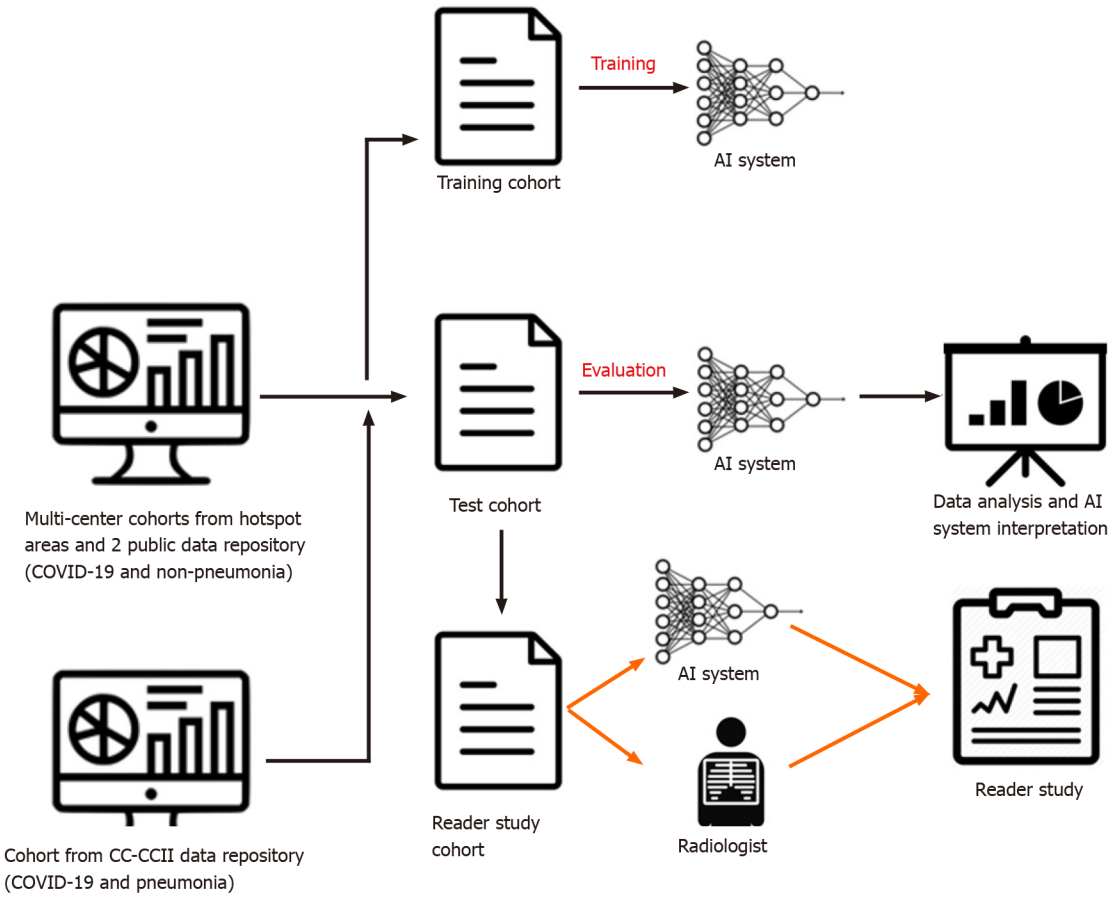


Figure 12 Basic workflow of the artificial intelligence system. AI: Artificial intelligence; COVID-19: Coronavirus disease 2019.

decisions relating to severity management and prioritization[90].

In May 2020, radiologist Laghi[91] wrote a correspondence letter in *The Lancet* detailing her concern that the diagnostic value of AI algorithms in CT scans was not supported by scientific evidence. In fact, since the high-resolution CT findings are not pathognomonic of COVID-19 infection and have poor accuracy in screening asymptomatic individuals according to the American College of Radiology, there have been growing concerns over the integration of AI radiology into the screening of this disease[92].

RADIOLOGY PANEL: FIRST AND SECOND WAVE

First wave experience

The overwhelming nature of COVID-19 has strained global healthcare services and greatly impacted radiology departments. To cope with increasing admissions during peaks, radiologists and radiology trainees have experienced redeployment to areas of clinical need. One hospital saw 21% of their total radiology employees reassigned to other duties[93]. Following official guidelines[94], medical facilities also rescheduled non-urgent elective procedures, and this had a major effect on total imaging volume. While the exact drop varies within institutions, a large New York metropolitan health system reported an 87%, 4%, and 45% reduction in outpatient, inpatient, and emergency imaging respectively, during the pandemic[95].

Moreover, it has become increasingly evident that COVID-19 is not limited to the lungs, rather it can affect other organs too. An early published clinical cohort of COVID-19 displayed acute cardiac injury, shock, and arrhythmia in 7.2%, 8.7%, and 16.7% of patients respectively, with a higher prevalence in patients requiring intensive care[96]. Neurological manifestations have also been recorded; another observational study demonstrated neurological symptoms in 36.4% of hospitalized COVID patients [97]. Alongside observations of kidney involvement and hypercoagulability in patients, this leaves a potentially important role for radiologists when considering

COVID-19 as a multisystem disease[98,99].

Regarding the role of imaging, our understanding has changed with the course of the pandemic. Chest CT was temporarily part of the official diagnostic criteria for COVID-19 due to the nature of the early emergency in China; however, since then, chest CT findings are no longer considered diagnostic. Current guidelines establish that RT-PCR assays are the standard for definitive COVID-19 diagnosis[100,101]. Instead, CXR and chest CT have been the most common imaging modalities specified for presumptive diagnosis, triage and management of patients with suspected or known COVID-19 infection[102]. After the diagnosis is confirmed, the role of imaging may be limited but while waiting for PCR positive it can be very useful for clinicians. Portable CXR is often used as the primary imaging study in suspected patients, chest CT is far more sensitive in detecting lung lesions but has been reserved for more specific cases[4,13].

FORWARD PREPARATION FOR THE SECOND WAVE

As radiologists get ready for the second wave of COVID-19, it is important to continue developing on lessons learned from the 1st wave. With that in mind, a general framework that can be applied to radiology departments when preparing for the second wave and beyond is the concepts of building, sustaining, and adapting[103].

The main idea of the first strategy is to create capacity before it is needed. This can be done by increasing hours of staff, getting more manpower, or by expanding operations into other sites as seen in Singapore General Hospital's (SGH) Emergency Department[103]. When faced with increased local transmission of COVID-19, management of an adjacent Ambulatory Surgery Centre was transferred to the ED, allowing for operations to be ramped up and for portable radiology services to grow [104]. Additional capacity can also be created by increasing portable imaging capability through renting extra units so they can be deployed into operations when needed[105].

Moving on to the second strategy of sustaining, the central idea here is to operate at a pace that is maintainable in the long-term. This would involve preserving supplies such as Personal Protective Equipment, preventing staff burnout, simplifying hastily designed processes, and alternating work times or work sites[103]. In the University of Alabama at Birmingham, home picture archiving and communication system workstations were rapidly deployed in anticipation of a potential COVID-19 crisis [106]. With this measure, the number of people coming on-site could be limited in the long-term while also contributing to social distancing amongst radiologists.

Lastly, the third strategy, adapting, highlights the importance of being flexible. Some ways this can be achieved include rapidly scaling up responses, reconfiguring spaces, improvising, and embracing new roles when faced with increased demands [103]. This is demonstrated at SGH, where in order to monitor changes in the pandemic, a smaller radiology disease outbreak task force was assembled to assess overnight incidents and anticipate changes during the day[4].

CONCLUSION

The burden of this disease is evident through the rampant rise in fatality, morbidity, and mortality rates across the world. Despite the integration of stringent public health measures, this spread continues and is leaving an everlasting impact on both humanity and the economy. Radiologists have significantly adjusted their practices in accordance with the pandemic and as frontline workers, it is essential for them to identify the classical findings associated with COVID-19 and use their expertise towards engaging in optimal strategies to slow disease progression. Advances in the role of radiology in COVID-19 research have piled up within a short-period, hence it is prudent to remain acquainted with important findings. Some notable findings consist of the early stage of disease producing a classical GGO appearance on majority of the CT scans, and the late stage of disease showing highly specific fibrotic lesions due to scarring of the lung parenchyma. The purpose of identifying these characteristic features and associating them with a time course can be crucial towards the management plan for each patient. Additionally, the role of radiology can further be integrated into the scoring systems discussed in this review for risk stratification and appropriate assessment and treatment strategies for infected cases. Nevertheless, medical imaging has been suggested to have promising value as a rapid adjunctive

tool in patients with COVID-19 through assisting with the diagnosis, evaluating patients with clinical deterioration, and providing the multidisciplinary team with vital examinations that could support the management strategies.

REFERENCES

1 **World Health Organization**. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases 19 March 2020. [cited 22 January 2021]. Available from: https://www.who.int/publications/i/item/10665-331501

2 **Böger B**, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. *Am J Infect Control* 2021; **49**: 21-29 [PMID: 32659413 DOI: 10.1016/j.ajic.2020.07.011]

3 **Liotti FM**, Menchinelli G, Marchetti S, Posteraro B, Landi F, Sanguinetti M, Cattani P. Assessment of SARS-CoV-2 RNA Test Results Among Patients Who Recovered From COVID-19 With Prior Negative Results. *JAMA Intern Med* 2021; **181**: 702-704 [PMID: 33180119 DOI: 10.1001/jamainternmed.2020.7570]

4 **Mossa-Basha M**, Meltzer CC, Kim DC, Tuite MJ, Kolli KP, Tan BS. Radiology Department Preparedness for COVID-19: *Radiology* Scientific Expert Review Panel. *Radiology* 2020; **296**: E106-E112 [PMID: 32175814 DOI: 10.1148/radiol.2020200988]

5 **Younes N**, Al-Sadeq DW, Al-Jighefee H, Younes S, Al-Jamal O, Daas HI, Yassine HM, Nasrallah GK. Challenges in Laboratory Diagnosis of the Novel Coronavirus SARS-CoV-2. *Viruses* 2020; **12**: 582 [PMID: 32466458 DOI: 10.3390/v12060582]

6 **Weiss SR**, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. *Microbiol Mol Biol Rev* 2005; **69**: 635-664 [PMID: 16339739 DOI: 10.1128/MMBR.69.4.635-664.2005]

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

8 **Corman VM**, Muth D, Niemeyer D, Drosten C. Chapter Eight - Hosts and Sources of Endemic Human Coronaviruses. In: Advances in Virus Research. Kielian M, Mettenleiter TC, Roossinck MJ, editors. Elsevier, 2018: 163-188 [DOI: 10.1016/bs.aivir.2018.01.001]

9 **Kakodkar P**, Kaka N, Baig MN. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus* 2020; **12**: e7560 [PMID: 32269893 DOI: 10.7759/cureus.7560]

10 **Kim EA**, Lee KS, Primack SL, Yoon HK, Byun HS, Kim TS, Suh GY, Kwon OJ, Han J. Viral pneumonias in adults: radiologic and pathologic findings. *Radiographics* 2002; **22**: S137-S149 [PMID: 12376607 DOI: 10.1148/radiographics.22.suppl_1.g02oc15s137]

11 **Luks AM**, Freer L, Grissom CK, McIntosh SE, Schoene RB, Swenson ER, Hackett PH. COVID-19 Lung Injury is Not High Altitude Pulmonary Edema. *High Alt Med Biol* 2020; **21**: 192-193 [PMID: 32281877 DOI: 10.1089/ham.2020.0055]

12 **Gralinski LE**, Baric RS. Molecular pathology of emerging coronavirus infections. *J Pathol* 2015; **235**: 185-195 [PMID: 25270030 DOI: 10.1002/path.4454]

13 **Manna S**, Wruble J, Maron SZ, Toussie D, Voutsinas N, Finkelstein M, Cedillo MA, Diamond J, Eber C, Jacobi A, Chung M, Bernheim A. COVID-19: A Multimodality Review of Radiologic Techniques, Clinical Utility, and Imaging Features. *Radiol Cardiothorac Imaging* 2020; **2**: e200210 [PMID: 33778588 DOI: 10.1148/ryct.2020200210]

14 **Lev MH**, Gonzalez RG. 17 - CT Angiography and CT Perfusion Imaging. In: Brain Mapping: The Methods. 2nd ed. Toga AW, Mazziotta JC, editors. San Diego: Academic Press, 2002: 427-484 [DOI: 10.1016/b978-012088592-3/50076-1]

15 **Singh B**, Kaur P, Reid RJ, Shamoon F, Bikkina M. COVID-19 and Influenza Co-Infection: Report of Three Cases. *Cureus* 2020; **12**: e9852 [PMID: 32832306 DOI: 10.7759/cureus.9852]

16 **Shi H**, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]

17 **Pormohammad A**, Ghorbani S, Khatami A, Farzi R, Baradaran B, Turner DL, Turner RJ, Bahr NC, Idrovo JP. Comparison of confirmed COVID-19 with SARS and MERS cases - Clinical characteristics, laboratory findings, radiographic signs and outcomes: A systematic review and meta-analysis. *Rev Med Virol* 2020; **30**: e2112 [PMID: 32502331 DOI: 10.1002/rmv.2112]

18 **Carotti M**, Salaffi F, Sarzi-Puttini P, Agostini A, Borgheresi A, Minorati D, Galli M, Marotto D, Giovagnoni A. Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med* 2020; **125**: 636-646 [PMID: 32500509 DOI: 10.1007/s11547-020-01237-4]

19 **Martini K**, Blüthgen C, Walter JE, Messerli M, Nguyen-Kim TDL, Frauenfelder T. Accuracy of Conventional and Machine Learning Enhanced Chest Radiography for the Assessment of COVID-19 Pneumonia: Intra-Individual Comparison with CT. *J Clin Med* 2020; **9**: 3576 [PMID: 33171999 DOI: 10.3390/jcm9113576]

20 **Rampa L**, Miceli A, Casilli F, Biraghi T, Barbara B, Donatelli F. Lung complication in COVID-19 convalescence: A spontaneous pneumothorax and pneumatocele case report. *J Respir Dis Med* 2020;

2 [DOI: 10.15761/jrdm.1000115]
21 **Kaufman AE**, Naidu S, Ramachandran S, Kaufman DS, Fayad ZA, Mani V. Review of radiographic findings in COVID-19. *World J Radiol* 2020; **12**: 142-155 [PMID: 32913561 DOI: 10.4329/wjr.v12.i8.142]
22 **Yasin R**, Gouda W. Chest X-ray findings monitoring COVID-19 disease course and severity. *Egypt J Radiol Nucl Med* 2020; **51**: 193 [DOI: 10.1186/s43055-020-00296-x]
23 **Borakati A**, Perera A, Johnson J, Sood T. Diagnostic accuracy of X-ray versus CT in COVID-19: a propensity-matched database study. *BMJ Open* 2020; **10**: e042946 [PMID: 33158840 DOI: 10.1136/bmjopen-2020-042946]
24 **Ng MY**, Lee EYP, Yang J, Yang F, Li X, Wang H, Lui MM, Lo CS, Leung B, Khong PL, Hui CK, Yuen KY, Kuo MD. Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review. *Radiol Cardiothorac Imaging* 2020; **2**: e200034 [PMID: 33778547 DOI: 10.1148/ryct.2020200034]
25 **Bao C**, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. *J Am Coll Radiol* 2020; **17**: 701-709 [PMID: 32283052 DOI: 10.1016/j.jacr.2020.03.006]
26 **Gillespie M**, Flannery P, Schumann JA, Dincher N, Mills R, Can A. Crazy-Paving: A Computed Tomographic Finding of Coronavirus Disease 2019. *Clin Pract Cases Emerg Med* 2020; **4**: 461-463 [PMID: 32926713 DOI: 10.5811/cpcem.2020.5.47998]
27 **Fu Z**, Tang N, Chen Y, Ma L, Wei Y, Lu Y, Ye K, Liu H, Tang F, Huang G, Yang Y, Xu F. CT features of COVID-19 patients with two consecutive negative RT-PCR tests after treatment. *Sci Rep* 2020; **10**: 11548 [PMID: 32665633 DOI: 10.1038/s41598-020-68509-x]
28 **Ali TF**, Tawab MA, ElHariri MA. CT chest of COVID-19 patients: What should a radiologist know? *Egypt J Radiol Nucl Med* 2020; **51**: 120 [DOI: 10.1186/s43055-020-00245-8]
29 **Pakdemirli E**, Mandalia U, Monib S. Positive Chest CT Features in Patients With COVID-19 Pneumonia and Negative Real-Time Polymerase Chain Reaction Test. *Cureus* 2020; **12**: e9942 [PMID: 32850265 DOI: 10.7759/cureus.9942]
30 **Sales AR**, Casagrande EM, Hochhegger B, Zanetti G, Marchiori E. The Reversed Halo Sign and COVID-19: Possible Histopathological Mechanisms Related to the Appearance of This Imaging Finding. *Arch Bronconeumol* 2021; **57** Suppl 1: 73-75 [PMID: 32792171 DOI: 10.1016/j.arbres.2020.06.029]
31 **Ojha V**, Mani A, Pandey NN, Sharma S, Kumar S. CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients. *Eur Radiol* 2020; **30**: 6129-6138 [PMID: 32474632 DOI: 10.1007/s00330-020-06975-7]
32 **Kwee TC**, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. *Radiographics* 2020; **40**: 1848-1865 [PMID: 33095680 DOI: 10.1148/rg.2020200159]
33 **Kong W**, Agarwal PP. Chest Imaging Appearance of COVID-19 Infection. *Radiol Cardiothorac Imaging* 2020; **2**: e200028 [PMID: 33778544 DOI: 10.1148/ryct.2020200028]
34 **Meirelles GSP**. COVID-19: a brief update for radiologists. *Radiol Bras* 2020; **53**: 320-328 [PMID: 33071376 DOI: 10.1590/0100-3984.2020.0074]
35 **Zhang Q**, Douglas A, Abideen ZU, Khanal S, Tzarnas S. Novel Coronavirus (2019-nCoV) in Disguise. *Cureus* 2020; **12**: e7521 [PMID: 32377469 DOI: 10.7759/cureus.7521]
36 **Mughal MS**, Rehman R, Osman R, Kan N, Mirza H, Eng MH. Hilar lymphadenopathy, a novel finding in the setting of coronavirus disease (COVID-19): A case report. *J Med Case Rep* 2020; **14**: 124 [PMID: 32771058 DOI: 10.1186/s13256-020-02452-3]
37 **Kovács A**, Palásti P, Veréb D, Bozsik B, Palkó A, Kincses ZT. The sensitivity and specificity of chest CT in the diagnosis of COVID-19. *Eur Radiol* 2021; **31**: 2819-2824 [PMID: 33051732 DOI: 10.1007/s00330-020-07347-x]
38 **Souza CA**, Müller NL, Johkoh T, Akira M. Drug-induced eosinophilic pneumonia: high-resolution CT findings in 14 patients. *AJR Am J Roentgenol* 2006; **186**: 368-373 [PMID: 16423940 DOI: 10.2214/AJR.04.1847]
39 **Rossi SE**, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. *Radiographics* 2000; **20**: 1245-1259 [PMID: 10992015 DOI: 10.1148/radiographics.20.5.g00se081245]
40 **Lin YH**, Hsu HS. Ground glass opacity on chest CT scans from screening to treatment: A literature review. *J Chin Med Assoc* 2020; **83**: 887-890 [PMID: 32675737 DOI: 10.1097/JCMA.0000000000000394]
41 **Gu J**, Yang L, Li T, Liu Y, Zhang J, Ning K, Su D. Temporal relationship between serial RT-PCR results and serial chest CT imaging, and serial CT changes in coronavirus 2019 (COVID-19) pneumonia: a descriptive study of 155 cases in China. *Eur Radiol* 2021; **31**: 1175-1184 [PMID: 32930834 DOI: 10.1007/s00330-020-07268-9]
42 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]
43 **Peng QY**, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; **46**: 849-850 [PMID: 32166346 DOI: 10.1007/s00134-020-05996-6]
44 **Poggiali E**, Dacrema A, Bastoni D, Tinelli V, Demichele E, Mateo Ramos P, Marcianò T, Silva M, Vercelli A, Magnacavallo A. Can Lung US Help Critical Care Clinicians in the Early Diagnosis of

Novel Coronavirus (COVID-19) Pneumonia? *Radiology* 2020; **295**: E6 [PMID: 32167853 DOI: 10.1148/radiol.2020200847]

45 **Via G**, Storti E, Gulati G, Neri L, Mojoli F, Braschi A. Lung ultrasound in the ICU: from diagnostic instrument to respiratory monitoring tool. *Minerva Anestesiol* 2012; **78**: 1282-1296 [PMID: 22858877]

46 **Vetrugno L**, Bove T, Orso D, Barbariol F, Bassi F, Boero E, Ferrari G, Kong R. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. *Echocardiography* 2020; **37**: 625-627 [PMID: 32239532 DOI: 10.1111/echo.14664]

47 **Testa A**, Soldati G, Copetti R, Giannuzzi R, Portale G, Gentiloni-Silveri N. Early recognition of the 2009 pandemic influenza A (H1N1) pneumonia by chest ultrasound. *Crit Care* 2012; **16**: R30 [PMID: 22340202 DOI: 10.1186/cc11201]

48 **Bitar ZI**, Maadarani OS, El-Shably AM, Al-Ajmi MJ. Diagnostic accuracy of chest ultrasound in patients with pneumonia in the intensive care unit: A single-hospital study. *Health Sci Rep* 2019; **2**: e102 [PMID: 30697596 DOI: 10.1002/hsr2.102]

49 **Youssef A**, Serra C, Pilu G. Lung ultrasound in the coronavirus disease 2019 pandemic: a practical guide for obstetricians and gynecologists. *Am J Obstet Gynecol* 2020; **223**: 128-131 [PMID: 32437667 DOI: 10.1016/j.ajog.2020.05.014]

50 **Moro F**, Buonsenso D, Moruzzi MC, Inchingolo R, Smargiassi A, Demi L, Larici AR, Scambia G, Lanzone A, Testa AC. How to perform lung ultrasound in pregnant women with suspected COVID-19. *Ultrasound Obstet Gynecol* 2020; **55**: 593-598 [PMID: 32207208 DOI: 10.1002/uog.22028]

51 **Gargani L**, Sicari R, Raciti M, Serasini L, Passera M, Torino C, Letachowicz K, Ekart R, Fliser D, Covic A, Balafa O, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Shavit L, Martinez-Castelao A, Coudert-Krier MJ, Rossignol P, Kraemer TD, Hannedouche T, Panichi V, Wiecek A, Pontoriero G, Sarafidis P, Klinger M, Hojs R, Seiler-Mußler S, Lizzi F, Onofriescu M, Zarzoulas F, Tripepi R, Mallamaci F, Tripepi G, Picano E, London GM, Zoccali C. Efficacy of a remote web-based lung ultrasound training for nephrologists and cardiologists: a LUST trial sub-project. *Nephrol Dial Transplant* 2016; **31**: 1982-1988 [PMID: 27672089 DOI: 10.1093/ndt/gfw329]

52 **Cardim N**, Dalen H, Voigt JU, Ionescu A, Price S, Neskovic AN, Edvardsen T, Galderisi M, Sicari R, Donal E, Stefanidis A, Delgado V, Zamorano J, Popescu BA. The use of handheld ultrasound devices: a position statement of the European Association of Cardiovascular Imaging (2018 update). *Eur Heart J Cardiovasc Imaging* 2019; **20**: 245-252 [PMID: 30351358 DOI: 10.1093/ehjci/jey145]

53 **News BW**. ICN CEO Howard Catton BBC World News interview on COVID-19. In: Who's Who. Bloomsbury Publishing plc, 2018 [DOI: 10.1093/ww/9780199540884.013.u17734]

54 **Buonsenso D**, Piano A, Raffaelli F, Bonadia N, de Gaetano Donati K, Franceschi F. Point-of-Care Lung Ultrasound findings in novel coronavirus disease-19 pnemoniae: a case report and potential applications during COVID-19 outbreak. *Eur Rev Med Pharmacol Sci* 2020; **24**: 2776-2780 [PMID: 32196627 DOI: 10.26355/eurrev_202003_20549]

55 **Lichtenstein DA**, Mezière GA, Lagoueyte JF, Biderman P, Goldstein I, Gepner A. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. *Chest* 2009; **136**: 1014-1020 [PMID: 19809049 DOI: 10.1378/chest.09-0001]

56 **Volpicelli G**, Lamorte A, Villén T. What's new in lung ultrasound during the COVID-19 pandemic. *Intensive Care Med* 2020; **46**: 1445-1448 [PMID: 32367169 DOI: 10.1007/s00134-020-06048-9]

57 **Allinovi M**, Parise A, Giacalone M, Amerio A, Delsante M, Odone A, Franci A, Gigliotti F, Amadasi S, Delmonte D, Parri N, Mangia A. Lung Ultrasound May Support Diagnosis and Monitoring of COVID-19 Pneumonia. *Ultrasound Med Biol* 2020; **46**: 2908-2917 [PMID: 32807570 DOI: 10.1016/j.ultrasmedbio.2020.07.018]

58 **Huang Y**, Wang S, Liu Y, Zhang Y, Zheng C, Zheng Y, Zhang C, Min W, Zhou H, Yu M, Hu M. A preliminary study on the ultrasonic manifestations of peripulmonary lesions of non-critical novel coronavirus pneumonia (COVID-19). *SSRN* 2020 [DOI: 10.2139/ssrn.3544750]

59 **Norbedo S**, Blaivas M, Raffaldi I, Caroselli C. Lung Ultrasound Point-of-View in Pediatric and Adult COVID-19 Infection. *J Ultrasound Med* 2021; **40**: 899-908 [PMID: 32894621 DOI: 10.1002/jum.15475]

60 **McDermott C**, Daly J, Carley S. Combatting COVID-19: is ultrasound an important piece in the diagnostic puzzle? *Emerg Med J* 2020; **37**: 644-649 [PMID: 32907844 DOI: 10.1136/emermed-2020-209721]

61 **Zhu F**, Zhao X, Wang T, Wang Z, Guo F, Xue H, Chang P, Liang H, Ni W, Wang Y, Chen L, Jiang B. Ultrasonic Characteristics and Severity Assessment of Lung Ultrasound in COVID-19 Pneumonia in Wuhan, China: A Retrospective, Observational Study. *Engineering* 2020; **7**: 367-375 [DOI: 10.1016/j.eng.2020.09.007]

62 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for International Standardization of the Use of Lung Ultrasound for Patients With COVID-19: A Simple, Quantitative, Reproducible Method. *J Ultrasound Med* 2020; **39**: 1413-1419 [PMID: 32227492 DOI: 10.1002/jum.15285]

63 **Schmid B**, Feuerstein D, Lang CN, Fink K, Steger R, Rieder M, Duerschmied D, Busch HJ, Damjanovic D. Lung ultrasound in the emergency department - a valuable tool in the management of patients presenting with respiratory symptoms during the SARS-CoV-2 pandemic. *BMC Emerg Med* 2020; **20**: 96 [PMID: 33287732 DOI: 10.1186/s12873-020-00389-w]

64 **Dargent A**, Chatelain E, Kreitmann L, Quenot JP, Cour M, Argaud L; COVID-LUS study group. Lung ultrasound score to monitor COVID-19 pneumonia progression in patients with ARDS. *PLoS One* 2020; **15**: e0236312 [PMID: 32692769 DOI: 10.1371/journal.pone.0236312]

65 **Manivel V**, Lesnewski A, Shamim S, Carbonatto G, Govindan T. CLUE: COVID-19 Lung ultrasound in emergency department. *Emerg Med Australas* 2020; **32**: 694-696 [PMID: 32386264 DOI: 10.1111/1742-6723.13546]

66 **Lu X**, Zhang M, Qian A, Tang L, Xu S. Lung ultrasound score in establishing the timing of intubation in COVID-19 interstitial pneumonia: A preliminary retrospective observational study. *PLoS One* 2020; **15**: e0238679 [PMID: 32881950 DOI: 10.1371/journal.pone.0238679]

67 **Speidel V**, Conen A, Gisler V, Fux CA, Haubitz S. Lung Assessment with Point-of-Care Ultrasound in Respiratory Coronavirus Disease (COVID-19): A Prospective Cohort Study. *Ultrasound Med Biol* 2021; **47**: 896-901 [PMID: 33487473 DOI: 10.1016/j.ultrasmedbio.2020.12.021]

68 **Alfuraih AM**. Point of care lung ultrasound in COVID-19: hype or hope? *BJR Open* 2020; **2**: 20200027 [PMID: 33178984 DOI: 10.1259/bjro.20200027]

69 **Prokop M**, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; **296**: E97-E104 [PMID: 32339082 DOI: 10.1148/radiol.2020201473]

70 **Bellini D**, Panvini N, Rengo M, Vicini S, Lichtner M, Tieghi T, Ippoliti D, Giulio F, Orlando E, Iozzino M, Ciolfi MG, Montechiarello S, d'Ambrosio U, d'Adamo E, Gambaretto C, Panno S, Caldon V, Ambrogi C, Carbone I. Diagnostic accuracy and interobserver variability of CO-RADS in patients with suspected coronavirus disease-2019: a multireader validation study. *Eur Radiol* 2021; **31**: 1932-1940 [PMID: 32968883 DOI: 10.1007/s00330-020-07273-y]

71 **Ma B**, Gong J, Yang Y, Yao X, Deng X, Chen X. Applicability of MuLBSTA scoring system as diagnostic and prognostic role in early warning of severe COVID-19. *Microb Pathog* 2021; **150**: 104706 [PMID: 33347962 DOI: 10.1016/j.micpath.2020.104706]

72 **Ebrahimian S**, Homayounieh F, Rockenbach MABC, Putha P, Raj T, Dayan I, Bizzo BC, Buch V, Wu D, Kim K, Li Q, Digumarthy SR, Kalra MK. Artificial intelligence matches subjective severity assessment of pneumonia for prediction of patient outcome and need for mechanical ventilation: a cohort study. *Sci Rep* 2021; **11**: 858 [PMID: 33441578 DOI: 10.1038/s41598-020-79470-0]

73 **Signoroni A**, Savardi M, Benini S, Adami N, Leonardi R, Gibellini P, Vaccher F, Ravanelli M, Borghesi A, Maroldi R, Farina D. BS-Net: Learning COVID-19 pneumonia severity on a large chest X-ray dataset. *Med Image Anal* 2021; **71**: 102046 [PMID: 33862337 DOI: 10.1016/j.media.2021.102046]

74 **Maroldi R**, Rondi P, Agazzi GM, Ravanelli M, Borghesi A, Farina D. Which role for chest x-ray score in predicting the outcome in COVID-19 pneumonia? *Eur Radiol* 2021; **31**: 4016-4022 [PMID: 33263159 DOI: 10.1007/s00330-020-07504-2]

75 **Zhao YM**, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; **25**: 100463 [PMID: 32838236 DOI: 10.1016/j.eclinm.2020.100463]

76 **Duan YN**, Qin J. Pre- and Posttreatment Chest CT Findings: 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology* 2020; **295**: 21 [PMID: 32049602 DOI: 10.1148/radiol.2020200323]

77 **Shi H**, Han X, Zheng C. Evolution of CT Manifestations in a Patient Recovered from 2019 Novel Coronavirus (2019-nCoV) Pneumonia in Wuhan, China. *Radiology* 2020; **295**: 20 [PMID: 32032497 DOI: 10.1148/radiol.2020200269]

78 **Li M**, Lei P, Zeng B, Li Z, Yu P, Fan B, Wang C, Zhou J, Hu S, Liu H. Coronavirus Disease (COVID-19): Spectrum of CT Findings and Temporal Progression of the Disease. *Acad Radiol* 2020; **27**: 603-608 [PMID: 32204987 DOI: 10.1016/j.acra.2020.03.003]

79 **Wei J**, Xu H, Xiong J, Shen Q, Fan B, Ye C, Dong W, Hu F. 2019 Novel Coronavirus (COVID-19) Pneumonia: Serial Computed Tomography Findings. *Korean J Radiol* 2020; **21**: 501-504 [PMID: 32100486 DOI: 10.3348/kjr.2020.0112]

80 **Pan Y**, Guan H, Zhou S, Wang Y, Li Q, Zhu T, Hu Q, Xia L. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol* 2020; **30**: 3306-3309 [PMID: 32055945 DOI: 10.1007/s00330-020-06731-x]

81 **Bernheim A**, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020; **295**: 200463 [PMID: 32077789 DOI: 10.1148/radiol.2020200463]

82 **Wang Y**, Dong C, Hu Y, Li C, Ren Q, Zhang X, Shi H, Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296**: E55-E64 [PMID: 32191587 DOI: 10.1148/radiol.2020200843]

83 **Xiong Y**, Sun D, Liu Y, Fan Y, Zhao L, Li X, Zhu W. Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes. *Invest Radiol* 2020; **55**: 332-339 [PMID: 32134800 DOI: 10.1097/RLI.0000000000000674]

84 **Tan HB**, Xiong F, Jiang YL, Huang WC, Wang Y, Li HH, You T, Fu TT, Lu R, Peng BW. The study of automatic machine learning base on radiomics of non-focus area in the first chest CT of

different clinical types of COVID-19 pneumonia. *Sci Rep* 2020; **10**: 18926 [PMID: 33144676 DOI: 10.1038/s41598-020-76141-y]

85 **Gillies RJ**, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. *Radiology* 2016; **278**: 563-577 [PMID: 26579733 DOI: 10.1148/radiol.2015151169]

86 **Machine learning in RayStation**. Infervision in the Frontlines Against the Coronavirus 2020. [cited 22 January 2021]. Available from: https://www.itnonline.com/content/infervision-frontlines-against-coronavirus

87 **McCall B**. COVID-19 and artificial intelligence: protecting health-care workers and curbing the spread. *Lancet Digit Health* 2020; **2**: e166-e167 [PMID: 32289116 DOI: 10.1016/S2589-7500(20)30054-6]

88 **Jin C**, Chen W, Cao Y, Xu Z, Tan Z, Zhang X, Deng L, Zheng C, Zhou J, Shi H, Feng J. Development and evaluation of an artificial intelligence system for COVID-19 diagnosis. *Nat Commun* 2020; **11**: 5088 [PMID: 33037212 DOI: 10.1038/s41467-020-18685-1]

89 **Harmon SA**, Sanford TH, Xu S, Turkbey EB, Roth H, Xu Z, Yang D, Myronenko A, Anderson V, Amalou A, Blain M, Kassin M, Long D, Varble N, Walker SM, Bagci U, Ierardi AM, Stellato E, Plensich GG, Franceschelli G, Girlando C, Irmici G, Labella D, Hammoud D, Malayeri A, Jones E, Summers RM, Choyke PL, Xu D, Flores M, Tamura K, Obinata H, Mori H, Patella F, Cariati M, Carrafiello G, An P, Wood BJ, Turkbey B. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets. *Nat Commun* 2020; **11**: 4080 [PMID: 32796848 DOI: 10.1038/s41467-020-17971-2]

90 **Yu Z**, Li X, Sun H, Wang J, Zhao T, Chen H, Ma Y, Zhu S, Xie Z. Rapid identification of COVID-19 severity in CT scans through classification of deep features. *Biomed Eng Online* 2020; **19**: 63 [PMID: 32787937 DOI: 10.1186/s12938-020-00807-x]

91 **Laghi A**. Cautions about radiologic diagnosis of COVID-19 infection driven by artificial intelligence. *Lancet Digit Health* 2020; **2**: e225 [PMID: 32373786 DOI: 10.1016/S2589-7500(20)30079-0]

92 **Bai HX**, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, Pan I, Shi LB, Wang DC, Mei J, Jiang XL, Zeng QH, Egglin TK, Hu PF, Agarwal S, Xie FF, Li S, Healey T, Atalay MK, Liao WH. Performance of Radiologists in Differentiating COVID-19 from Non-COVID-19 Viral Pneumonia at Chest CT. *Radiology* 2020; **296**: E46-E54 [PMID: 32155105 DOI: 10.1148/radiol.2020200823]

93 **Shi J**, Giess CS, Martin T, Lemaire KA, Curley PJ, Bay C, Mayo-Smith WW, Boland GW, Khorasani R. Radiology Workload Changes During the COVID-19 Pandemic: Implications for Staff Redeployment. *Acad Radiol* 2021; **28**: 1-7 [PMID: 33036897 DOI: 10.1016/j.acra.2020.09.008]

94 **American College of Radiology**. ACR COVID-19 Clinical Resources for Radiologists. 2020 [cited 22 January 2021]. Available from: https://www.acr.org/clinical-resources/COVID-19-Radiology-Resources

95 **Naidich JJ**, Boltyenkov A, Wang JJ, Chusid J, Hughes D, Sanelli PC. Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Imaging Case Volumes. *J Am Coll Radiol* 2020; **17**: 865-872 [PMID: 32425710 DOI: 10.1016/j.jacr.2020.05.004]

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

97 **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683-690 [PMID: 32275288 DOI: 10.1001/jamaneurol.2020.1127]

98 **Ronco C**, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol* 2020; **16**: 308-310 [PMID: 32273593 DOI: 10.1038/s41581-020-0284-7]

99 **Tang N**, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; **18**: 844-847 [PMID: 32073213 DOI: 10.1111/jth.14768]

100 **American College of Radiology**. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. 2020 [cited 22 January 2021]. Available from: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection

101 **Zu ZY**, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology* 2020; **296**: E15-E25 [PMID: 32083985 DOI: 10.1148/radiol.2020200490]

102 **Panayiotou A**, Rafailidis V, Puttick T, Satchithananda K, Gray A, Sidhu PS. Escalation and de-escalation of the radiology response to COVID-19 in a tertiary hospital in South London: The King's College Hospital experience. *Br J Radiol* 2020; **93**: 20201034 [PMID: 33112652 DOI: 10.1259/bjr.20201034]

103 **Jeffrey S**. Klein M, Bien Soo Tan, MBBS, Lionel Tim-Ee Cheng, MBBS, Marta Heilbrun, MD, Dushyant Sahani, MD. RSNA Hosts Second Webinar on Radiology Surge and Second Surge Preparedness. [cited 22 January 2021]. Available from: https://www.rsna.org/en/news/2020/June/COVID-19-Surge-Preparedness-Part-Two

104 **Quah LJJ**, Tan BKK, Fua TP, Wee CPJ, Lim CS, Nadarajan G, Zakaria ND, Chan SJ, Wan PW, Teo LT, Chua YY, Wong E, Venkataraman A. Reorganising the emergency department to manage

the COVID-19 outbreak. *Int J Emerg Med* 2020; **13**: 32 [PMID: 32552659 DOI: 10.1186/s12245-020-00294-w]

105 **Cheng LT**, Chan LP, Tan BH, Chen RC, Tay KH, Ling ML, Tan BS. Déjà Vu or Jamais Vu? *AJR Am J Roentgenol* 2020; **214**: 1206-1210 [PMID: 32130047 DOI: 10.2214/AJR.20.22927]

106 **Tridandapani S**, Holl G, Canon CL. Rapid Deployment of Home PACS Workstations to Enable Social Distancing in the Coronavirus Disease (COVID-19) Era. *AJR Am J Roentgenol* 2020; **215**: 1351-1353 [PMID: 32432912 DOI: 10.2214/AJR.20.23495]

World Journal of Radiology

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

World J Radiol 2021 September 28; 13(9): 283-293

DOI: 10.4329/wjr.v13.i9.283

ISSN 1949-8470 (online)

MINIREVIEWS

Role of cardiac magnetic resonance imaging in the diagnosis and management of COVID-19 related myocarditis: Clinical and imaging considerations

Lavannya Atri, Michael Morgan, Sean Harrell, Wael AlJaroudi, Adam E Berman

ORCID number: Lavannya Atri 0000-0002-0601-5575; Michael Morgan 0000-0002-4780-5944; Sean Harrell 0000-0002-1381-3049; Wael AlJaroudi 0000-0003-0890-4437; Adam E Berman 0000-0002-9023-1130.

Author contributions: Atri L and Morgan M wrote the paper; Harrell S, AlJaroudi W, Berman AE made critical revisions and added content to the manuscript; Berman AE conceived the topic and provided oversight of the writing, editing and submission process.

Conflict-of-interest statement: Authors declare no conflict of interest for this article. This manuscript is not under review elsewhere and there is no prior publication of manuscript contents. The views expressed in this article are solely those of the authors.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works

Lavannya Atri, Michael Morgan, Sean Harrell, Wael AlJaroudi, Adam E Berman, Division of Cardiology, Medical College of Georgia, Augusta University, Augusta, GA 30912, United States

Adam E Berman, Division of Health Policy, Medical College of Georgia, Augusta University, Augusta, GA 30912, United States

Adam E Berman, Division of Health Economics and Modeling, Medical College of Georgia, Augusta University, Augusta, GA 30912, United States

Corresponding author: Lavannya Atri, MS, Division of Cardiology, Medical College of Georgia, Augusta University, 1120 15th Street, Augusta, GA 30912, United States. latri@augusta.edu

Abstract

There is a growing evidence of cardiovascular complications in coronavirus disease 2019 (COVID-19) patients. As evidence accumulated of COVID-19 mediated inflammatory effects on the myocardium, substantial attention has been directed towards cardiovascular imaging modalities that facilitate this diagnosis. Cardiac magnetic resonance imaging (CMRI) is the gold standard for the detection of structural and functional myocardial alterations and its role in identifying patients with COVID-19 mediated cardiac injury is growing. Despite its utility in the diagnosis of myocardial injury in this population, CMRI's impact on patient management is still evolving. This review provides a framework for the use of CMRI in diagnosis and management of COVID-19 patients from the perspective of a cardiologist. We review the role of CMRI in the management of both the acutely and remotely COVID-19 infected patient. We discuss patient selection for this imaging modality; T1, T2, and late gadolinium enhancement imaging techniques; and previously described CMRI findings in other cardiomyopathies with potential implications in COVID-19 recovered patients.

Key Words: Cardiac magnetic resonance imaging; COVID-19; Cardiovascular magnetic resonance; Myocarditis; Coronavirus; Cardiovascular complications

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: February 28, 2021
Peer-review started: February 28, 2021
First decision: May 6, 2021
Revised: May 27, 2021
Accepted: August 30, 2021
Article in press: August 30, 2021
Published online: September 28, 2021

P-Reviewer: Gaisenok O, Kelle S
S-Editor: Wang JL
L-Editor: A
P-Editor: Liu JH

Core Tip: Cardiovascular magnetic resonance imaging (CMRI) is a powerful imaging modality used in defining cardiac tissue characterization. As the prevalence and incidence of coronavirus disease 2019 (COVID-19) continues to rise, the utility of CMRI in defining COVID-19 related myocardial damage is growing. This review discusses the impact of CMRI in diagnosing myocardial involvement in acutely ill and recovered COVID-19 patients as well as its implications for patient management.

Citation: Atri L, Morgan M, Harrell S, AlJaroudi W, Berman AE. Role of cardiac magnetic resonance imaging in the diagnosis and management of COVID-19 related myocarditis: Clinical and imaging considerations. *World J Radiol* 2021; 13(9): 283-293
URL: https://www.wjgnet.com/1949-8470/full/v13/i9/283.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i9.283

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for the coronavirus disease 2019 (COVID-19) pandemic, continues to spread across the United States (US) and globally. As of January 21, 2021, the US reported over 23 million confirmed cases of COVID-19 as well as over 400000 COVID-19 related mortalities[1]. It has been previously reported that COVID-19 patients often have complications involving acute myocardial injury. These injuries are the most frequently reported cardiovascular abnormality in COVID-19, and occur in approximately 8%-12% of all patients[2]. Other cardiovascular effects of COVID-19 include endothelial damage, systolic heart failure, and arrhythmias[3]. Proposed mechanisms for cardiac injury include those mediated by systemic inflammation, direct viral attack on cardiomyocytes, myocardial interstitial fibrosis, overactive cytokine and interferon immune response, coronary plaque destabilization, and hypoxia[4,5].

Myocarditis is an increasingly recognized complication of COVID-19[6]. While endomyocardial biopsy remains the gold standard for tissue diagnosis, this procedure is invasive, characterized by potential serious complications and may be impractical in certain patient populations. Non-invasive imaging modalities, however, provide a safe alternative to aid in the diagnosis and management of myocarditis. While echocardiography possesses distinct advantages including low cost, accessibility, and faster interpretation times that may be beneficial in resource-scarce settings, many patients with early or mild myocarditis may have a normal echocardiogram[7]. Computed tomography (CT) modalities lack high quality myocardial tissue characterization that is essential for the diagnosis of myocarditis while exposing patients to significant amounts of radiation and contrast materials. Nuclear imaging is another potential modality to aid in the diagnosis of myocarditis, but lacks the spatial resolution to distinguish mid or epicardial myocardial perfusion defects (myocarditis) from subendocardial perfusion defects (ischemic) with significant partial volume effect and hence limited diagnostic accuracy[7].

Cardiovascular magnetic resonance imaging (CMRI) techniques remain the preferred modality for assessing patients with suspected myocarditis. CMRI provides detailed anatomical visualization, tissue-level analysis, safety, quantitative accuracy, and inter-observer consistency[7,8]. CMRI techniques are not without their limitations. These include higher cost when compared to echocardiography, longer exam times, and reliance on imaging interpretation by readers specifically trained in this discipline. Despite these limitations, CMRI remains the preferred imaging modality in the assessment of COVID-19 patients suspected of myocarditis and has the potential of playing a pivotal role in early diagnosis COVID-19-related cardiac injury. Finally, CMRI has the unique ability to evaluate subclinical and chronic cardiac involvement following COVID-19 infection.

CMRI AND CARDIAC TISSUE CHARACTERIZATION

CMRI represents the gold standard for the noninvasive cardiac tissue characterization, detection of acute and chronic myocardial changes, and myocardial viability[9-12].

This volumetric and functional assessment utility has expanded its indications for not only diagnostic purposes, but also treatment guidance and patient follow-up as is currently being investigated in those patients with COVID-19 related acute myocarditis[13]. CMRI is also currently used to risk stratify patients with ischemic heart disease and myocarditis, assess precise ejection fraction, quantify scar tissue, and predict location of re-entrant circuits within the scar to guide catheter ablation[14]. The future of CMRI continues to grow with the incorporation of artificial intelligence, post-processing techniques and development of new MR sequences such as T1 and T2 mapping[13].

T1 mapping

Non-ischemic cardiomyopathies may present with acute edema and diffuse tissue fibrosis that is captured well using T1 mapping[15]. T1 mapping techniques may identify the heterogeneity of damaged cardiac tissue without the use of contrast. The native T1 values increase in areas of edema and fibrosis as seen in acute myocarditis (including the acute phase of COVID-19) and the T1 values decrease in areas of lipid overload as seen in Anderson-Fabry diseases[13,16]. These elevated T1 values can also be seen early amyloid deposition, aortic stenosis, and dilated cardiomyopathy[13].

T2 mapping

T2 mapping technique is similar to T1 imaging as it also identifies areas of inflammation and edema. Being highly sensitive to the water content of myocardial tissue, T2 can reliably identify patients with inflammatory cardiomyopathies and is indicated to detect inflammation associated with viral myocardial damage, myocardial infarction, sarcoidosis, toxicity from chemotherapeutic drugs, transplant rejection as well as detection of iron overload[13,16,17].

Late gadolinium enhancement

Late gadolinium enhancement (LGE) imaging techniques involves the use of gadolinium as a contrast agent to identify heterogeneity within myocardial tissue. LGE imaging represents a cornerstone of CMRI as it is used to define chronic myocardial fibrosis and necrosis caused by ischemia as well as myocardial fibrosis frequently present in non-ischemic dilated cardiomyopathy. Damaged cardiac tissue has a slower gadolinium washout time than healthy tissue, which allows for not only identification of myocardial scarring, but also its quantification[11,12,18]. LGE images of COVID-19 patients suspected of myocardial involvement revealed enhancement at the left ventricular base, suggestive of myocarditis (Figure 1).

Renal function should be assessed prior to the use of LGE as its use is relatively contraindicated for patients with significant renal impairment, although new generation Gadolinium agents seem to be safer to use[14,16,19]. Current guidelines proposed by the European Society of Cardiology, American Heart Association (AHA) and American College of Cardiology indicate the use of CMRI for diagnosis and management of coronary artery disease and cardiomyopathies, with a class I recommendation for suspected infiltrative causes[13,14,20].

Although data regarding CMRI characteristics of COVID-19 myocarditis is limited to case reports and series, a small study did compare 8 patients with COVID-19 myocarditis to 8 patients with non-COVID-19 myocarditis and 12 healthy patients[21]. Patients with suspected acute COVID-19 myocarditis (with elevated troponin and CRP) were found to have a pattern of diffuse myocardial edema detected as diffuse globally higher T1 and T2 myocardial relaxation times. Comparatively1, the patients with non-COVID-19 myocarditis had a more focal disease with prolonged T1 and T2 relaxation times and more visible myocardial edema and LGE lesions. It was also noted that skeletal muscle T1 was elevated in COVID-19 myocarditis patients, which impacted the T2 ratio to not be elevated significantly. Severe wall-motion abnormalities due to stress-induced cardiomyopathy and small pericardial effusions were also detected as CMRI enhancements in the COVID-19 myocarditis group[21].

ROLE OF CMRI IN PATIENTS INFECTED WITH COVID-19

A review of the literature

An increased prevalence of myocardial injury has been reported in patients affected by COVID-19. As described above, these findings may range from evidence of acute myocarditis to fibrosis remote from time of infection. Given these considerations,

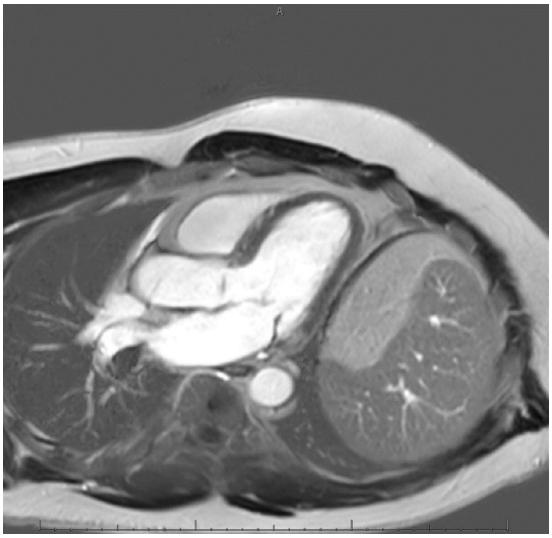


Figure 1 Delayed cardiac magnetic resonance image obtained after Gd administration showing patchy late Gd enhancement in the mid-myocardium of the basal inferolateral and mid anteroseptal walls consistent with prior myocarditis in patient who recovered from coronavirus disease 2019.

CMRI has played an important role (Table 1) in non-invasive cardiac evaluations in COVID-19 populations[16]. Despite this growing understanding of COVID-19 myocardial involvement, cases of COVID-19 myocarditis are likely underreported due to lack of imaging to reduce viral spread[22]. As a result, data at the population level regarding COVID-19 myocarditis is currently lacking. One recent study from Annie *et al*[23] showed the prevalence of COVID-19 myocarditis across a large multi-national registry to be 0.01% (256 patients). Despite this small prevalence, these patients were associated with increased mortality, underscoring the importance of diagnosing patients with myocarditis[23]. Due to the limitation of available large-scale data, however, our literature review is primarily centered around case-control studies. Kariyanna *et al*[24] performed a systematic review of myocarditis in COVID-19. Global case reports and retrospective studies were included in an effort to better describe trends exhibited by COVID-19 patients suspected of having myocarditis. It was determined that absence of troponin elevation was insufficient to exclude myocarditis. The most consistent findings in patients with suspected myocarditis were bilateral ground glass opacities detected on chest CT and late gadolinium enhancement from CMRI, both of which findings were observed in all patients in the study. Myocardial edema was reported in more than half of these patients, and it appears as though tissue characterization through the use of LGE and T1/T2 mapping is more useful at detecting myocardial damage than assessing ventricular function[25,26].

Understanding the complications that follow COVID-19 infection is an evolving area of research. Currently, there are several studies reporting CMRI findings in convalescent COVID-19 patients. In the largest prospective CMRI study performed to date examining 100 recovered COVID-19 positive patients, Puntmann *et al*[25] found that 78% of the patients had abnormal CMRI findings. These findings suggested ongoing cardiac inflammation independent of the severity of initial COVID-19 clinical presentation. Of the 78 patients diagnosed with COVID-19 related myocardial involvement, raised T1 was found in 73, raised T2 in 60, and abnormal LGE findings in 32. The elevated T1 Levels indicated diffuse myocardial fibrosis, while the elevated T2 Levels represented edema. The patients with both T1 and T2 elevated relaxation times reflected active myocardial edema that may have resulted from virus-mediated acute cardiac injury or dysregulation of an innate inflammatory immune response, whereas the patients with increased T1 but normal T2 Levels were felt to demonstrate healed residual diffuse myocardial injury[25,27]. These values were confirmed with the use of histological findings in severe cases. Furthermore, the abnormal pericardial LGE reflected cardiac tissue injury due to myocardial inflammation that was further supported by the pericardial effusion and active pericarditis[25]. It was also found that left and right ventricular ejection fraction represents a suboptimal marker of early disease detection and outcomes prediction as compared to direct tissue characterization by CMRI.

Table 1 Summary of existing data surrounding the use of cardiac magnetic resonance imaging use in coronavirus disease 2019 patients

Ref.	Study design	Sample size	CMRI findings	Other diagnostic findings
Kariyanna *et al*[24], 2020	Systematic review of 9 case reports and 2 retrospective studies	11 COVID-19 patients with reported myocardial inflammation or myocarditis	LGE highlighted in 100% of the patients	Elevated cardiac markers (Troponin, CK-MB, BNP) in 9 cases. Bilateral ground glass opacities seen in all patients with CT (6 cases). ECG abnormalities (ST-elevation and T-wave inversion) in 7 cases, and decreased LVEF in 6 cases. Active inflammation reported in the all biopsies performed (2 cases) and cardiomegaly reported in 7 cases
Puntmann *et al*[25], 2020	Prospective observational cohort study	100 recovered COVID-19 patients	Raised T1 in 73% of patients, raised T2 in 60%, LGE findings in 32%, and pericardial enhancement in 22%	Elevated troponin in 71% of patients, and significantly elevated Troponin in 5%. Endomyocardial biopsy revealed active lymphocytic inflammation. Lower LVEF and RVEF noted
Huang *et al* [26], 2020	Retrospective study	26 recovered COVID-19 patients who reported cardiac symptoms and underwent CMRI	Elevated T2 and/or LGE in 58% (15 patients) with 14 patients having myocardial edema and 8 LGE +. Global T1, T2, and extracellular volume were elevated in patients with abnormal CMRIs	Decreased RVEF, cardiac index, and stroke volume found in patients with positive CMRI findings
Clark *et al* [27], 2020	Retrospective cohort analysis	22 collegiate athletes with prior COVID-19 infection	LGE found in 9% (2 athletes)	All patients had normal Troponin, normal ECG, normal LVEF. LV mass was higher and RVEF was lower in athletes compared to control group
Li *et al*[28], 2021	Prospective observational cohort study	40 COVID-19 patients with moderate to severe pneumonia and no cardiovascular medical history	LGE findings in 3% (1 patient), elevated extracellular volume values in 60% (24 patients)	Normal LV and RV size and function. 70% (24 patients) had lower LV 2D-global longitudinal strain with subclinical changes of myocardial dysfunction

CMRI: Cardiac magnetic resonance imaging; COVID-19: Coronavirus disease 2019; LGE: Late gadolinium enhancement; CK-MB: Creatine kinase-MB; BNP: B-type natriuretic peptide; CT: Computed tomography; ECG: Electrocardiogram; LVEF: Left ventricular ejection fraction; RVEF: Right ventricular ejection fraction LV: Left ventricular; RV: Right ventricular.

This study highlights the considerable potential for cardiac involvement even in COVID-19 patients who had a milder presentation or those without cardiovascular comorbidities. The persistence of myocardial damage beyond the acute phase of infection was illustrated, but the extent of this potentially chronic injury is yet to be determined and requires further investigation.

Huang *et al*[26] reported a single-center retrospective study from China and found that out of 26 patients who reported cardiac symptoms during COVID-19 recovery, 15 of them had evidence of myocardial abnormalities on CMRI evaluation. Major findings included myocardial edema, fibrosis, and right ventricular impairment through the use of T1, T2, and LGE imaging. Of note, all patients had no previous history of myocardial injury. This, taken with the fact that the median length of time between symptom onset and CMRI scan was 50 days, suggests persistent COVID-19 cardiac involvement in a majority of this patient cohort. Further follow-up of patients with CMR abnormalities is necessary to confirm long-lasting myocardial involvement following resolution of COVID-19 infection.

While the detection of abnormal CMRI findings in patients with presenting true cardiac symptoms may seem intuitive, the necessity of excluding cardiac involvement in asymptomatic or minimally symptomatic represents an evolving concept amongst the global cardiovascular community. Subclinical myocardial involvement remains a common finding among COVID-19 patients who had a CMRI performed[25,28]. Indeed, Li *et al*[28] identified 28 out of 40 COVID-19 patients with myocardial dysfunction based upon reduced left ventricular 2D-global longitudinal strain when compared to healthy controls. In addition, 24 of the 40 patients showed elevated extracellular volume fraction compared to healthy controls indicating diffuse interstitial fibrosis in a majority of these patients. Interestingly, only one patient in this study demonstrated the presence of LGE. This reduced percentage of patients with LGE compared to findings from other studies could be a result of differing inclusion and exclusion criteria. Regardless, these findings indicate the appreciable prevalence of subclinical cardiac abnormalities recognized by CMRI months after COVID-19 recovery.

Owing to concern for the potential development of ventricular arrhythmias and sudden cardiac death (SCD) secondary to myocarditis in general, and expected similarly with COVID-19 myocarditis specifically, it is important to assess the extent of myocardial damage[29-32]. The first sign of underlying cardiac disease is oftentimes SCD in patients with ventricular arrhythmias[31]. This is especially true of patient populations that are at increased risk for arrhythmia development such as competitive athletes[30,32]. In light of the still unknown prevalence of COVID-19 related chronic cardiovascular sequelae, the question may be raised as to when a clinician should screen patients using CMRI. Phelan *et al*[30] provide recommendations on how to manage high risk recovering COVID-19 athletes. Initial restriction from play for 3 to 6 mo is recommended to allow for resolution of active inflammation[30]. Athletics can be resumed upon normalization of left ventricular function and cardiac biomarkers and absence of arrhythmias[30].

CMRI can reproducibly and accurately localize tissue injury, and thus has the ability to play an important role in fatal arrhythmia risk stratification along with prediction of reentrant circuits to guide ablation procedures[14]. LGE in particular has been shown to be the best predictor of all-cause mortality in biopsy-proven viral myocarditis, emphasizing the utility of CMR in COVID-19 patients[31,33].

While myocarditis appears to be the main form of cardiac involvement in COVID-19 patients, other forms of myocardial injury have also been observed to a smaller extent. These include but are not limited to myocardial infarction, pulmonary embolism, and Takotsubo cardiomyopathy[34-37]. These cardiovascular conditions may present similarly with chest pain, dyspnea, and positive troponin; however, they may be distinguished with CMRI[38], which further emphasizes the utility of CMRI in COVID-19 patients with signs of cardiac involvement.

MANAGEMENT RECOMMENDATIONS/GUIDELINES

Although the role of CMRI in the diagnosis of COVID-19 related cardiac injury is accepted, its practical utilization in both the inpatient and outpatient venues faces challenges in this continuously expanding patient population. In an effort to address these concerns, the Society of Cardiovascular Magnetic Resonance (SCMR) created specific guidelines treating the use of CMRI in COVID-19 patients[39,40]. These treatment guidelines cover a variety of imaging settings, including the acutely ill patient suspected of having acute COVID-19 related myocardial injury. In these instances, the SCMR recommends a short imaging protocol of 10-15 minutes for patients with active COVID-19 infection and a poor functional status[16]. CMRI can be performed on ventilated patients through special guidelines but is highly discouraged unless absolutely clinically necessary[39]. A holistic approach is recommended with the safety of patients and healthcare workers in mind and the use of clinical judgement to suspect acute myocardial injury[39]. If used in an inpatient setting, a dedicated CMRI scanner should be established when possible to limit the spread of COVID-19 [16]. In most circumstances, CMRI should be postponed until after resolution of the patient's contagious state and performed in an outpatient setting[27,39]. Once completed, further cardiovascular recommendations may be made based upon imaging findings. Given the breadth of patients affected by COVID-19, it is possible to detect preexisting and undiagnosed cardiac abnormalities and/or true COVID-19 related injury. Consequently, cardiovascular specialists must adopt a tailored approach to the treatment of these patients in light of their clinical circumstances. For example, patients with cardiomyopathy detected on CMRI may be candidates for consultation by a dedicated congestive heart failure treatment team[41].

APPROACHES TO THE ROLE OF CMRI IN THE COVID-19 ERA

Due to the novelty of the COVID-19 pandemic, there is a lack of consensus on how to manage the long-term cardiac effects of COVID-19. The high prevalence and disease burden of the COVID-19 pandemic and the constraints it's placed on healthcare resources make the determination of CMRI guidelines a difficult healthcare decision with ethical dimensions. Our center recommends using a risk stratification method to determine if a CMRI is needed for each individual patient (Table 2). High risk individuals include patients who have an abnormal echocardiogram, abnormal electrocardiogram (EKG), positive troponin levels, or history of myocarditis, myocardial infarction, or non-obstructive coronary artery disease. These patients should

Table 2 Proposed indications for cardiac magnetic resonance imaging in coronavirus disease 2019 patients

CMRI is indicated	CMRI not indicated
High risk patients with 2 or more of the following criteria	Low risk patients with all of the following criteria
Symptomatic	Asymptomatic
Elevated troponin	Negative troponin
Abnormal echocardiogram	Normal echocardiogram
Abnormal EKG	
High risk for ventricular arrhythmia or sudden death	
Myocardial infarction	
Clinical suspicion for myocardial injury	

CMRI: Cardiac magnetic resonance imaging; EKG: Echocardiogram.

receive a CMRI if available.

While suspicion of myocarditis can be determined based on biomarkers, EKG, and echocardiography, these tests may not be sufficient to determine the true etiology of cardiac involvement. EKG manifestations of myocarditis vary considerably and most commonly involve sinus tachycardia and nonspecific T wave and ST segment changes [42]. Echocardiography may demonstrate increased wall thickness and hyperechogenicity but more often than not provide inconclusive findings[43]. These tests provide little use in differentiating myocarditis from similarly presenting processes such as myocardial infarction or pulmonary embolus. If the aforementioned workup does not point towards a definitive diagnosis of myocarditis, CMRI may be indicated to provide direct tissue characterization, assess cardiac function indirectly based on the degree of inflammation present, and produce the confidence necessary to establish the diagnosis of myocarditis[42,44,45]. In addition, contrast-enhanced MRI may be a useful, noninvasive tool for long-term follow-up of patients with acute myocarditis and provide more accurate data on predicting outcome. A small study of 16 patients with myocarditis found that contrast enhancement ratio at 4 wk after disease onset was predictive of long-term outcomes[12].

Patients who are asymptomatic or have negative labs or normal echocardiogram findings are low priority for receiving CMRI. While post-COVID-19 asymptomatic myocardial involvement has been documented in the literature as mentioned above, this group of individuals with no symptoms should forgo CMRI at this time unless symptoms arise due to constraints on healthcare resources amidst the pandemic.

There is, however, a large gray area between these patient extremes. Athletes, for example, are a unique patient population as they are at higher risk of sudden cardiac death if they resume vigorous exercise with signs of myocarditis[32]. While there is disagreement in the approach of these patients, we believe clinicians should defer to the 2015 AHA Return to Play guidelines[32]. If there are any abnormalities on imaging, athletes should sit out from play with repeat imaging likely warranted in three to six months[32]. Reintroduction to play can take place gradually if biomarkers and EKG findings normalize and imaging shows no active inflammation[32]. At this time, it is unclear if resolution of myocarditis-related LGE is necessary for athletes to resume competition, so physicians should continue to use clinical judgment in their assessment of these patients. The Big Ten Athletics organization has taken the lead on evaluating their collegiate athletes following COVID-19 infection by creating a Big Ten Cardiac Registry[46]. Every student-athlete who tests positive undergoes cardiac testing involving EKG, biomarkers, echocardiogram, and CMRI to thoroughly evaluate cardiac structure and function[46]. This cautious approach is ideal but may not be practical for resource-scarce areas across the country, highlighting the importance of center-specific guidelines. It should be emphasized that determining appropriate imaging guidelines is an ongoing process that should utilize new findings as they are brought forward.

While athletes make up a unique subset of patients, the general public also stands to benefit from CMR imaging as indicated in Table 2.

LIMITATIONS OF THE USE CMRI IN PATIENTS WITH COVID-19

There are significant practical limitations regarding the use of CMRI in COVID-19 patients. In addition to limited availability at the global scale, CMRI represents a more expensive and time-consuming imaging modality when compared to conventional alternatives such as echocardiography. Additionally, consistent interpretation of CMRI images is vital to the widespread applicability of CMRI prognostic data[30]. This may be difficult to achieve considering many medical providers do not have access to the imaging modality itself or to cardiac imaging specialists who can accurately interpret the acquired images[47]. The lack of easy access to CMRI imaging creates the potential for selection bias in studies reporting CMRI results. These limitations must be taken into consideration during the creation of imaging guidelines of COVID-19 patients worldwide. Actively contagious COVID-19 patients with suspected cardiac involvement pose a unique challenge to clinicians. In order to reduce COVID-19 spread, CMR imaging may not be appropriate in COVID-19 patients who are actively contagious, thus placing a limitation on CMRI use in the early stage of COVID-19 infection[16]. Finally, it should also be noted that the CMRI studies conducted on COVID-19 patients discussed above all lack a pre-infection CMRI for comparison. Therefore, although unlikely, it is feasible that some included patients may have had preexisting changes detectable by CMRI following an unrelated COVID-19 infection. The lack of internal control limits the applicability of these research findings; nevertheless, the reported prevalence of myocardial abnormalities detected in these studies appears higher than that encountered both in clinical practice and the literature and thus deserves consideration.

FUTURE DIRECTION

The COVID-19 pandemic has created an unprecedented quest to obtain and synthesize data in a brief amount of time. A major topic, and one that is of particular concern, is the cardiovascular effects seen both acutely and in the chronic setting. Myocardial injury secondary to COVID-19 and the use of CMRI is an evolving subject. A systematic review of the literature, while limited, yields important insights into the use of CMRI.

In regards to active COVID-19 infection with concern for acute myocardial injury, CMRI has a more limited role. CMRI should be used in the acute setting when the findings will alter management and treatment strategies. Additionally, CMRI is able to aid in the diagnosis of myocardial infarction, RV strain in pulmonary embolism, and Takatsubo cardiomyopathy[34]. Given the infectious nature of the coronavirus, the risk of exposure and transmission of COVID-19 to healthcare workers should be kept in mind. CMRI should be performed cautiously or postponed unless they alter the treatment and management of patients in a time-critical manner.

Although CMRI usage will be constricted the general population vastly due to cost and availability limitations, we suspect a major use of CMRI moving forward will be in athletes who have recovered from COVID-19. This is due to the increased risk of adverse events including sudden cardiac death for this specific population. As demonstrated by Phelan *et al*[30], CMRI is recommended in athletes if clinical concern is elevated, despite normal or unremarkable biomarkers and/or Echocardiogram and EKG. Additionally, Rink *et al*[46] has created an athlete registry and will be performing CMRI on every student athlete that has recovered from COVID-19. As high school, collegiate, and professional sports begin their seasons, much consideration and caution will be present in those athletes who have recovered from COVID-19. Given what we know about evidence of LGE and associated ventricular events, indications for withholding athletes from competitive sport may certainly arise.

CONCLUSION

As a relatively new imaging modality with ongoing research, guidelines regarding CMRI use continue to evolve as new techniques and advances emerge. The role of CMRI in the diagnosis of COVID-19 related illness is evolving as well. Small studies have demonstrated the presence of cardiac injury even in minimally or asymptomatic COVID-19 patients. While the long-term sequelae of COVID-19 mediated cardiac disease is unknown, the diagnostic yield of CMRI places it squarely in the forefront of imaging strategies for this growing patient population. While factors such as

availability and cost may limit the widespread adoption of CMRI, its use in selected populations such as competitive athletes remain important. Further studies examining the prognostic utility of CMRI findings in the recovered COVID-19 population appears warranted.

REFERENCES

1 **Center for Disease Control and Prevention**. CDC COVID Data Tracker, 2021. Available from: https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days

2 **Paramasivam A**, Priyadharsini JV, Raghunandhakumar S, Elumalai P. A novel COVID-19 and its effects on cardiovascular disease. *Hypertens Res* 2020; **43**: 729-730 [PMID: 32355222 DOI: 10.1038/s41440-020-0461-x]

3 **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]

4 **Bansal M**. Cardiovascular disease and COVID-19. *Diabetes Metab Syndr* 2020; **14**: 247-250 [PMID: 32247212 DOI: 10.1016/j.dsx.2020.03.013]

5 **Babapoor-Farrokhran S**, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. *Life Sci* 2020; **253**: 117723 [PMID: 32360126 DOI: 10.1016/j.lfs.2020.117723]

6 **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]

7 **Friedrich MG**, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol* 2009; **53**: 1475-1487 [PMID: 19389557 DOI: 10.1016/j.jacc.2009.02.007]

8 **Agdamag ACC**, Edmiston JB, Charpentier V, Chowdhury M, Fraser M, Maharaj VR, Francis GS, Alexy T. Update on COVID-19 Myocarditis. *Medicina (Kaunas)* 2020; **56** [PMID: 33317101 DOI: 10.3390/medicina56120678]

9 **Ferreira VM**, Piechnik SK, Robson MD, Neubauer S, Karamitsos TD. Myocardial tissue characterization by magnetic resonance imaging: novel applications of T1 and T2 mapping. *J Thorac Imaging* 2014; **29**: 147-154 [PMID: 24576837 DOI: 10.1097/RTI.0000000000000077]

10 **Mather AN**, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Timing of cardiovascular MR imaging after acute myocardial infarction: effect on estimates of infarct characteristics and prediction of late ventricular remodeling. *Radiology* 2011; **261**: 116-126 [PMID: 21828188 DOI: 10.1148/radiol.11110228]

11 **Kim RJ**, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000; **343**: 1445-1453 [PMID: 11078769 DOI: 10.1056/NEJM200011163432003]

12 **Wagner A**, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, Klocke FJ, Bonow RO, Kim RJ, Judd RM. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003; **361**: 374-379 [PMID: 12573373 DOI: 10.1016/S0140-6736(03)12389-6]

13 **Busse A**, Rajagopal R, Yücel S, Beller E, Öner A, Streckenbach F, Cantré D, Ince H, Weber MA, Meinel FG. Cardiac MRI-Update 2020. *Radiologe* 2020; **60**: 33-40 [PMID: 32385547 DOI: 10.1007/s00117-020-00687-1]

14 **Nelson T**, Garg P, Clayton RH, Lee J. The Role of Cardiac MRI in the Management of Ventricular Arrhythmias in Ischaemic and Non-ischaemic Dilated Cardiomyopathy. *Arrhythm Electrophysiol Rev* 2019; **8**: 191-201 [PMID: 31463057 DOI: 10.15420/aer.2019.5.1]

15 **Nakamori S**, Bui AH, Jang J, El-Rewaidy HA, Kato S, Ngo LH, Josephson ME, Manning WJ, Nezafat R. Increased myocardial native T_1 relaxation time in patients with nonischemic dilated cardiomyopathy with complex ventricular arrhythmia. *J Magn Reson Imaging* 2018; **47**: 779-786 [PMID: 28737018 DOI: 10.1002/jmri.25811]

16 **Kelle S**, Bucciarelli-Ducci C, Judd RM, Kwong RY, Simonetti O, Plein S, Raimondi F, Weinsaft JW, Wong TC, Carr J. Society for Cardiovascular Magnetic Resonance (SCMR) recommended CMR protocols for scanning patients with active or convalescent phase COVID-19 infection. *J Cardiovasc Magn Reson* 2020; **22**: 61 [PMID: 32878639 DOI: 10.1186/s12968-020-00656-6]

17 **Wheen P**, Armstrong R, Daly CA. Recent Advances in T1 and T2 Mapping in the Assessment of Fulminant Myocarditis by Cardiac Magnetic Resonance. *Curr Cardiol Rep* 2020; **22**: 47 [PMID: 32472218 DOI: 10.1007/s11886-020-01295-0]

18 **Neilan TG**, Coelho-Filho OR, Danik SB, Shah RV, Dodson JA, Verdini DJ, Tokuda M, Daly CA, Tedrow UB, Stevenson WG, Jerosch-Herold M, Ghoshhajra BB, Kwong RY. CMR quantification of myocardial scar provides additive prognostic information in nonischemic cardiomyopathy. *JACC Cardiovasc Imaging* 2013; **6**: 944-954 [PMID: 23932642 DOI: 10.1016/j.jcmg.2013.05.013]

19 **Schieda N**, Blaichman JI, Costa AF, Glikstein R, Hurrell C, James M, Jabehdar Maralani P, Shabana W, Tang A, Tsampalieros A, van der Pol CB, Hiremath S. Gadolinium-Based Contrast Agents in Kidney Disease: A Comprehensive Review and Clinical Practice Guideline Issued by the Canadian Association of Radiologists. *Can J Kidney Health Dis* 2018; **5**: 2054358118778573 [PMID: 29977584 DOI: 10.1177/2054358118778573]

20 **von Knobelsdorff-Brenkenhoff F**, Pilz G, Schulz-Menger J. Representation of cardiovascular magnetic resonance in the AHA / ACC guidelines. *J Cardiovasc Magn Reson* 2017; **19**: 70 [PMID: 28942735 DOI: 10.1186/s12968-017-0385-z]

21 **Luetkens JA**, Isaak A, Öztürk C, Mesropyan N, Monin M, Schlabe S, Reinert M, Faron A, Heine A, Velten M, Dabir D, Boesecke C, Strassburg CP, Attenberger U, Zimmer S, Duerr GD, Nattermann J. Cardiac MRI in Suspected Acute COVID-19 Myocarditis. *Radiol Cardiothorac Imaging* 2021; **3**: e200628 [PMID: 33969316 DOI: 10.1148/ryct.2021200628]

22 **Panchal A**, Kyvernitakis A, Mikolich JR, Biederman RWW. Contemporary use of cardiac imaging for COVID-19 patients: a three center experience defining a potential role for cardiac MRI. *Int J Cardiovasc Imaging* 2021; **37**: 1721-1733 [PMID: 33559800 DOI: 10.1007/s10554-020-02139-2]

23 **Annie FH**, Embrey S, Alkhaimy H, Elashery AR, Nanjundappa A. association between myocarditis and mortality in COVID-19 patients in a large registry. *J Am Coll Cardiol* 2021; **77**: 3037 [DOI: 10.1016/S0735-1097(21)04392-8]

24 **Kariyanna PT**, Sutarjono B, Grewal E, Singh KP, Aurora L, Smith L, Chandrakumar HP, Jayarangaiah A, Goldman SA, Salifu MO, McFarlane IM. A Systematic Review of COVID-19 and Myocarditis. *Am J Med Case Rep* 2020; **8**: 299-305 [PMID: 32747875]

25 **Puntmann VO**, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265-1273 [PMID: 32730619 DOI: 10.1001/jamacardio.2020.3557]

26 **Huang L**, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020; **13**: 2330-2339 [PMID: 32763118 DOI: 10.1016/j.jcmg.2020.05.004]

27 **Clark DE**, Parikh A, Dendy JM, Diamond AB, George-Durrett K, Fish FA, Fitch W, Hughes SG, Soslow JH. COVID-19 Myocardial Pathology Evaluated Through scrEening Cardiac Magnetic Resonance (COMPETE CMR). *medRxiv* 2020 [PMID: 32908996 DOI: 10.1101/2020.08.31.20185140]

28 **Li X**, Wang H, Zhao R, Wang T, Zhu Y, Qian Y, Liu B, Yu Y, Han Y. Elevated Extracellular Volume Fraction and Reduced Global Longitudinal Strains in Participants Recovered from COVID-19 without Clinical Cardiac Findings. *Radiology* 2021; **299**: E230-E240 [PMID: 33434112 DOI: 10.1148/radiol.2021203998]

29 **Schumm J**, Greulich S, Wagner A, Grün S, Ong P, Bentz K, Klingel K, Kandolf R, Bruder O, Schneider S, Sechtem U, Mahrholdt H. Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis. *J Cardiovasc Magn Reson* 2014; **16**: 14 [PMID: 24461053 DOI: 10.1186/1532-429X-16-14]

30 **Phelan D**, Kim JH, Elliott MD, Wasfy MM, Cremer P, Johri AM, Emery MS, Sengupta PP, Sharma S, Martinez MW, La Gerche A. Screening of Potential Cardiac Involvement in Competitive Athletes Recovering From COVID-19: An Expert Consensus Statement. *JACC Cardiovasc Imaging* 2020; **13**: 2635-2652 [PMID: 33303102 DOI: 10.1016/j.jcmg.2020.10.005]

31 **Mavrogeni S**, Petrou E, Kolovou G, Theodorakis G, Iliodromitis E. Prediction of ventricular arrhythmias using cardiovascular magnetic resonance. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 518-525 [PMID: 23324829 DOI: 10.1093/ehjci/jes302]

32 **Maron BJ**, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd, Cooper LT Jr, Link MS, Maron MS; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. *Circulation* 2015; **132**: e273-e280 [PMID: 26621644 DOI: 10.1161/CIR.0000000000000239]

33 **Grün S**, Schumm J, Greulich S, Wagner A, Schneider S, Bruder O, Kispert EM, Hill S, Ong P, Klingel K, Kandolf R, Sechtem U, Mahrholdt H. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 2012; **59**: 1604-1615 [PMID: 22365425 DOI: 10.1016/j.jacc.2012.01.007]

34 **Giustino G**, Croft LB, Oates CP, Rahman K, Lerakis S, Reddy VY, Goldman M. Takotsubo Cardiomyopathy in COVID-19. *J Am Coll Cardiol* 2020; **76**: 628-629 [PMID: 32517962 DOI: 10.1016/j.jacc.2020.05.068]

35 **Modin D**, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, Fralick M, Schou M, Lamberts M, Gerds T, Fosbøl EL, Phelps M, Kragholm KH, Andersen MP, Køber L, Torp-Pedersen C, Solomon SD, Gislason G, Biering-Sørensen T. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. *Circulation* 2020; **142**: 2080-2082 [PMID: 33054349 DOI: 10.1161/CIRCULATIONAHA.120.050809]

36 **Bilaloglu S**, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA* 2020; **324**: 799-801 [PMID: 32702090 DOI: 10.1001/jama.2020.13372]

37 **Poissy J**, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S; Lille ICU Haemostasis COVID-19 Group. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation* 2020; **142**: 184-186 [PMID: 32330083 DOI: 10.1161/CIRCULATIONAHA.120.047430]

38 **Doltra A**, Amundsen BH, Gebker R, Fleck E, Kelle S. Emerging concepts for myocardial late gadolinium enhancement MRI. *Curr Cardiol Rev* 2013; **9**: 185-190 [PMID: 23909638 DOI: 10.2174/1573403x113099990030]

39 **Han Y**, Chen T, Bryant J, Bucciarelli-Ducci C, Dyke C, Elliott MD, Ferrari VA, Friedrich MG, Lawton C, Manning WJ, Ordovas K, Plein S, Powell AJ, Raman SV, Carr J. Society for Cardiovascular Magnetic Resonance (SCMR) guidance for the practice of cardiovascular magnetic resonance during the COVID-19 pandemic. *J Cardiovasc Magn Reson* 2020; **22**: 26 [PMID: 32340614 DOI: 10.1186/s12968-020-00628-w]

40 **Allen BD**, Wong TC, Bucciarelli-Ducci C, Bryant J, Chen T, Dall'Armellina E, Finn JP, Fontana M, Francone M, Han Y, Hays AG, Jacob R, Lawton C, Manning WJ, Ordovas K, Parwani P, Plein S, Powell AJ, Raman SV, Salerno M, Carr JC. Society for Cardiovascular Magnetic Resonance (SCMR) guidance for re-activation of cardiovascular magnetic resonance practice after peak phase of the COVID-19 pandemic. *J Cardiovasc Magn Reson* 2020; **22**: 58 [PMID: 32772930 DOI: 10.1186/s12968-020-00654-8]

41 **Friedrich MG**. Cardiac MR in Times of COVID. 2020 Mar 24. In: JCMR Journal Club. Available from: https://scmr.org/resource/dynamic/blogs/20200414_133132_16845.pdf

42 **Basman C**, Agrawal PR, McRee C, Saravolatz L, Chen-Scarabelli C, Scarabelli TM. Diagnostic Approach to Myocarditis Mimicking Myocardial Infarction at Initial Presentation. *Cardiol Res* 2016; **7**: 209-213 [PMID: 28197294 DOI: 10.14740/cr485w]

43 **Friedrich MG**, Marcotte F. Cardiac magnetic resonance assessment of myocarditis. *Circ Cardiovasc Imaging* 2013; **6**: 833-839 [PMID: 24046380 DOI: 10.1161/CIRCIMAGING.113.000416]

44 **Puntmann VO**, Valbuena S, Hinojar R, Petersen SE, Greenwood JP, Kramer CM, Kwong RY, McCann GP, Berry C, Nagel E; SCMR Clinical Trial Writing Group. Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part I - analytical validation and clinical qualification. *J Cardiovasc Magn Reson* 2018; **20**: 67 [PMID: 30231886 DOI: 10.1186/s12968-018-0484-5]

45 **Olimulder MA**, van Es J, Galjee MA. The importance of cardiac MRI as a diagnostic tool in viral myocarditis-induced cardiomyopathy. *Neth Heart J* 2009; **17**: 481-486 [PMID: 20087452 DOI: 10.1007/BF03086308]

46 **Big Ten Cardiac Registry Steering Committee**, Rink LD, Daniels CJ, Boersma D, Borchers J, Busch J, Kovan J, Kratochvil CJ, Rifat S, Rosenthal G, Chung EH. Competitive Sports, the Coronavirus Disease 2019 Pandemic, and Big Ten Athletics. *Circ Cardiovasc Qual Outcomes* 2020; **13**: e007608 [PMID: 33125280 DOI: 10.1161/CIRCOUTCOMES.120.007608]

47 **Pfeiffer MP**, Biederman RW. Cardiac MRI: A General Overview with Emphasis on Current Use and Indications. *Med Clin North Am* 2015; **99**: 849-861 [PMID: 26042886 DOI: 10.1016/j.mcna.2015.02.011]

World Journal of Radiology

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

World J Radiol 2021 September 28; 13(9): 294-306

DOI: 10.4329/wjr.v13.i9.294

ISSN 1949-8470 (online)

SYSTEMATIC REVIEWS

Review on radiological evolution of COVID-19 pneumonia using computed tomography

Chiara Casartelli, Fabiana Perrone, Maurizio Balbi, Veronica Alfieri, Gianluca Milanese, Sebastiano Buti, Mario Silva, Nicola Sverzellati, Melissa Bersanelli

ORCID number: Chiara Casartelli 0000-0002-7638-5299; Fabiana Perrone 0000-0001-8090-770X; Maurizio Balbi 0000-0002-8436-3655; Veronica Alfieri 0000-0003-0456-069X; Gianluca Milanese 0000-0003-1974-4854; Sebastiano Buti 0000-0003-0876-0226; Mario Silva 0000-0002-2538-7032; Nicola Sverzellati 0000-0002-4820-3785; Melissa Bersanelli 0000-0002-6527-6281.

Author contributions: Bersanelli M, Perrone F and Casartelli C designed the work, planned the literature review according to PRISMA methods and identified the areas of interests to discuss; Perrone F and Casartelli C collected the data; Casartelli C, Balbi M and Alfieri V wrote the first draft of the manuscript; Bersanelli M revised the manuscript for relevant scientific content and copyediting; Buti S, Milanese G, Silva M and Sverzellati N revised the manuscript for relevant scientific content; All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: Bersanelli M received honoraria as a speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, Astra Zeneca, Pierre Fabre, and Pfizer and as a consultant for advisory role by

Chiara Casartelli, Fabiana Perrone, Sebastiano Buti, Melissa Bersanelli, Medical Oncology Unit, University Hospital of Parma, Parma 43126, Italy

Chiara Casartelli, Fabiana Perrone, Nicola Sverzellati, Melissa Bersanelli, Department of Medicine and Surgery, University of Parma, Parma 43126, Italy

Maurizio Balbi, Gianluca Milanese, Mario Silva, Nicola Sverzellati, Division of Radiology, University of Parma, Parma 43126, Italy

Veronica Alfieri, Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma 43126, Italy

Corresponding author: Fabiana Perrone, MD, Doctor, Medical Oncology Unit, University Hospital of Parma, Via A. Gramsci, 14, Parma 43126, Italy. fabiana.perrone89@libero.it

Abstract

BACKGROUND

Pneumonia is the main manifestation of coronavirus disease 2019 (COVID-19) infection. Chest computed tomography is recommended for the initial evaluation of the disease; this technique can also be helpful to monitor the disease progression and evaluate the therapeutic efficacy.

AIM

To review the currently available literature regarding the radiological follow-up of COVID-19-related lung alterations using the computed tomography scan, to describe the evidence about the dynamic evolution of COVID-19 pneumonia and verify the potential usefulness of the radiological follow-up.

METHODS

We used pertinent keywords on PubMed to select relevant studies; the articles we considered were published until October 30, 2020. Through this selection, 69 studies were identified, and 16 were finally included in the review.

RESULTS

Summarizing the included works' findings, we identified well-defined stages in the short follow-up time frame. A radiographic deterioration reaching a peak roughly within the first 2 wk; after the peak, an absorption process and repairing signs are observed. At later radiological follow-up, with the limitation of little

Novartis, BMS, IPSEN, and Pfizer; she also received fees for copyright transfer by Sciclone Pharmaceuticals and research funding by Roche S.p.A., Seqirus UK, Pfizer, Novartis, BMS, Astra Zeneca, and Sanofi Genzyme. Buti S received honoraria as a speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca and Novartis; he also received research funding from Novartis. All the other authors declare they have no conflicts of interest to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

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

Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: July 18, 2021

evidence available, the lesions usually did not recover completely.

CONCLUSION

Following computed tomography scan evolution over time could help physicians better understand the clinical impact of COVID-19 pneumonia and manage the possible sequelae; a longer follow-up is advisable to verify the complete resolution or the presence of long-term damage.

Key Words: COVID-19; Computed tomography; Pneumonia; Radiological evolution; Follow-up; Long-term consequences; Lung damage; SARS-CoV-2

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Given the recent discovery and study of severe acute respiratory syndrome coronavirus 2 infection, the evolution of coronavirus disease 2019 pneumonia has not been entirely defined yet. Chest computed tomography is an effective method to identify and follow coronavirus disease 2019 pneumonia over time. In this review, we considered the radiological changes on computed tomography scan and described the possible clinical pulmonary sequelae in order to understand the long-term outcome of coronavirus disease 2019 pneumonia better.

Citation: Casartelli C, Perrone F, Balbi M, Alfieri V, Milanese G, Buti S, Silva M, Sverzellati N, Bersanelli M. Review on radiological evolution of COVID-19 pneumonia using computed tomography. *World J Radiol* 2021; 13(9): 294-306
URL: https://www.wjgnet.com/1949-8470/full/v13/i9/294.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i9.294

INTRODUCTION

SARS-CoV-2, which stands for severe acute respiratory syndrome coronavirus 2, was first identified in December 2019 in Wuhan, China. The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has rapidly spread from China to all around the world within a few months, leading the World Health Organization to declare it a pandemic on March 11, 2020[1].

The transmission of SARS-CoV-2 happens through direct, indirect or close contact with infected people through infected secretions, such as saliva and respiratory secretions or their respiratory droplets. The main organ affected is the lung, with pneumonia being the major manifestation of the infection[2].

The gold standard for SARS-CoV-2 diagnosis is real-time reverse transcription-polymerase chain reaction. However, computed tomography (CT) is recommended for initial evaluation and diagnosis, and it is also useful in monitoring the disease progression and evaluating the therapeutic efficacy[3,4].

Until now, many reports have focused on CT scan features at diagnosis[5-7]. On the other hand, there are relatively few studies evaluating serial temporal changes in patients who underwent repeated CT examinations and, particularly, in the late follow-up.

Our aim is to review the literature currently available on the radiological follow-up of COVID-19-related lung alterations using the CT scan to describe the evidence about the dynamic evolution of COVID-19 pneumonia.

MATERIALS AND METHODS

We conducted this systematic review according to the Preferred Reporting Items guidelines for Systematic Reviews and Meta-Analysis (PRISMA) Statement[8]. The primary aim was to collect, describe and discuss the dynamic radiological evolution of COVID-19 pneumonia.

Revised: July 28, 2021
Accepted: August 13, 2021
Article in press: August 13, 2021
Published online: September 28, 2021

P-Reviewer: Braga MB
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Liu JH

Search strategy

Two authors (Casartelli C and Perrone F) carried out a comprehensive systematic search for published articles on the MEDLINE/PubMed library until October 31, 2020. Given the absence of articles on this topic before December 2019, when the first COVID-19 outbreak started, no upper limit for the search was chosen.

The following search keywords were used: "COVID-19" [all fields] AND "computed tomography" [all fields] AND "evolution" [all fields]. The reference lists of the included articles and reviews/meta-analyses on our research topic were also reviewed to identify additional relevant papers.

Study selection and eligibility criteria

Retrospective studies, prospective studies and case reports describing the evolution of COVID-19 pneumonia on CT scan were included. Only English language articles were considered eligible. Studies with insufficient radiological data were excluded. We planned qualitative analysis only, forecasting a high heterogeneity between the eligible studies, likely preventing quantitative analyses.

Data extraction and synthesis

The study characteristics (first author, year of publication, type of study, number of patients included, CT scan follow-up, dynamic evolution and main CT manifestations) were extracted from the included articles by a single author (Casartelli C). Two reviewers (Perrone F and Casartelli C) initially performed the data extraction, and then it was independently reviewed by an additional reviewer (Bersanelli M).

Any doubt or disagreement was discussed with a fourth investigator (Buti S) and resolved with all investigators' consensus.

RESULTS

General description

The study selection led to the inclusion of 16 reports: 13 retrospective studies[9-21], 1 prospective study[22] and 2 case series[23,24]. The outline of the search is reported in Figure 1.

These reports (more specifically, 15 from China[9-23], 1 from Italy[24]) have analyzed several cases of pneumonia caused by SARS-CoV-2 diagnosed through CT without contrast (Table 1).

Most of the reports have considered moderate/common pneumonia; if pneumonia was not explicitly classified, most of the articles included patients with a good and defined prognosis, who were ultimately discharged from the hospital, while patients with severe/critical pneumonia were generally excluded.

Four studies have also included a minority group of patients showing severe/critical pneumonia[10,14,17,20]; the 11 patients described by Sun Q *et al*[23] case series had severe pneumonia[23].

Scoring system

The most common score used to evaluate dynamic CT evolution was a semi-quantitative scoring system, which considered the total area of involvement of the lesions. The nature of the semi-quantitative scoring system was similar in the studies considered, even with some adjustments and discrepancies among them.

For example, Liang *et al*[11] assigned a 0-4 score based on the percentage of each lung lobe involvement; in agreement with this, the overall lung total severity score was reached by summing up the five lobe scores, with a possible range from 0 to 20.

Zhou *et al*[12] divided each lung into six zones, and the total score, given by the sum of the different lung regions, could reach a maximum of 48.

Zhang *et al*[15] used yet another adaptation of the system based on the lung segments involved, assigning a score based on the percentage of ground glass opacities (GGOs) and consolidation, with a possible range from 0 to 36.

The study from Liu *et al*[17], analyzing the CT of discharged patients, focused the score on non-GGO lesions since extended GGO areas were defined as a basic manifestation of convalescence, which could lead to an overestimation of the CT score.

Other authors, considering the limited accuracy and sensitivity of the semi-quantitative score based mainly on visual evaluation, proposed evaluating dynamic evolution by quantitative techniques.

Table 1 Characteristics and findings of the studies included in the systematic review

Ref.	Type of study	Patients included	Mean age in yr, range	CT scan follow-up	CT evaluation, scoring system
Han *et al*[9], 2020	Retrospective	17 surviving and discharged patients with COVID-19 pneumonia	40 ± 6	4 wk (4 weekly CT scan during hospitalization)	Semi-quantitative
Wang *et al* [10], 2020	Retrospective	63 patients with asymptomatic/mild, 378 with moderate, 43 with severe/critically COVID-19 pneumonia	47 (33-57)	From symptoms onset to beyond day 15	Quantitative
Liang *et al* [11], 2020	Retrospective	88 patients with mild COVID-19 pneumonia	42.7 (4-82)	3 wk after disease onset	Semi-quantitative
Sun *et al*[23], 2021	Case series	11 patients with severe COVID-19 pneumonia	52 (33-75)	CT scan during hospitalization (not well defined, at least 3 wk during hospitalization)	Qualitative
Zhou *et al* [12], 2020	Retrospective	100 patients with COVID-19 pneumonia (without ARDS)	52.3 ± 13.1 (27-80)	CT during hospitalization (from symptoms onset to beyond day 21)	Semi-quantitative
Wang *et al* [13], 2020	Retrospective	126 patients with COVID-19 pneumonia, (severe and critical cases excluded)	41.2 ± 10.8	CT scan during hospitalization (mean days of hospitalization 22 ± 5 d (12-40)	Qualitative
Wang *et al* [14], 2020	Retrospective	79 patients with non-severe (mild/common) COVID-19 pneumonia, 27 with severe pneumonia	48.0 ± 15.4	CT scan during hospitalization (mean days of hospitalization 25) + CT scan at 2-4 wk after discharge	Semi-quantitative
Zhang *et al* [15], 2020	Retrospective	33 patients with moderate COVID-19 pneumonia	49.0 ± 15.5	CT scan during hospitalization (mean days of hospitalization 20.8, range 18-37)	Semi-quantitative
Feng *et al*[16], 2020	Retrospective	19 patients with COVID-19 pneumonia	43.6 ± 15.5 (10-67)	0-34 d after symptoms onset	Quantitative
Liu *et al*[17], 2020	Retrospective	149 discharged patients with COVID-19 pneumonia (142 pneumonia, 7 severe pneumonia, no critical patients included)	43 (36-56)	Basal CT scan at discharge and at 1st, 2nd and 3rd week after discharge	Semi-quantitative
Pan *et al*[18], 2020	Retrospective	105 patients with COVID-19 pneumonia (severe pneumonia excluded)	48.6 ± 13.1 (23-72)	1-47 d after symptoms onset	Semi-quantitative
Zhuang *et al* [19], 2021	Retrospective	22 patients with COVID-19 pneumonia with solitary pulmonary lesion	40.7 ± 10.3 (23-54)	CT scan during hospitalization (mean days of hospitalization 19 d, range: 11-44) + first CT scan after discharge	Semi-quantitative
Urciuoli and Guerriero [24], 2020	Case series	6 patients with mild COVID-19 pneumonia	59.5	First CT on admission and 4 mo after symptoms onset	Qualitative
Zhang *et al* [20], 2020	Retrospective	53 patients with common COVID-19 pneumonia, 20 patients with severe COVID-19 pneumonia	45 ± 14 common pneumonia, 50 ± 15 severe pneumonia	0-30 d after symptoms onset	Quantitative
Pan *et al*[21], 2020	Retrospective	21 patients with COVID-19 pneumonia (severe pneumonia excluded)	40 ± 9 (25-63)	0-26 d after symptoms onset	Semi-quantitative
Wang *et al* [22], 2020	Prospective	90 patients with COVID-19 pneumonia	45 ± 14 (5-43)	0-24 d after symptoms onset	Semi-quantitative

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; CT: Computed tomography.

For example, Feng *et al*[16] measured the total volume (V_T) and mean CT value (CT), and from these, they calculated the mass (m): $V_T \times (CT + 1000)$[16].

In the report from Wang *et al*[10], quantitative CT measurements of pulmonary opacities, including volume, density and location, were extracted through deep learning algorithms.

In another report, quantitative CT features were automatically calculated using intelligent artificial algorithms, giving back the percentage of GGO volume, consolidation volume and total lesion volume[15].

Other reports described the evolution of lung lesions qualitatively[13,23,24].

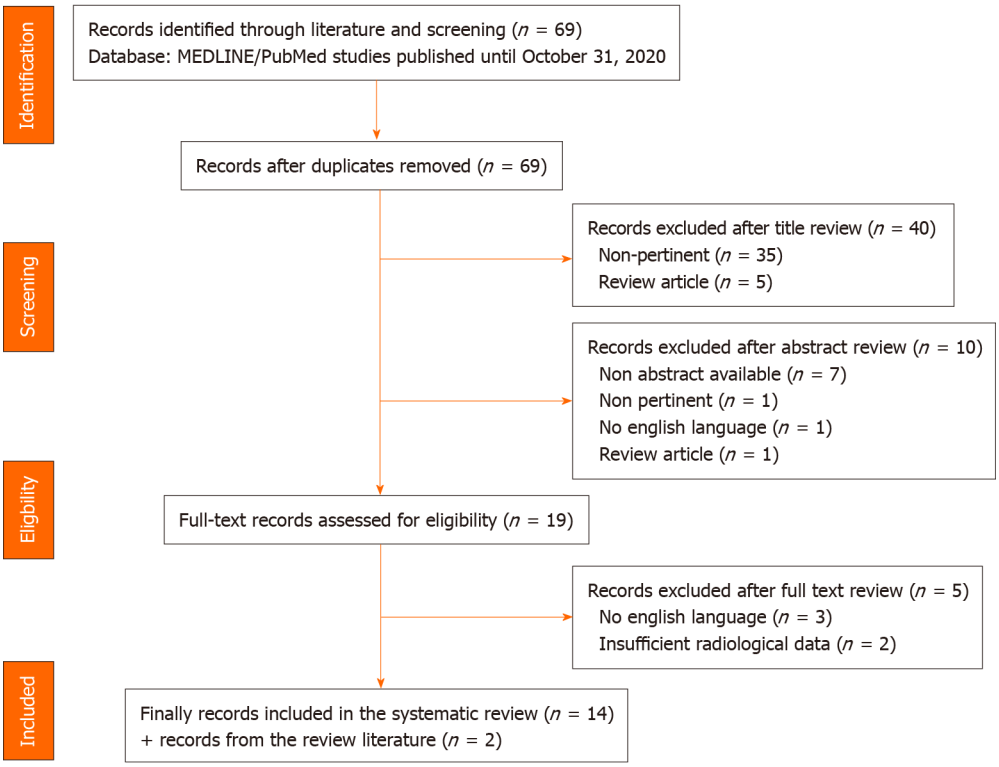


Figure 1 PRISMA flow diagram.

Radiological dynamic evolution: Severity and timing

Almost all the reports present a short-term radiological follow-up, focusing on the first few weeks from the symptoms appearance and studying serial CT scan approximately in the first 4 wk during hospitalization (Table 1).

It has been observed that the initial CT features and dynamic evolution of COVID-19 pneumonia have specific characteristics and regularity.

Several reports identify well-defined stages, from the onset of the symptoms to radiological recovery.

The most common pattern of radiographic evolution found is as follows. First, there is a progressive rapid radiographic deterioration, during which the lesions keep growing until they reach a peak; once this peak is reached, the lesions stop growing and are gradually reabsorbed and repairing signs appear. Almost all the studies found that the peak was reached roughly within 2 wk after the symptoms appearance, and after that lung abnormalities started to decrease.

There are some exceptions. Zhang *et al*[15] found an earlier peak, 8 d after symptoms onset, and lung lesions improved after 11 d. Wang *et al*[22] discovered a similar peak at around 6-11 d; in this case, though, a significant extent of lung lesions was found for longer times after the peak, showing a slower recovery.

Specific patterns of temporal evolution and relative peaks are shown in Table 2.

When severe pneumonia was considered separately, the disease seemed to have a slightly longer evolution, showing the peak later than for moderate pneumonia cases.

In the report from Zhang *et al*[20], severe pneumonia exhibited a peak approximately 17 d after symptoms onset (compared to moderate pneumonia, which peaked at 12 d in the same study). In the report from Wang *et al*[10], the opacity volume kept increasing even after 15 d in the severe/critical group. Four reports had taken into account a longer CT follow-up, considering CT scan after discharge[14,17,19,24].

Zhuang *et al*[19] considered both CT during hospitalization and the first CT after discharge (22-51 d after symptoms onset). During the latter phase, further absorption of the lung lesions compared with the previous radiological exam was observed, but not all patients showed a complete resolution.

Liu *et al*[17] studied the radiological evolution during the first few weeks after discharge, in particular 1, 2 and 3 wk after discharge. The aim was to determine the cumulative percentage of complete radiological resolution at each time point. They discovered that lung lesions could be entirely absorbed with no sequelae, and they suggested that the optimal time point for an early radiological estimation might be 2

Table 2 Computed tomography scan features of lung lesions according to the follow-up timing of coronavirus disease 2019 pneumonia

Ref.	Short-term follow-up, dynamic evolution during hospitalization period: Severity and timing	Main CT features at short-term follow-up	Late follow- up, dynamic evolution after hospital discharge	Main CT features at late follow- up
Han *et al* [9], 2020	Initial deterioration to a peak at the 2nd week followed by improvement in the 3rd and 4th week	GGO decreased from 1st week to 2nd week, then increased in 3 and 4. Consolidation and a mixed pattern noted in 2 wk. Crazy paving pattern had the highest frequency in 2nd week	N/A	N/A
Wang *et al* [10], 2020	Severe/critically ill group: Opacity volume continued to increase beyond 15 d. Moderate group: Peak on days 13-15 (the opacity density began to drop from day 10 to day 12). Asymptomatic/mild group: Highest opacity volume on days 1-3 and almost resolved after 15 d	GGO in the early stages, followed by appearance of consolidations. In the severe/critically ill group: Decreasing trend of GGO, increasing trend of consolidation over time	N/A	N/A
Liang *et al* [11], 2020	Total severity score showed an increasing trend in the first 2 wk, followed by a slight decrease in the 3rd week	GGO was the most common finding over time, consolidation decreased 2 wk after symptom onset. Reticulations and linear opacities and fibrosis became increasing prevalent later in the disease course	N/A	N/A
Sun *et al* [23], 2021	Improvement in the first 3 wk after hospitalization	Decrease in consolidation and GGO overtime and appearance of fibrous-like stripes	N/A	N/A
Zhou *et al* [12], 2020	3 stages: Early rapid progressive stage (1-7 d from symptom onset); > advanced stage with peak levels of abnormalities on CT at 8-14 d; > improvement after 14 d (particularly, after 21 d the absorption was more obvious)	GGO, GGO + reticular pattern/consolidation in the rapid progressive stage. ↑ GGO + reticular pattern and consolidation in the advanced stage. ↓ GGO + reticular pattern and consolidation and ↑ subpleural line, bronchus distortion, and fibrotic strips in the absorption stage	N/A	N/A
Wang *et al* [13], 2020	3 stages: Progression process; > absorption process; > stage of discharge	↑ GGO with consolidation (↑ crazy paving pattern, ↑ vascular thickening sign ↑ air bronchogram sign) in the progression process. Absorption of consolidation displayed as inhomogeneous partial GGOs with fibrosis shadows, occurrence of the fishing net on trees sign, ↑ fibrosis sign, ↑ subpleural line sign in the absorption process. Further absorption of GGOs, consolidation and fibrosis shadows and no appearance of new lesions in the stage of discharge	N/A	N/A
Wang *et al* [14], 2020	Radiological aggravation (< 2 wk) and improvement (> 2 wk)	GGO decreased while mixed GGO and consolidation increased from 1 wk to 2 wk after onset; linear opacity increased from 2 wk to 3 wk after onset	1-2 mo after symptom onset (median day 38): In 1/3 of cases complete absorption of lesions. Patients with more severe lesions at day 8-14 (> consolidations, CT score > 4, > 3 lobes involved) were more prone to have pulmonary residuals	Mainly linear opacities
Zhang *et al* [15], 2020	4 stages: Early stage (0-5 d); > peak stage (6-10 d); > absorption stage (11-15 d); > recovery stage (≥ 16 d)	Mainly GGO, (vascular thickening, bronchial wall thickening, and consolidation were also noted) in the early stage. ↑ GGO, vascular and bronchial thickening, and consolidation (mean peak at 8 d) in the peak stage. GGO and consolidation were predominantly present, with ↑ bronchial wall thickening and vascular thickening in the absorption stage. GGO and consolidation were partially absorbed, and bronchial wall thickening and vascular thickening ↓ (residual GGO and subpleural parenchymal bands) in the recovery stage	N/A	N/A
Feng *et al* [16], 2020	3 stages: Progressive stage (0-5 d); > peak stage (5-15 d). The greatest severity showed	GGO and interlobular/intralobular septal thickening were the most frequent CT manifestation	N/A	N/A

	approximately 7-8 d from onset; > absorption stage (15-30 d)			
Liu *et al* [17], 2020	N/A	N/A	At 3 wk follow up CT scan: Complete absorption of lesions in more than half of the patients	Gradually decrease of GGO and fibrous stripe (GGO during the first and fibrous stripe the 3rd week after discharge). "Tinted" sign and bronchovascular bundle distortion
Pan *et al* [18], 2020	5 stages: 0-3, 4-7, 8-14, 15-21, and > 21 d from symptoms onset (stages A-E, respectively). The total CT score of lung involvement was significantly higher in Stage C. The lung lesions in most patients improved after 14 d since initial symptom onset	Proportion of GGO was similar in each stage, consolidation gradually ↑ from Stage A to C and gradually ↓ from Stage C to E	N/A	N/A
Zhuang *et al*[19], 2021	Lung involvement peak at approximately 11 d, then lung lesions improved significantly	Mainly GGO in the first scan (0-4 d), crazy-paving pattern and consolidation in scan-2 (4-22 d), lesions were gradually absorbed and tended to be stable and linear opacities were noted in the scan-3 (before discharge, 6-41 d)	1st CT scan after discharge (22-51 d): Further absorption of lung lesions	Various presentations: negative CT scan, GGO, consolidation, linear opacities
Urciuoli and Guerriero [24], 2020	N/A	N/A	Persistence of lung abnormalities in 5/6 cases even if all the patients completely asymptomatic	Various presentations: 1 negative CT scan; in 2 patients, persistence of mixed pattern (GGO and fibrous streaks); in 1 patient fibrotic stripes, in 1 patient mixed pattern (interlobular septal thickening and patchy GGO); in 1 patient fibrotic pattern
Zhang *et al* [20], 2020	5 stages: Stage 1 (0-3 d), stage 2 (4-7 d), stage 3 (8-14 d), stage 4 (15-21 d), and stage 5 (22-30 d). PTV peaks at 12 d in common pneumonia, at 17 d in severe pneumonia	Common pneumonia: No significant differences in the PTV, PGV and PCV between stages 1-4 (percent of lesions was reduced in stage 5 compared with stage 4). Severe pneumonia PTV, PGV and PCV ↑ from stage 2 to stage 4 and ↓ in stage 5	N/A	N/A
Pan *et al* [21], 2020	4 stages: Early stage (0-4 d); progressive stage (5-8 d); peak stage (10-13 d); and absorption stage (≥ 14 d). Peak at 10 d after symptoms onset. CT signs improvement at approximately 14 d	GGO in the early stage, ↑ crazy-paving pattern and consolidation in the progressive stage, consolidation in the peak stage, progressive resolution of consolidation in the absorption stage	N/A	N/A
Wang *et al* [22], 2020	Lung abnormalities increased quickly after the onset of symptoms, peaked around 6-11 d, and were followed by persistence of high levels in extent for a long duration (slow absorption of the lesions)	GGOs trend: "first falling then rising". Consolidation was the second most common feature seen in the first 11 d. Mixed pattern: The second most predominant pattern since illness days 12-17	N/A	N/A

CT: Computer tomography; GGO: Ground glass opacity; N/A: Not applicable; PCV: Percentage of consolidation volume; PGV: Percentage of ground glass opacity volume; PTV: Percentage of total lesion volume.

wk after discharge. In their analysis, the cumulative percentage of the complete radiological resolution was 8%, 42%, 50% and 53% at discharge and during the 1st, 2nd and 3rd week after discharge, respectively[17].

Wang *et al*[14] conducted a study including both common and severe pneumonia, showing that approximately 1/3 of cases had complete absorption of lesions in the first 1-2 mo after symptom onset (median day 38). In their study, patients with more severe lung involvement at days 8-14 (peak) were more prone to have pulmonary residuals.

Urciuoli and Guerriero[24] considered a longer follow-up, with the study of CT up to 4 mo after the onset of the symptoms; the sample of this report was relatively small, as it considered only 6 patients with mild pneumonia. Interestingly, the follow-up CT scan revealed the persistence of lung abnormalities in 5 cases out of 6, even if all patients were completely asymptomatic at that point[24].

CT scan features of lung lesions at follow-up

The main features of lung lesions in the retrieved reports were multiple, bilateral, with a peripheral subpleural distribution.

In the short-term follow-up some features recurred. Consolidations and GGOs were always described, and often a mixed pattern was noted. Consolidations were more frequent during the peak, sometimes with accompanying signs such as a "crazy paving pattern" or "vascular thickening sign;" after the peak, they were gradually absorbed.

GGOs were described mainly in the early phase, but they could be observed also in later stages. In fact, in the report from Pan *et al*[18] the proportion of GGOs was similar in each stage. In those from Wang *et al*[22], the observed trend of GGOs was described as "first falling then rising" as they were present both in the first phase and in the last CT scan.

After the peak, besides GGOs, repairing CT signs, such as linear opacities, fibrous stripes, subpleural line sign and fibrosis shadows, were noted. Wang *et al*[13] proposed, in the absorption process, a particular sign called "fishing net on trees." This sign "indicated that the pulmonary lesions were in the stage of obvious absorption but not complete absorption. CT showed that the large area of consolidation was reduced, the density was reduced, the edge had shrunk, and there were significantly more bands and incomplete absorption of fibrosis shadows. The area was similar to a fishing net hanging on a branch that was not fully spread under the background of the increased bronchovascular bundle"[13].

In the longer-term follow-up, CT scans showed various presentations. Zhuang *et al*[19] observed in the first CT scan after discharge further absorption of the lung lesions. Also, GGOs, consolidations and linear opacities were still found in some patients. In the case series of Urciuoli and Guerriero[24], 2 patients presented persistence of a mixed pattern with GGO and fibrous streaks, 1 patient fibrotic stripes, 1 patient a mixed pattern with interlobular septal thickening and patchy GGOs and 1 patient fibrotic pattern[24].

Wang *et al*[22], who followed the CT scan until 4 wk after discharge, found mainly linear opacities. Liu *et al*[17] still observed in some patients GGOs and fibrous stripes even at the 3 wk radiological follow-up, even with a decreasing trend (GGO during the 1st week and fibrous stripes during the 3rd wk). Two additional signs were found during the evolution: "tinted" sign and bronchovascular bundle distortion. The "tinted" sign was demonstrated to coincide with an extension of the GGO area and a decrease in its density. According to the authors, the appearance of this pattern probably implied the gradual resolution of inflammation with re-expansion of alveoli. The bronchovascular bundle may be caused by inflammatory distraction or subsegmental atelectasis[17].

DISCUSSION

Current evidence of the temporal evolution of COVID-19 pneumonia derives from studies evaluating a relatively short follow-up period, and data about long-term radiological (and clinical) sequelae are still awaited[17,22,25,26]. The hallmark of early COVID-19 pneumonia includes bilateral, peripheral GGOs and consolidation often showing features resembling organizing pneumonia, such as a perilobular distribution and "reversed halo" sign (*i.e.* a focal, rounded area of ground-glass surrounded by a ring or arc of denser consolidation)[27,28]. These findings are non-specific and variably comprise foci of edema, organization and diffuse alveolar damage that are not too far removed from patients with other acute injuries, even noninfectious[29,30]. Notably, up to 56% of patients have been reported to demonstrate no abnormalities in the first 3 d after onset of symptoms, while conversely patients with no symptoms may show abnormal CT findings[31]. Moreover, still in the initial phase of the disease, pulmonary opacities may be unilateral and lack the characteristic peripheral distribution, possibly reducing diagnostic confidence in differentiating COVID-19 from potential mimickers such as heart failure and other infections[21,32].

The severity of acute COVID-19 manifestations is likely to peak within 2 wk from the disease onset, though reported temporal evolution varies depending on the studied population[12,13,18,21,31]. In this phase, patients may show an increasing extent of pulmonary consolidation, which parallels lung injury evolution. With the awareness of the heterogeneous studies included in the present analysis and intrinsic individual variation of the disease course, patients have been found to enter the so-called absorption stage roughly 14 d from the disease onset[12,13,18,21]. During this

period, consolidation tends to wane, while other findings such as linear opacities, parenchymal bands and reticulation possibly emerge, sometimes leading to a "fibrotic-like" appearance[26]. Even in this last case, it remains unclear whether residual abnormalities truly represent irreversible disease or will solve over time as no studies with a follow-up period greater than 6 mo have been performed so far[26,33]. Remarkably, most studies examined CT patterns in isolation at various time points rather than temporal changes of each pulmonary finding, providing valuable information about the overall disease evolution but missing the opportunity to examine regional linkages between patterns. Future studies are needed to explore how underlying pathogenetic pathways such as diffuse alveolar damage and an auto-inflammatory response would determine imaging features of COVID-19. In this regard, the role of baseline risk factors such as vascular thrombosis and interstitial lung abnormalities remains poorly investigated.

Besides providing clues to assess COVID-19 morphological changes, CT has been used to enrich clinical and laboratory findings to quantify disease severity in the acute setting and longitudinal evolution[12,18,21]. Various methods have been employed to assess CT lung involvement in COVID-19, including qualitative, semi-quantitative and software-based quantitative scoring systems[12,18,21,34-37]. In the included works, most CT scores were based on semi-quantitative methods, while only two studies used artificial intelligence techniques. Several parameters such as symptoms, oxygenation status and laboratory measures of infection and inflammation have been found to correlate with parenchymal involvement at CT, highlighting the potential role of imaging in predicting the clinical course of COVID-19 and optimizing patient care[38-40]. However, further evidence is needed to demonstrate CT scoring usefulness to manage COVID-19 and its actual impact on clinical decision-making in the acute and follow-up setting.

Clinical compendium: Pulmonary sequelae of COVID-19

The clinical counterpart of long-term radiological outcomes of COVID-19 pneumonia is a topic of growing interest. After the first wave of COVID-19, the awareness of patients suffering from residual symptoms, persistent beyond the acute phase of the disease, became very common, leading to the description of a post-COVID syndrome or Long-COVID[41]. However, the type and severity of respiratory impairment or functional sequelae are still unknown.

The current knowledge gained from the previous coronavirus outbreaks (SARS-CoV-1 in 2002-2004 and Middle East respiratory syndrome coronavirus in 2012) and the general understanding about outcomes in the acute distress respiratory syndrome suggest that some COVID-19 survivors might experience impaired lung function and exercise limitation, and some of them develop interstitial lung disease in the mid-long term[42-44].

Up until recently, only a few retrospective studies, including small samples, showed that patients might experience a reduction of forced vital capacity (13 patients at 6 wk)[45] and of forced vital capacity, forced expiratory volume in the first second, total lung capacity (TLC) and diffusion lung carbon monoxide (DLCO) (55 patients at 3 mo)[46].

In one of the largest cohorts studied to date describing the medium-term consequences of the infection (767 patients, follow-up at median time of 81 d after discharge), 51.4% of the patients reported being still symptomatic, with fatigue (55.0%), exertional dyspnea (45.8%) and post-traumatic psychological consequences (30.5%) as the most reported symptoms. Impaired lung function was found in 19% of the patients (reduced DLCO with or without restrictive pattern)[47].

Anastasio *et al*[48] recently published a study on 379 patients evaluated 4 mo after the diagnosis of COVID-19. Almost 69% of the patients reported almost one residual symptom. Patients who had pneumonia showed lower SpO_2 at rest and during the six-minute walking test and TLC compared with patients without prior pneumonia. Furthermore, the authors found an association between SpO_2/FiO_2 ratio and the pneumonia severity index during the acute phase, and mid-term alteration in SpO_2 at rest and during six-minute walking test, TLC, residual volume and forced vital capacity[48].

In an Italian study with 238 patients enrolled, DLCO was reduced less than 80% of the predicted value in more than half of the patients at 4 mo follow-up, and in 15.5% of the cases were less than 60%. More than 50% of the patients showed functional impairment assessed with Short Physical Performance Battery and 2-minute walk test[49].

In another large cohort of 647 patients evaluated at 3 mo follow-up, patients reported ongoing symptoms, in particularly fatigue (13%), palpitation (10%) and

dyspnea (9%). Those symptoms were significantly higher in patients who experienced severe COVID-19 compared to non-severe patients. In this cohort, only 81 patients were assessed with lung function test. More than half of the patients showed reduced DLCO. Similarly to symptoms, an impaired DLCO was more frequently associated with severe cases than non-severe (68% *vs* 42%). On a multivariate analysis, a CT total severity score > 10.5 and acute distress respiratory syndrome were significantly associate with impaired DLCO[50].

Similar results were found in a smaller cohort of 22 patients at 3 mo follow-up. Furthermore, on multivariate analysis, low TLC was associated with the need for mechanical ventilation and low forced expiratory volume in the first second with a high APACHE II score[51].

In a cohort of 119 patients who survived severe COVID-19 evaluated at 2 mo after discharge, respiratory symptoms (breathlessness 32%, cough 7%) were less frequent than persistent fatigue (68%), sleep disturbance (57%), anxiety and depression (22% and 18%, respectively) and post-traumatic stress disorder (25%). Despite radiological resolution in 87% of the patients, 41% reported persistent limitations in everyday life, and 44% had a Modified British Medical Research Council Questionnaire grade above the pre-COVID19 baseline[52]. A similar study on 134 patients found breathlessness as the most commonly reported symptoms (68%) followed by myalgia (51.5%), extreme fatigue (39.6%), low mood (37.3%) and sleep disturbance (35.1%)[53].

Long-term follow-up will help understand the impact of COVID-19 pneumonia on lung pathophysiology. Therefore, it is advisable to schedule serial follow-up in patients that still present lung function impairment or exercise limitation.

CONCLUSION

At present, the available literature focus on the acute phase of radiological follow-up of COVID-19 pneumonia and describes well-defined stages in the first few weeks after the onset of the symptoms.

The most common finding seems to be a peak of lung involvement reached roughly within the first 2 wk, characterized mainly by the growth of GGOs and consolidations. After that peak, these manifestations are gradually absorbed, and repairing signs, such as linear opacities, fibrous stripes, subpleural line sign and fibrosis shadows, tend to appear.

When considering later follow-up, up to 4 mo, lesions are usually not completely absorbed. A longer follow-up is definitely needed, especially to check whether the later signs are reversible and how they affect patients' conditions. Following CT scan evolution over time could help physicians better understand the clinical impact of COVID-19 pneumonia and manage the possible sequelae.

ARTICLE HIGHLIGHTS

Research background

Pneumonia is the main manifestation of severe acute respiratory syndrome coronavirus 2 infection. Chest computed tomography is an effective way to detect and keep track of coronavirus disease 2019 pneumonia cases over time.

Research motivation

As of now, few studies evaluated serial computed tomography scan temporal changes during the course of severe acute respiratory syndrome coronavirus 2 pneumonia.

Research objectives

This systematic review describes the dynamic evolution of coronavirus disease 2019 pneumonia, considering the available literature on this topic.

Research methods

A systematic review according to PRISMA guidelines was performed. Pertinent keywords on PubMed were used.

Research results

Different and well-defined stages characterized the first few weeks after the onset of

the symptoms.

Research conclusions

A peak of lung involvement within the first 2 wk, followed by the gradual absorption of the lesions and the advent of repairing signs was observed. Later follow-up showed that lesions were usually not completely absorbed, at least up to 4 mo.

Research perspectives

Longer follow-up is needed to check whether the later signs are reversible and how they affect patients' conditions.

REFERENCES

1 **World Health Organization**. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. [cited 11 February 2020] In: World Health Organization [Internet]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020

2 **World Health Organization**. Transmission of SARS-CoV-2: implications for infection prevention precautions. [cited 11 February 2020] In: World Health Organization [Internet]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions

3 **World Health Organization**. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). [cited 11 February 2020] In: World Health Organization [Internet]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

4 **Qiu T**, Liang S, Dabbous M, Wang Y, Han R, Toumi M. Chinese guidelines related to novel coronavirus pneumonia. *J Mark Access Health Policy* 2020; **8**: 1818446 [PMID: 33133431 DOI: 10.1080/20016689.2020.1818446]

5 **Shi H**, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]

6 **Xu X**, Yu C, Qu J, Zhang L, Jiang S, Huang D, Chen B, Zhang Z, Guan W, Ling Z, Jiang R, Hu T, Ding Y, Lin L, Gan Q, Luo L, Tang X, Liu J. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1275-1280 [PMID: 32107577 DOI: 10.1007/s00259-020-04735-9]

7 **Li K**, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. *Invest Radiol* 2020; **55**: 327-331 [PMID: 32118615 DOI: 10.1097/RLI.0000000000000672]

8 **Kristjansson M**, Bieluch VM, Byeff PD. Mycobacterium haemophilum infection in immunocompromised patients: case report and review of the literature. *Rev Infect Dis* 1991; **13**: 906-910 [PMID: 1962107 DOI: 10.1093/clinids/13.5.906]

9 **Han X**, Cao Y, Jiang N, Chen Y, Alwalid O, Zhang X, Gu J, Dai M, Liu J, Zhu W, Zheng C, Shi H. Novel Coronavirus Disease 2019 (COVID-19) Pneumonia Progression Course in 17 Discharged Patients: Comparison of Clinical and Thin-Section Computed Tomography Features During Recovery. *Clin Infect Dis* 2020; **71**: 723-731 [PMID: 32227091 DOI: 10.1093/cid/ciaa271]

10 **Wang YC**, Luo H, Liu S, Huang S, Zhou Z, Yu Q, Zhang S, Zhao Z, Yu Y, Yang Y, Wang D, Ju S. Dynamic evolution of COVID-19 on chest computed tomography: experience from Jiangsu Province of China. *Eur Radiol* 2020; **30**: 6194-6203 [PMID: 32524223 DOI: 10.1007/s00330-020-06976-6]

11 **Liang T**, Liu Z, Wu CC, Jin C, Zhao H, Wang Y, Wang Z, Li F, Zhou J, Cai S, Liang Y, Zhou H, Wang X, Ren Z, Yang J. Evolution of CT findings in patients with mild COVID-19 pneumonia. *Eur Radiol* 2020; **30**: 4865-4873 [PMID: 32291502 DOI: 10.1007/s00330-020-06823-8]

12 **Zhou S**, Zhu T, Wang Y, Xia L. Imaging features and evolution on CT in 100 COVID-19 pneumonia patients in Wuhan, China. *Eur Radiol* 2020; **30**: 5446-5454 [PMID: 32367418 DOI: 10.1007/s00330-020-06879-6]

13 **Wang C**, Shi B, Wei C, Ding H, Gu J, Dong J. Initial CT features and dynamic evolution of early-stage patients with COVID-19. *Radiol Infect Dis* 2020; **7**: 195-203 [PMID: 32864406 DOI: 10.1016/j.jrid.2020.08.002]

14 **Wang Y**, Jin C, Wu CC, Zhao H, Liang T, Liu Z, Jian Z, Li R, Wang Z, Li F, Zhou J, Cai S, Liu Y, Li H, Liang Y, Tian C, Yang J. Organizing pneumonia of COVID-19: Time-dependent evolution and outcome in CT findings. *PLoS One* 2020; **15**: e0240347 [PMID: 33175876 DOI: 10.1371/journal.pone.0240347]

15 **Zhang H**, Liu X, Yu P, Cheng M, Wang W, Sun Y, Zeng B, Fan B. Dynamic CT assessment of disease change and prognosis of patients with moderate COVID-19 pneumonia. *J Xray Sci Technol* 2020; **28**: 851-861 [PMID: 32741802 DOI: 10.3233/XST-200711]

16 **Feng X**, Ding X, Zhang F. Dynamic evolution of lung abnormalities evaluated by quantitative CT techniques in patients with COVID-19 infection. *Epidemiol Infect* 2020; **148**: e136 [PMID: 32624074

DOI: 10.1017/S0950268820001508]
17 **Liu D**, Zhang W, Pan F, Li L, Yang L, Zheng D, Wang J, Liang B. The pulmonary sequalae in discharged patients with COVID-19: a short-term observational study. *Respir Res* 2020; **21**: 125 [PMID: 32448391 DOI: 10.1186/s12931-020-01385-1]
18 **Pan Y**, Xia L, Wang Y, Guan H. Dynamic changes in computed tomography manifestations of 105 patients with novel coronavirus pneumonia in Wuhan, China. *J Int Med Res* 2020; **48**: 300060520972913 [PMID: 33213239 DOI: 10.1177/0300060520972913]
19 **Zhuang Y**, Lin L, Xu X, Xia T, Yu H, Fu G, Yang Y, Wang M, Sun H. Dynamic changes on chest CT of COVID-19 patients with solitary pulmonary lesion in initial CT. *Jpn J Radiol* 2021; **39**: 32-39 [PMID: 32886292 DOI: 10.1007/s11604-020-01037-w]
20 **Zhang Y**, Liu Y, Gong H, Wu L. Quantitative lung lesion features and temporal changes on chest CT in patients with common and severe SARS-CoV-2 pneumonia. *PLoS One* 2020; **15**: e0236858 [PMID: 32706819 DOI: 10.1371/journal.pone.0236858]
21 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]
22 **Wang Y**, Dong C, Hu Y, Li C, Ren Q, Zhang X, Shi H, Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296**: E55-E64 [PMID: 32191587 DOI: 10.1148/radiol.2020200843]
23 **Sun Q**, Li Q, Gao F, Li J, Xu X, Huang X. Evolution of computed tomography manifestations of eleven patients with severe coronavirus disease 2019 (COVID-19) pneumonia. *Int J Clin Pract* 2021; **75**: e13654 [PMID: 32770797 DOI: 10.1111/ijcp.13654]
24 **Urciuoli L**, Guerriero E. Chest CT Findings after 4 Months from the Onset of COVID-19 Pneumonia: A Case Series. *Diagnostics (Basel)* 2020; **10** [PMID: 33152991 DOI: 10.3390/diagnostics10110899]
25 **Guler SA**, Ebner L, Aubry-Beigelman C, Bridevaux PO, Brutsche M, Clarenbach C, Garzoni C, Geiser TK, Lenoir A, Mancinetti M, Naccini B, Ott SR, Piquilloud L, Prella M, Que YA, Soccal PM, von Garnier C, Funke-Chambour M. Pulmonary function and radiological features 4 mo after COVID-19: first results from the national prospective observational Swiss COVID-19 Lung study. *Eur Respir J* 2021; **57** [PMID: 33419891 DOI: 10.1183/13993003.03690-2020]
26 **Han X**, Fan Y, Alwalid O, Li N, Jia X, Yuan M, Li Y, Cao Y, Gu J, Wu H, Shi H. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology* 2021; **299**: E177-E186 [PMID: 33497317 DOI: 10.1148/radiol.2021203153]
27 **Chung M**, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A, Li K, Li S, Shan H. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020; **295**: 202-207 [PMID: 32017661 DOI: 10.1148/radiol.2020200230]
28 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]
29 **Carsana L**, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, Rech R, Colombo R, Antinori S, Corbellino M, Galli M, Catena E, Tosoni A, Gianatti A, Nebuloni M. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020; **20**: 1135-1140 [PMID: 32526193 DOI: 10.1016/S1473-3099(20)30434-5]
30 **Vasquez-Bonilla WO**, Orozco R, Argueta V, Sierra M, Zambrano LI, Muñoz-Lara F, López-Molina DS, Arteaga-Livias K, Grimes Z, Bryce C, Paniz-Mondolfi A, Rodríguez-Morales AJ. A review of the main histopathological findings in coronavirus disease 2019. *Hum Pathol* 2020; **105**: 74-83 [PMID: 32750378 DOI: 10.1016/j.humpath.2020.07.023]
31 **Bernheim A**, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020; **295**: 200463 [PMID: 32077789 DOI: 10.1148/radiol.2020200463]
32 **Parekh M**, Donuru A, Balasubramanya R, Kapur S. Review of the Chest CT Differential Diagnosis of Ground-Glass Opacities in the COVID Era. *Radiology* 2020; **297**: E289-E302 [PMID: 32633678 DOI: 10.1148/radiol.2020202504]
33 **Wells AU**, Devaraj A, Desai SR. Interstitial Lung Disease after COVID-19 Infection: A Catalog of Uncertainties. *Radiology* 2021; **299**: E216-E218 [PMID: 33502279 DOI: 10.1148/radiol.2021204482]
34 **Li K**, Fang Y, Li W, Pan C, Qin P, Zhong Y, Liu X, Huang M, Liao Y, Li S. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur Radiol* 2020; **30**: 4407-4416 [PMID: 32215691 DOI: 10.1007/s00330-020-06817-6]
35 **Yin X**, Min X, Nan Y, Feng Z, Li B, Cai W, Xi X, Wang L. Assessment of the Severity of Coronavirus Disease: Quantitative Computed Tomography Parameters *vs* Semiquantitative Visual Score. *Korean J Radiol* 2020; **21**: 998-1006 [PMID: 32677384 DOI: 10.3348/kjr.2020.0423]
36 **Pu J**, Leader JK, Bandos A, Ke S, Wang J, Shi J, Du P, Guo Y, Wenzel SE, Fuhrman CR, Wilson DO, Sciurba FC, Jin C. Automated quantification of COVID-19 severity and progression using chest CT images. *Eur Radiol* 2021; **31**: 436-446 [PMID: 32789756 DOI: 10.1007/s00330-020-07156-2]
37 **Lassau N**, Ammari S, Chouzenoux E, Gortais H, Herent P, Devilder M, Soliman S, Meyrignac O, Talabard MP, Lamarque JP, Dubois R, Loiseau N, Trichelair P, Bendjebbar E, Garcia G, Balleyguier

C, Merad M, Stoclin A, Jegou S, Griscelli F, Tetelboum N, Li Y, Verma S, Terris M, Dardouri T, Gupta K, Neacsu A, Chemouni F, Sefta M, Jehanno P, Bousaid I, Boursin Y, Planchet E, Azoulay M, Dachary J, Brulport F, Gonzalez A, Dehaene O, Schiratti JB, Schutte K, Pesquet JC, Talbot H, Pronier E, Wainrib G, Clozel T, Barlesi F, Bellin MF, Blum MGB. Integrating deep learning CT-scan model, biological and clinical variables to predict severity of COVID-19 patients. *Nat Commun* 2021; **12**: 634 [PMID: 33504775 DOI: 10.1038/s41467-020-20657-4]

38 **Zhao W**, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol* 2020; **214**: 1072-1077 [PMID: 32125873 DOI: 10.2214/AJR.20.22976]

39 **Leonardi A**, Scipione R, Alfieri G, Petrillo R, Dolciami M, Ciccarelli F, Perotti S, Cartocci G, Scala A, Imperiale C, Iafrate F, Francone M, Catalano C, Ricci P. Role of computed tomography in predicting critical disease in patients with covid-19 pneumonia: A retrospective study using a semiautomatic quantitative method. *Eur J Radiol* 2020; **130**: 109202 [PMID: 32745895 DOI: 10.1016/j.ejrad.2020.109202]

40 **Lanza E**, Muglia R, Bolengo I, Santonocito OG, Lisi C, Angelotti G, Morandini P, Savevski V, Politi LS, Balzarini L. Quantitative chest CT analysis in COVID-19 to predict the need for oxygenation support and intubation. *Eur Radiol* 2020; **30**: 6770-6778 [PMID: 32591888 DOI: 10.1007/s00330-020-07013-2]

41 **Mahase E**. Covid-19: What do we know about "long covid"? *BMJ* 2020; **370**: m2815 [PMID: 32665317 DOI: 10.1136/bmj.m2815]

42 **Hui DS**, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, Ko FW, Chan MC, Chan DP, Tong MW, Rainer TH, Ahuja AT, Cockram CS, Sung JJ. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; **60**: 401-409 [PMID: 15860716 DOI: 10.1136/thx.2004.030205]

43 **Antonio GE**, Wong KT, Hui DS, Wu A, Lee N, Yuen EH, Leung CB, Rainer TH, Cameron P, Chung SS, Sung JJ, Ahuja AT. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology* 2003; **228**: 810-815 [PMID: 12805557 DOI: 10.1148/radiol.2283030726]

44 **Herridge MS**, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293-1304 [PMID: 21470008 DOI: 10.1056/NEJMoa1011802]

45 **Fumagalli A**, Misuraca C, Bianchi A, Borsa N, Limonta S, Maggiolini S, Bonardi DR, Corsonello A, Di Rosa M, Soraci L, Lattanzio F, Colombo D. Pulmonary function in patients surviving to COVID-19 pneumonia. *Infection* 2021; **49**: 153-157 [PMID: 32725597 DOI: 10.1007/s15010-020-01474-9]

46 **Zhao YM**, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; **25**: 100463 [PMID: 32838236 DOI: 10.1016/j.eclinm.2020.100463]

47 **Venturelli S**, Benatti SV, Casati M, Binda F, Zuglian G, Imeri G, Conti C, Biffi AM, Spada MS, Bondi E, Camera G, Severgnini R, Giammarresi A, Marinaro C, Rossini A, Bonaffini PA, Guerra G, Bellasi A, Cesa S, Rizzi M. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiol Infect* 2021; **149**: e32 [PMID: 33461632 DOI: 10.1017/S0950268821000145]

48 **Anastasio F**, Barbuto S, Scarnecchia E, Cosma P, Fugagnoli A, Rossi G, Parravicini M, Parravicini P. Medium-term impact of COVID-19 on pulmonary function, functional capacity and quality of life. *Eur Respir J* 2021 [PMID: 33574080 DOI: 10.1183/13993003.04015-2020]

49 **Bellan M**, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, Baldon G, Bartolomei G, Battaglia M, Battistini S, Binda V, Borg M, Cantaluppi V, Castello LM, Clivati E, Cisari C, Costanzo M, Croce A, Cuneo D, De Benedittis C, De Vecchi S, Feggi A, Gai M, Gambaro E, Gattoni E, Gramaglia C, Grisafi L, Guerriero C, Hayden E, Jona A, Invernizzi M, Lorenzini L, Loreti L, Martelli M, Marzullo P, Matino E, Panero A, Parachini E, Patrucco F, Patti G, Pirovano A, Prosperini P, Quaglino R, Rigamonti C, Sainaghi PP, Vecchi C, Zecca E, Pirisi M. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. *JAMA Netw Open* 2021; **4**: e2036142 [PMID: 33502487 DOI: 10.1001/jamanetworkopen.2020.36142]

50 **Qin W**, Chen S, Zhang Y, Dong F, Zhang Z, Hu B, Zhu Z, Li F, Wang X, Wang Y, Zhen K, Wang J, Wan Y, Li H, Elalamy I, Li C, Zhai Z, Wang C. Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at 3-month follow-up. *Eur Respir J* 2021; **58** [PMID: 33574077 DOI: 10.1183/13993003.03677-2020]

51 **Truffaut L**, Demey L, Bruyneel AV, Roman A, Alard S, De Vos N, Bruyneel M. Post-discharge critical COVID-19 Lung function related to severity of radiologic lung involvement at admission. *Respir Res* 2021; **22**: 29 [PMID: 33478527 DOI: 10.1186/s12931-021-01625-y]

52 **D'Cruz RF**, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, Patrick T, Walder D, Heitmann A, Lee K, Madula R, McNulty W, Macedo P, Lyall R, Warwick G, Galloway JB, Birring SS, Patel A, Patel I, Jolley CJ. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res* 2021; **7** [PMID: 33575312 DOI: 10.1183/23120541.00655-2020]

53 **Sykes DL**, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 2021; **199**: 113-119 [PMID: 33569660 DOI: 10.1007/s00408-021-00423-z]

World Journal of Radiology

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

World J Radiol 2021 September 28; 13(9): 307-313

DOI: 10.4329/wjr.v13.i9.307

ISSN 1949-8470 (online)

CASE REPORT

Neonatal infratentorial subdural hematoma contributing to obstructive hydrocephalus in the setting of therapeutic cooling: A case report

Lee K Rousslang, Elizabeth A Rooks, Jaren T Meldrum, Kristopher G Hooten, Jonathan R Wood

ORCID number: Lee K Rousslang 0000-0003-0875-1952; Elizabeth A Rooks 0000-0001-6763-4081; Jaren T Meldrum 0000-0001-7072-2621; Kristopher G Hooten 0000-0001-5471-1658; Jonathan R Wood 0000-0002-0295-6079.

Author contributions: Rousslang LK is the primary author; Rooks EA assisted by performing research background for the case and contributing portions of the writing; Meldrum JT assisted by providing primary edits and the initial radiological read; Hooten KG was the primary surgeon, and provided surgical insights into the case; Wood JR is the senior author who contributed final edits and portions of the unedited manuscript.

Informed consent statement: Informed written consent was obtained.

Conflict-of-interest statement: The authors have no financial, personal, or other vested interests in the information contained within this document.

CARE Checklist (2016) statement: The manuscript was checked according to the CARE Checklist (2016) statement.

Lee K Rousslang, Jonathan R Wood, Department of Radiology, Tripler Army Medical Center, Medical Center, HI 96859, United States

Elizabeth A Rooks, Department of Neuroscience, Duke University, Durham, NC 27708, United States

Jaren T Meldrum, Department of Radiology, Alaska Native Medical Center, Anchorage, AK 99508, United States

Kristopher G Hooten, Department of Neurosurgery, Tripler Army Medical Center, Medical Center, HI 96859, United States

Corresponding author: Lee K Rousslang, MD, Doctor, Department of Radiology, Tripler Army Medical Center, 1 Jarrett White Rd, Medical Center, HI 96859, United States.
lee.k.rousslang.civ@mail.mil

Abstract

BACKGROUND

Symptomatic neonatal subdural hematomas usually result from head trauma incurred during vaginal delivery, most commonly during instrument assistance. Symptomatic subdural hematomas are rare in C-section deliveries that were not preceded by assisted delivery techniques. Although the literature is inconclusive, another possible cause of subdural hematomas is therapeutic hypothermia.

CASE SUMMARY

We present a case of a term neonate who underwent therapeutic whole-body cooling for hypoxic ischemic encephalopathy following an emergent C-section delivery for prolonged decelerations. Head ultrasound on day of life 3 demonstrated a rounded mass in the posterior fossa. A follow-up brain magnetic resonance imaging confirmed hypoxic ischemic encephalopathy and clarified the subdural hematomas in the posterior fossa causing mass effect and obstructive hydrocephalus.

CONCLUSION

The aim of this report is to highlight the rarity and importance of mass-like subdural hematomas causing obstructive hydrocephalus, particularly in the setting of hypoxic ischemic encephalopathy and therapeutic whole-body cooling.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Specialty type: Radiology, Nuclear Medicine and Medical Imaging

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: March 30, 2021
Peer-review started: March 30, 2021
First decision: June 7, 2021
Revised: June 22, 2021
Accepted: September 8, 2021
Article in press: September 8, 2021
Published online: September 28, 2021

P-Reviewer: Cazorla E
S-Editor: Wang JL
L-Editor: A
P-Editor: Liu JH

Key Words: Hypoxic ischemic encephalopathy; Neonatal subdural hematoma; Therapeutic hypothermia; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Screening head ultrasound during hypothermia protocols for hypoxic ischemic encephalopathy (HIE) warrant scrutiny for hemorrhage in unexpected locations. Symptomatic subdural hematomas warrant a high degree of clinical suspicion, particularly due to their rarity in children delivered by C-section. This report highlights the emerging association of HIE, therapeutic hypothermia, and perinatal intracranial hemorrhage. Prompt imaging and neurosurgical intervention may relieve hemorrhage induced obstructive hydrocephalus during therapeutic cooling with good neurological outcomes, preventing need for permanent cerebrospinal fluid diversion. Familiarity with the key imaging characteristics and clinical exam features of mass-like subdural hematomas can help the treatment team consider the diagnosis, and potentially enable a prompt recovery.

Citation: Rousslang LK, Rooks EA, Meldrum JT, Hooten KG, Wood JR. Neonatal infratentorial subdural hematoma contributing to obstructive hydrocephalus in the setting of therapeutic cooling: A case report. *World J Radiol* 2021; 13(9): 307-313
URL: https://www.wjgnet.com/1949-8470/full/v13/i9/307.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i9.307

INTRODUCTION

Perinatal symptomatic subdural hematomas (SDH) are rare. They most commonly occur in the posterior fossa and are classically thought to result from venous disruption caused by birth trauma[1,2]. Although there are case reports of neonatal SDH after spontaneous vaginal delivery, or in-utero, it is still rare to observe a symptomatic SDH following an atraumatic C-section[3,4]. Hypoxic ischemic encephalopathy (HIE) has recently emerged as a potential cause of SDH, but the evidence is unclear and debated, with much of it based on autopsy[5-8]. Therapeutic hypothermia also appears to contribute to SDH, and whole-body cooling has been shown to impair hemostasis *in vivo*[9]. Additionally, Wang *et al*[10] recently reported a case of therapeutic cooling that is thought to have led to a massive SDH.

To the best of our knowledge, this is the first case in the literature to date of a neonate who developed a mass-like subdural hemorrhage of the posterior fossa while undergoing whole-body cooling causing obstructive hydrocephalus, following a non-traumatic C-section delivery.

CASE PRESENTATION

Personal and family history

A boy was born at 38 wk and 5 d to a gravida 3, aborta 2 mother *via* emergent C-section for prolonged decelerations and arrest of descent which was thought to be related to maternal difficulty in coordinating pushing efforts with contractions while receiving epidural anesthesia. The decelerations did not respond to changes in maternal positioning, or administration of supplemental oxygen and intravenous fluids. The mother had no pre-existing conditions, and was up to date with all vaccinations. His prenatal course was completely normal, including a 20-wk anatomy scan demonstrating normal brain imaging. Thick meconium was present at delivery, which was otherwise uncomplicated.

Physical examination

His birth weight was 4.0 kg, with APGAR scores of 1^{1}, 3^{5}, 4^{10}, and 6^{15}. At birth he was apneic, with a heart rate < 60, requiring chest compressions and intubation. Shortly after intubation he developed pulmonary hemorrhage and acute hypoxemic

respiratory failure that responded well to endotracheal epinephrine. His respiratory issues were thought to be caused by the aspiration of the thick meconium.

Laboratory examinations

Immediately after birth, his international normalized ratio (INR) was 2.3, with prothrombin time of 25.6 s, activated partial thromboplastin time of 65 s, and platelets of 81 × 10^3 platelets/uL. To correct his coagulopathy, he was given platelets, cryoprecipitate, and fresh frozen plasma for hemostasis, with downtrend in INR to 1.0 and uptrend in platelets to normal levels (> 150 × 10^3 platelets/uL) over the next four days.

Imaging examinations

Head ultrasound (HUS) on the first day of life (DOL) demonstrated left grade 1 germinal matrix hemorrhage, but no other intra-cranial hemorrhage. The patient was then started on whole-body cooling for HIE.

On his fourth day of whole-body cooling, the patient was found to have an increasing head circumference, increasing fontanelle size and fullness, and apneic events, suggestive of obstructive hydrocephalus. His exam further revealed a poor gag reflex and diminished response to stimuli with decreased spontaneous movement. Head ultrasound demonstrated a newly visualized mass in the infratentorial region, thought to represent a cerebellar or tentorial hemorrhage (Figure 1) and the patient was re-warmed.

FINAL DIAGNOSIS

A same-day brain magnetic resonance imaging (MRI) was performed, revealing a 2.5 cm hematoma in the posterior fossa causing extensive mass effect on the cerebellum, and effacement of the fourth ventricle leading to an obstructive hydrocephalus. There was also widespread hypoxic ischemic injury (Figure 2 and Figure 3). A ventricular access device was placed that day for intermittent cerebrospinal fluid (CSF) diversion.

On DOL 20, due to an increase in apneic and bradycardic episodes, and increasing hydrocephalus on HUS, a repeat MRI was performed, and demonstrated acute on chronic bleeding into the subdural space (Figure 4).

TREATMENT

Later on DOL 20, the patient underwent successful supratentorial burr-hole evacuation of the subdural hematoma as well as a sub-occipital craniectomy with an infratentorial, supracerebellar evacuation of the thrombus.

OUTCOME AND FOLLOW-UP

Post-operative imaging demonstrated near complete resolution of the subdural hematoma (Figure 5). MRI at 15 mo of age (Figure 6) demonstrated improved hydrocephalus. At the time of submission, the patient is 29 mo old, and suffers from right spastic hemiplegic cerebral palsy, an expressive aphasia, and strabismus.

DISCUSSION

While asymptomatic SDH are commonplace after delivery, symptomatic SDH are rare in neonates, with an incidence of approximately 3.8-5.2 of 10000 Live births[11-13]. SDH typically occur in the posterior fossa and are thought to arise from head trauma during vaginal delivery[1,2]. Infratentorial SDH most commonly results from falx or tentorial tears with bridging vein disruption and are worrisome because of their propensity to cause obstructive hydrocephalus, even with small volume bleeds[2]. Elective C-section deliveries are rarely associated with symptomatic SDH, likely due to lower rates of birth trauma.

Many researchers have conjectured that SDH can be secondary to cerebral ischemia [5-8]. The prevailing theory is that ischemia leads to damage of immature blood

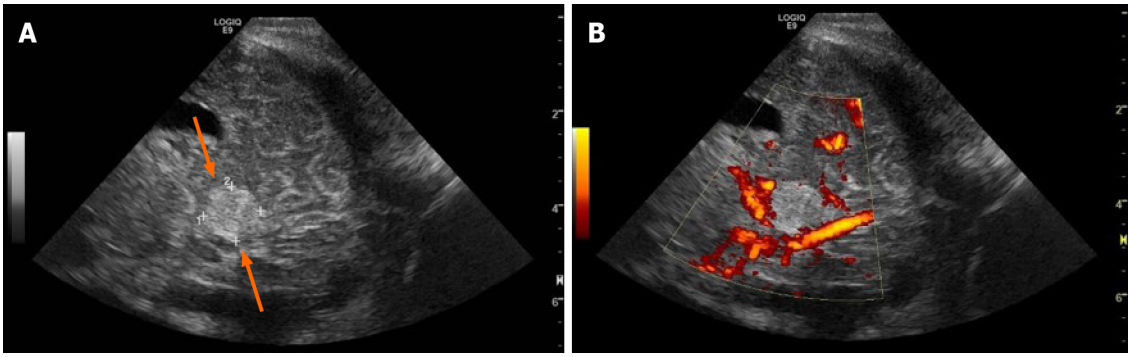


Figure 1 Head ultrasound through an oblique posterior parietal approach on 3rd day of life. The figure demonstrates an echogenic mass (arrows) in the posterior fossa, inferior to the tentorium, measuring 1.2 cm in its greatest dimension (A) with flow in the straight sinus and lack of flow on power Doppler within the mass (B).

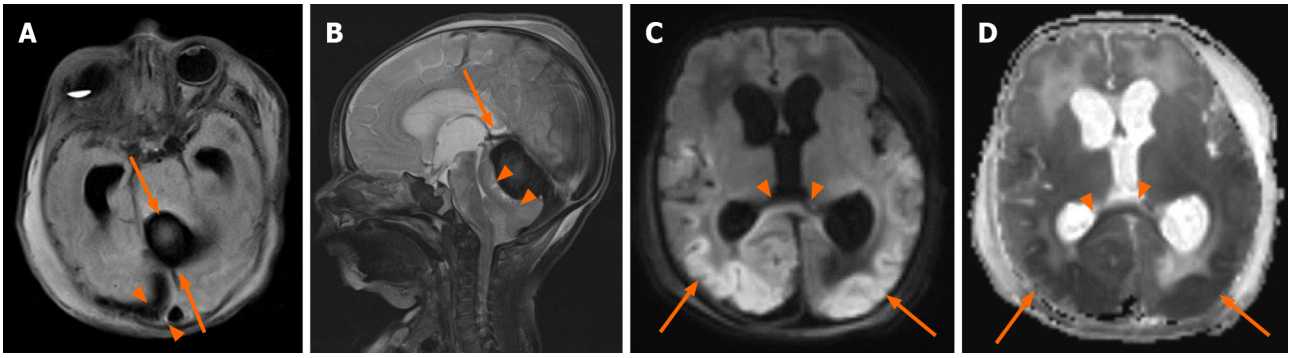


Figure 2 Axial T2 fluid-attenuated inversion recovery on 4th day of life. A: A 2.3 cm × 1.7 cm × 2.5 cm rounded thrombus (arrows) and subdural hemorrhage (arrowheads) as well as transverse sinus thrombosis; B: Sagittal T2 demonstrates thrombus (arrow) in posterior fossa superior to cerebellum causing downward mass effect on the cerebellum and fourth ventricle (arrowheads); C, D: Axial diffusion weighted imaging (C) and corresponding ADC map (D) demonstrate diffusion restriction in the corpus callosum (arrowheads), posterior parietal, temporal, and occipital lobes. Other scattered areas of diffusion restriction were noted throughout the brain and brainstem including the pons, cerebellum and posterior frontal lobes (not shown).

vessels, especially those of the richly vascularized falx cerebri, causing microvascular permeability that leads to intradural hemorrhage (IDH), which is then exacerbated by increased venous pressure[8]. IDH then leads to damage of the weak cell layer between the arachnoid and the dura, causing SDH[8]. However, other smaller studies still debate this theory[14].

The delayed presentation of the SDH in the setting of therapeutic cooling and HIE is what makes this case unique. Our patient's HIE was likely due to meconium aspiration and pulmonary hemorrhage resulting in asphyxia and acute hypoxemic respiratory failure requiring intubation at birth. The presence of the germinal matrix hemorrhage on initial head ultrasound did not preclude the whole-body cooling protocol from being initiated. Although initial therapeutic hypothermia is not known to cause spontaneous SDH, in-vivo studies have shown that hypothermia can impair hemostasis[15]. Furthermore, many of the studies involved in evaluating whole-body cooling were not powered to assess for harm[10]. Given this case involved a C-section with no significant birth trauma, and a delay in the clinical and radiographic presentation of the hemorrhage, it is likely in this case as Cohen *et al*[8] suggests that the SDH occurred as a result of cerebral ischemia, and hypothermia exacerbated the condition.

Successful treatment of neonatal posterior fossa subdural hematomas has been reported in the literature as early as 1940. In the largest reported clinical series of 15 infants, Perrin *et al*[4] demonstrated that successful surgical evacuation of posterior fossa hemorrhages can relieve obstructive hydrocephalus and prevent the need for permanent CSF diversion with good neurologic outcomes. Generally, conservative management is recommended initially but in the presence of hydrocephalus, a worsening clinical exam, or an enlarging hematoma, surgical evacuation should be considered.

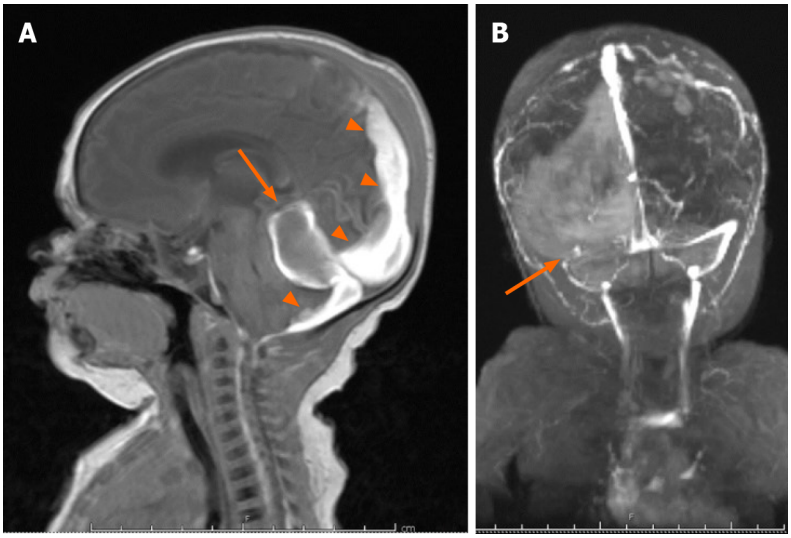


Figure 3 Brain magnetic resonance imaging on 10th day of life. A: Follow-up brain magnetic resonance imaging on 10th day of life re-demonstrates the posterior fossa mass (arrow), with interval high signal on sagittal T1 consistent with evolving blood products, as well as persistent subdural hematoma (arrowheads); B: PA coronal MRI venography demonstrates absent flow in the transverse sinus consistent with transverse sinus thrombosis.

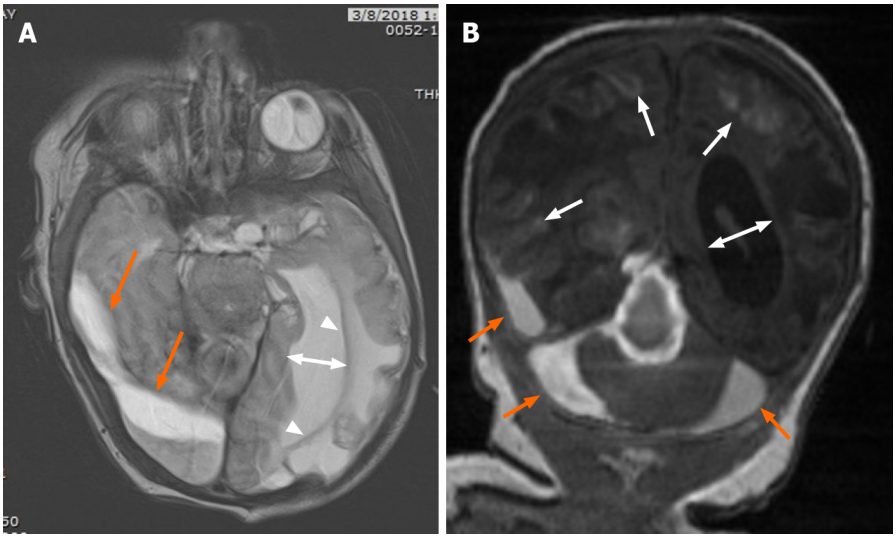


Figure 4 Follow-up magnetic resonance imaging on 20th day of life. A: Follow-up magnetic resonance imaging on 20th day of life revealed evolving blood products (orange arrows) in the subdural space on axial T2, with interval left greater than right cystic encephalomalacia in the parietal and occipital lobes and left greater than right ex-vacuo dilatation of the lateral ventricles (two direction arrow); B: Coronal T1 demonstrates degrading blood product in the right temporal lobe subdural space, and central and peripheral infratentorial subdural spaces (orange arrows) with cortical laminar necrosis (arrows) and increasing obstructive hydrocephalus (two-direction arrow).

CONCLUSION

Screening HUS during hypothermia protocols for HIE warrant scrutiny for hemorrhage in unexpected locations. Symptomatic subdural hematomas warrant a high degree of clinical suspicion, particularly due to their rarity in children delivered by C-section. This report highlights the emerging association of HIE, therapeutic hypothermia, and perinatal intracranial hemorrhage. Prompt imaging and neurosurgical intervention may relieve hemorrhage induced obstructive hydrocephalus during therapeutic cooling with good neurological outcomes, preventing need for permanent CSF diversion. Familiarity with the key imaging characteristics and clinical exam features of mass-like SDH can help the treatment team consider the diagnosis, and potentially enable a prompt recovery.

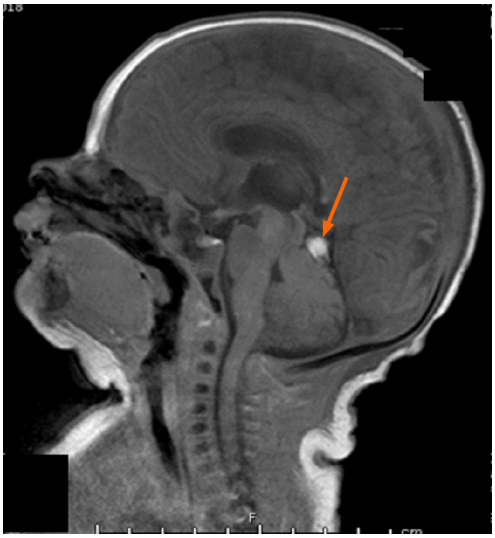


Figure 5 A sagittal T1 magnetic resonance imaging done immediately after subdural hematomas evacuation demonstrates near complete resolution of the subdural hematomas (arrow) and resolution of the obstructive hydrocephalus.

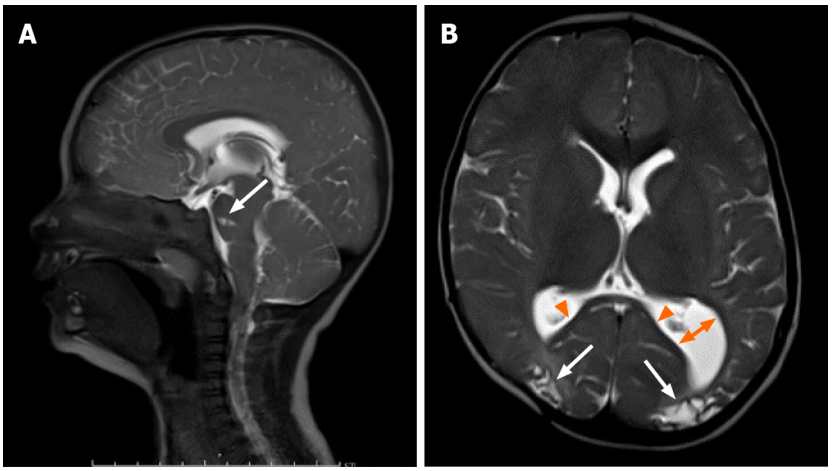


Figure 6 Follow-up magnetic resonance imaging at 15 mo. A: Follow-up magnetic resonance imaging at 15 mo demonstrates continued resolution of the subdural hematomas and obstructive hydrocephalus on sagittal T2. Note the focal encephalomalacia at the pons (arrow); B: Axial T2 demonstrates encephalomalacic change manifested by thinning of the posterior corpus callosum (arrowheads), decreased gray and white matter of the posterior occipital regions bilaterally (arrows), and colpocephaly of the left lateral ventricle (two direction arrow).

ACKNOWLEDGEMENTS

The views expressed in this manuscript are those of the authors, and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the United States Government.

REFERENCES

1 **Menezes AH**, Smith DE, Bell WE. Posterior fossa hemorrhage in the term neonate. *Neurosurgery* 1983; **13**: 452-456 [PMID: 6633841 DOI: 10.1227/00006123-198310000-00021]
2 **Perlman JM**. Brain injury in the term infant. *Semin Perinatol* 2004; **28**: 415-424 [PMID: 15693398 DOI: 10.1053/j.semperi.2004.10.003]
3 **Gunn TR**, Mok PM, Becroft DM. Subdural hemorrhage in utero. *Pediatrics* 1985; **76**: 605-610 [PMID: 3900908]
4 **Perrin RG**, Rutka JT, Drake JM, Meltzer H, Hellman J, Jay V, Hoffman HJ, Humphreys RP. Management and outcomes of posterior fossa subdural hematomas in neonates. *Neurosurgery* 1997; **40**: 1190-9; discussion 1199 [PMID: 9179892 DOI: 10.1097/00006123-199706000-00016]
5 **Steinbok P**, Haw CS, Cochrane DD, Kestle JR. Acute subdural hematoma associated with cerebral

infarction in the full-term neonate. *Pediatr Neurosurg* 1995; **23**: 206-215 [PMID: 8835211 DOI: 10.1159/000120960]

6 **McCubbin K**, Thoma L, Mena H, Gill JR. Subdural Hemorrhage and Hypoxia in Children Less than Two Years Old. *Acad Forensic Pathol* 2013; **3**: 213-221 [DOI: 10.23907/2013.027]

7 **Henzi BC**, Wagner B, Verma RK, Bigi S. Perinatal infratentorial haemorrhage: a rare but possibly life-threatening condition. *BMJ Case Rep* 2017; **2017** [PMID: 29196306 DOI: 10.1136/bcr-2017-221144]

8 **Cohen MC**, Scheimberg I. Evidence of occurrence of intradural and subdural hemorrhage in the perinatal and neonatal period in the context of hypoxic Ischemic encephalopathy: an observational study from two referral institutions in the United Kingdom. *Pediatr Dev Pathol* 2009; **12**: 169-176 [PMID: 19007301 DOI: 10.2350/08-08-0509.1]

9 **Rohrer MJ**, Natale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med* 1992; **20**: 1402-1405 [PMID: 1395660 DOI: 10.1097/00003246-199210000-00007]

10 **Wang D**, McMillan H, Bariciak E. Subdural haemorrhage and severe coagulopathy resulting in transtentorial uncal herniation in a neonate undergoing therapeutic hypothermia. *BMJ Case Rep* 2014; **2014** [PMID: 25100805 DOI: 10.1136/bcr-2013-203080]

11 **Chamnanvanakij S**, Rollins N, Perlman JM. Subdural hematoma in term infants. *Pediatr Neurol* 2002; **26**: 301-304 [PMID: 11992759 DOI: 10.1016/s0887-8994(01)00420-9]

12 **Gupta SN**, Kechli AM, Kanamalla US. Intracranial hemorrhage in term newborns: management and outcomes. *Pediatr Neurol* 2009; **40**: 1-12 [PMID: 19068247 DOI: 10.1016/j.pediatrneurol.2008.09.019]

13 **Rooks VJ**, Eaton JP, Ruess L, Petermann GW, Keck-Wherley J, Pedersen RC. Prevalence and evolution of intracranial hemorrhage in asymptomatic term infants. *AJNR Am J Neuroradiol* 2008; **29**: 1082-1089 [PMID: 18388219 DOI: 10.3174/ajnr.A1004]

14 **Byard RW**, Blumbergs P, Rutty G, Sperhake J, Banner J, Krous HF. Lack of evidence for a causal relationship between hypoxic-ischemic encephalopathy and subdural hemorrhage in fetal life, infancy, and early childhood. *Pediatr Dev Pathol* 2007; **10**: 348-350 [PMID: 17929988 DOI: 10.2350/06-08-0154.1]

15 **Wang CH**, Chen NC, Tsai MS, Yu PH, Wang AY, Chang WT, Huang CH, Chen WJ. Therapeutic Hypothermia and the Risk of Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore)* 2015; **94**: e2152 [PMID: 26632746 DOI: 10.1097/MD.0000000000002152]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 October 28; 13(10): 314-353

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 10 October 28, 2021

FRONTIER

MINIREVIEWS

ORIGINAL ARTICLE

Prospective Study

World Journal of Radiology

Monthly Volume 13 Number 10 October 28, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Radiology*, Ozum Tuncyurek, MD, EDIR, Associate Professor, Chief, Department of Radiology, Faculty of Medicine, Near East University, Nicosia 99138, Turkey. ozum.tuncyurek@neu.edu.tr

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJR* as 0.51.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
October 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 October 28; 13(10): 314-326

DOI: 10.4329/wjr.v13.i10.314

ISSN 1949-8470 (online)

FRONTIER

Current trends and perspectives in interventional radiology for gastrointestinal cancers

Elisa Reitano, Nicola de'Angelis, Giorgio Bianchi, Letizia Laera, Stavros Spiliopoulos, Roberto Calbi, Riccardo Memeo, Riccardo Inchingolo

ORCID number: Elisa Reitano 0000-0002-4286-8866; Nicola de'Angelis 0000-0002-1211-4916; Giorgio Bianchi 0000-0003-0245-3460; Letizia Laera 0000-0003-2183-8817; Stavros Spiliopoulos 0000-0003-1860-0568; Roberto Calbi 0000-0003-0934-8890; Riccardo Memeo 0000-0002-1668-932X; Riccardo Inchingolo 0000-0002-0253-5936.

Author contributions: Reitano E contributed to the manuscript concept, the study design, literature search, data interpretation, and article drafting; de'Angelis N, Bianchi G, Laera L, Spiliopoluos S, Calbi R and Memeo R contributed to the concept, the study design, data analysis, data interpretation, and manuscript critical revision; Inchingolo R contributed to the concept, the study design, data analysis, data interpretation, article drafting and manuscript critical revision; all authors read and approve the final version of the manuscript.

Conflict-of-interest statement: All the authors are aware of the content of the manuscript and have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

Elisa Reitano, Division of General Surgery, Department of Translational Medicine, University of Eastern Piedmont, Novara 28100, Italy

Nicola de'Angelis, Giorgio Bianchi, Unit of Minimally Invasive and Robotic Digestive Surgery, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Italy

Letizia Laera, Department of Oncology, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Italy

Stavros Spiliopoulos, 2nd Department of Radiology, School of Medicine, National and Kapodistrian University of Athens, Athens 12461, Greece

Roberto Calbi, Department of Radiology, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70124, Italy

Riccardo Memeo, Unit of Hepato-Pancreatic-Biliary Surgery, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Italy

Riccardo Inchingolo, Interventional Radiology Unit, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Italy

Corresponding author: Riccardo Inchingolo, MD, Chief Doctor, Director, Interventional Radiology Unit, "F. Miulli" General Regional Hospital, Strada per Santeramo, Acquaviva delle Fonti 70021, Italy. riccardoin@hotmail.it

Abstract

Gastrointestinal (GI) cancers often require a multidisciplinary approach involving surgeons, endoscopists, oncologists, and interventional radiologists to diagnose and treat primitive cancers, metastases, and related complications. In this context, interventional radiology (IR) represents a useful minimally-invasive tool allowing to reach lesions that are not easily approachable with other techniques. In the last years, through the development of new devices, IR has become increasingly relevant in the context of a more comprehensive management of the oncologic patient. Arterial embolization, ablative techniques, and gene therapy represent useful and innovative IR tools in GI cancer treatment. Moreover, IR can be useful for the management of GI cancer-related complications, such as bleeding, abscesses, GI obstructions, and neurological pain. The aim of this study is to show the principal IR techniques for the diagnosis and treatment of GI cancers and

accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

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

Received: March 28, 2021
Peer-review started: March 28, 2021
First decision: June 3, 2021
Revised: June 12, 2021
Accepted: October 9, 2021
Article in press: October 9, 2021
Published online: October 28, 2021

P-Reviewer: Kamada Y, Kanat O, Vasani J
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

related complications, as well as to describe the future perspectives of IR in this oncologic field.

Key Words: Interventional radiology; Radiology; Colorectal cancer; Gastric cancer; Malignancy; Embolization

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Interventional radiology is a minimally-invasive tool for the diagnosis and treatment of different gastrointestinal cancers, representing a useful alternative to more invasive approaches such as surgery and endoscopy. Hereby, we describe the different radiological techniques for the diagnosis and treatment of gastrointestinal cancers and related complications, underlining the role of this specialty in cancer patient's care.

Citation: Reitano E, de'Angelis N, Bianchi G, Laera L, Spiliopoulos S, Calbi R, Memeo R, Inchingolo R. Current trends and perspectives in interventional radiology for gastrointestinal cancers. *World J Radiol* 2021; 13(10): 314-326
URL: https://www.wjgnet.com/1949-8470/full/v13/i10/314.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i10.314

INTRODUCTION

Gastrointestinal (GI) cancers are currently among the five most common cancers worldwide for both men and women[1]. According to the GLOBOCAN 2018, colon cancer and gastric cancer represents respectively the 3rd and 5th most common cancers [2,3]. Some GI, such as the pancreatic cancer (PC), are rarer but burdened by a high mortality rate[4]. PC represents the thirteen most common cancer and the seventh most common cause of cancer-related death[4]. The incidence of GI cancer shows significant geographical variations, with colorectal cancer incidence higher in Western Countries and North America[3,5], whereas gastric cancer incidence is higher in Asia and Africa[2]. These geographical differences are mainly linked to environmental and lifestyle factors such as nutritional habits, alcohol intake, genetics, and obesity[2,5].

Nowadays, the "gold standard" management of cancers involves a multi-specialist staff consisting of oncologists, surgeons, endoscopists, and radiologists to provide a multi-disciplinary diagnostic and treatment approach to the oncologic patient.

Interventional radiology (IR) is getting a key role in oncologic patients' cares, being an essential tool in both the initial diagnosis and the subsequent treatment, as well as in the management of the related complications[6]. IR provides adequate diagnostic samples through a minimally invasive access, which can be obtained under imagine guidance by percutaneous and needle aspiration[7]. Therapeutic applications of IR in oncology are mainly focused on local cancer treatment, including radiofrequency (RF) ablation or trans-arterial chemoembolization (TACE)[8]. Cancers complications, such as pain, bleeding, organ obstructions, or venous thrombosis can also be managed by IR, with the eventual placement of gastrostomy or jejunostomy in selected patients[9, 10].

This article aims to analyse the current roles of IR in GI cancer management and provide an extensive overview of the current literature on the topic. In this article, only cancers located in the GI tract (from the esophagus to the colon) will be considered. Liver, pancreas, and biliary tract will not be taken into account, as they should require a separate discussion.

IR IN THE DIAGNOSIS OF GI CANCERS

The adequate treatment of GI cancers depends on a timely definitive diagnosis and the staging of the disease[11]. Imaging techniques improved the assessment and staging of cancers, but the histological analysis represents the gold standard for the definitive diagnosis of this disease. Biopsies samples are required to assess the biomarker status of different solid GI cancers and should be performed not only for the initial diagnosis

but at multiple end-points, to detect the cancer progression, predict the prognosis and guide the next-line therapy[12]. The improvement of the histological and cytological analysis, especially in the field of immunochemical examination, enables the identification of the primary tumor site and predicts the sensitivity to chemotherapeutic drugs[13].

Minimally invasive techniques have a prominent role in this contest. Endoscopy currently represents the first-level procedure for the histological diagnosis of GI cancers. However, lesions located within the submucosa or subserosa (such as lymphoma or gastrointestinal stromal tumours), may be difficult to diagnose with this approach[14]. Cancers located in the small bowel or colon could be not always reachable by the endoscope, due to their location or to stenosis of the lumen[14]. In this case, biopsies can obtain by interventional radiologists through direct visualization under image guidance of the masses, allowing the safe passage of the needle and minimising the trauma to the surrounding areas. In biopsy planning, imaging techniques help to define lesion location, accessibility, and suitability for biopsy also providing the identification of the mass to sample, in the context of multiple lesions [6]. In case of metastasis on the liver, not accessible by endoscopy, IR-biopsy can help to identify the primary tumour and define a tissue diagnosis[6].

The choice of imaging guidance modality is multifactorial and there are different options. Ultrasonography (US) is a fast and cost-effective technique, that guarantees real-time imaging, allowing the monitoring of the needle trajectory to the target lesion, without radiation exposure. US-guided percutaneous biopsy provides the diagnosis of solid abdominal organ lesions located in the spleen, pancreas, or lymph nodes, with high diagnostic accuracy and low complications and mortality rates[15]. Moreover, US is useful in guiding biopsies with intracavitary access and must be considered as a diagnostic alternative tool for the diagnosis of low rectal lesions and stromal tumours [16]. The success of US depends on different factors, such as the operator experience [16]. However, different studies suggested US superiority to computed tomography (CT)-guided biopsies, in case of lesions visible with ultrasounds[15,16]. CT-guided biopsy provides a more defined anatomical image, allowing a more precise needle localization when compared to US, showing to be particularly useful in case of pelvic or deep biopsies, which can be difficult to be performed using US. However, CT-guided biopsies have a low real-time guidance capability to track the needle and the target location, requiring intermittent sweeps of the region of interest to confirm the location of the needle during the procedure, thus increasing the biopsy time. The principal disadvantage of the procedure is clearly linked to the radiations exposure expecially for the patients, with radiation dose-related to different factors such as the total scan time, the peak tube kilovoltage (kVP), and milliamperage (mA), the part of the body that must be scanned and the size of the patient[17]. CT-fluoroscopy is an alternative method resulting from technical advantages of the common CT, which allows near real-time imaging of the needled trajectory, reducing the procedural time. Fluoroscopic images are acquired at a lower mA, reducing the radiation dose to the patient, but increasing the radiation dose to the staff, due to the proximity of the physician to the x-ray source during the procedure[18]. However, recent available fusion image guidance systems allow decreasing the radiation exposure through real-time projection during the US-guided biopsies of a needle on to pre-existing CT or magnetic resonance imaging (MRI) image, improving at the same time the accuracy of the procedure[19]. Cone-beam computed tomography (CBCT) guided biopsy, represents the last frontier in the field of IR. Although its extensive use in pleural and pulmonary masses, its virtual navigation system allowed to increase the diagnostic accuracy of the target lesion through a 3D visualization and real-time guidance of the needle trajectory[20], with initial applications also for the diagnosis of GI lesions[21].

IR IN GI CANCERS TREATMENT

Arterial embolization

Arterial embolization (AE) is a useful therapeutic option for hypervascular cancer treatment. Therefore, AE is widely used in liver metastasis treatment, instead of primary GI cancers[22].

Imagine-guided cancer treatment represents a minimally invasive alternative or adjunct to surgery in the management of GI tumours[23,24]. AE consists of the identification of the arterial supply of a solid tumour in CT or MRI and the devascularization of the pathological tissue through transcatheter embolization[24]. Vessels occlusion can be achieved using polyvinyl alcohol, blood clots, coils, and liquid

embolic introduced into the tumour bed through fluoroscopic arterial catheterization in IR[25,26]. The interruption of the cancer supplies induced hypoxia and inhibits the tumour growth. Therefore AE can be used in conjunction with ablative treatments or as an alternative to surgery[26]. Indeed, in the case of hypervascular cancers, this technique helps to reduce operative blood loss[27]. AE has a prominent role in the treatment of hepatic metastasis, especially from colon or rectal cancer[28-30]. In this context, a modification of this technique, the TACE, allowed the infusion of a single or combination of chemotherapy agents in the hepatic pathological tissue through the selective hepatic artery embolization[31-33]. This technique reduces the systematic dose of chemotherapy agents, allowing them to reach a higher local concentration. TACE should be repeated for more sessions until the complete devascularization of the pathological tissue[32]. Finally, separate mention should be given to the radioembolization, despite its use is limited to hepatic pathological tissue. It consists of beta-radiation emitting radio-isotopes directly into the mass employing microspheres (glass or resin) resulting in selective tissue necrosis[32].

Ablative techniques

Local cancers ablation is an alternative technique for early stages or not candidate for surgical resection[34]. Tumour ablation mediated by IR allowed pathological tissue necrosis in different modalities, including RF, microwave, and cryotherapy[34]. RF ablation (RFA) is mainly applied in liver metastasis of gastric and colon cancers[35, 36]. RFA consists of the administration of electrical energy to a tissue, through an electrode connected in a closed-loop circuit to a monopolar or bipolar energy source [8]. The tissue reached a temperature higher than 60 degrees Celsius with consequent thermal damage. RFA is a safe technique with a lower mortality rate (0.3%) and complication rate (2.2%)[8], with an efficacy, described also in the context of skeletal, renal, and lung metastasis with curative or palliative purpose[37-39]. Conversely to RFA, cryotherapy induces cell necrosis by applying subfreezing temperatures, using nitrogen or argon gas under high pressure[40]. The process of freezing-thawing must be repeated to obtain an effective ablation due to the mechanical stress-induced to the cell membranes[41]. CT identifies the ablated zone in real-time as a low-density area [41]. Acting by a mechanism of osmosis and necrosis, different studies suggested that the intracellular content that remains intact allows inducing an immune-specific reaction with an onco-suppressive effect outside the ablated tissue. However, these considerations are based on preclinical studies[42,43], and prospective clinical trials are needed to confirm these data. Microwave ablation is based on the application of electromagnetic energy within a range of at least 915 MHz, agitating the water molecules in target tissue and inducing cell death through coagulation necrosis[44]. Despite microwave showed equivalent or higher clinical efficacy if compared to RFA, however, RFA showed lower recurrence rates and a higher survival rate achieving extensive necrosis after few sessions, with less post-procedural pain[45,46]. In any case, the decision of which ablation methods should be used, must take into consideration several factors such as the tumour type and location (especially the proximity to vulnerable areas) and patients' comorbidities.

Gene therapy

Advanced in immunology and molecular oncology led to the development of gene therapy. It consists of the administration of genetic agents into a tissue in order to stimulate the immune response, reduce the oncogenic expression, modulate the angiogenesis or modify the response to chemotherapeutics[47]. The selective arterial injections of genetic agents are followed by the vessel embolization, to assure the administration of the substance directly into the mass, limiting the adverse effects and increasing the local dwell time[47]. Genetics agents are typically transferred into the cell through vector agents which allow them to cross cell membranes[48]. Vectors are usually plasmids, phospholipidic agents, or viruses like adenovirus, Epstein-Barr virus, and retroviruses (which provided a lasting genetic expression)[48]. However, clinical studies on gene therapies are very limited and, although the results look promising (especially in the treatment of liver metastases), further studies are needed to confirm the data[48,49].

IR in the treatment of GI cancers complications

IR has also a role in the minimally invasive treatments of different GI cancers complications, avoiding reoperations and allowing a speeding recovery time[50]. Therefore, IR plays a key role in the field of oncology, contributing to revolutionize the postoperative management of these patients. Indeed, IR allows management of

possible complications, which would otherwise require a new surgery, in a minimally invasive way.

IR also provides a palliative treatment in advanced GI cancers stages, through diminishing pain or allowing symptoms reduction[9,51].

Bleeding

Besides the role of AE and its modification in the treatment of hepatic pathological tissues, its use in GI cancers is limited to acute bleeding treatments[23,52]. Bleeding from advanced gastric cancers accounts for 1% to 8% of the upper gastrointestinal bleedings (UGIB), causing delays in chemotherapy and increasing transfusion requirements[53,54]. Moreover, endoscopy represents the gold standard for UGIB, being able to recognize the exact source of bleeding[55]. However, in presence of profuse bleeding masking the exact source, endoscopy may fail to stop it[56,57]. Due to advances in angiography systems and haemostatic materials, IR embolization is recognized as an alternative modality in patients in whom endoscopy fails or is not indicated[58,59] IR embolization is also used in the treatment of lower gastrointestinal bleedings (LGIB), defined as bleeding originating distal to the ligament of Treitz[60]. The introduction of super-selective embolization with coaxial microcatheter systems and embolic agents (such as pledgets of absorbable gelatine sponge, polyvinyl alcohol, or other spherical particulates, micro-coils, and liquid embolic agents) represents a useful tool in LGBI[60,61]. According to the American College Guidelines[62] in the treatment of LGIB, it should be considered in high-risk patients with ongoing bleeding who do not respond adequately to the volume resuscitation and who are unlikely to tolerate bowel preparation and colonoscopy (Figure 1). Although its major complication is ischemia, it should be preferred as a first-line approached in these selected patients[63]. A new frontier for the treatment of LGIB is CBCT embolization, which allowed a fast identification of the bleeding site and simplifying the placement of the microcrater in the vessel, without requiring sequential angiography[64]. The indications and possible complications of these techniques are the same as the traditional AE, with the theoretical advantage of greater safety and efficacy due to the modern and accurate tools[64].

AE represents a useful tool also for postoperative bleeding, allowing to stop the bleeding avoiding surgical reoperation, with minimally invasive access[65]. Another possible complication of surgery is the arteriovenous or arterio-enteric fistulas, life-threatening conditions[66]. Although conventional angiography is rarely used as the first-line imaging modality for its diagnosis, angioembolization allowed minimally invasive management of the fistula and to avoid major surgery[67].

Finally, in the event of an arterial bleeding from pseudoanurysm, endovascular treatment with covered self-expanding stent-grafts placement was reported as an effective method. It is performed under local anesthesia, which avoids the need for general or locoregional anesthesia in unstable, high-risk patients[65,66].

Abscess drainage

An intrabdominal abscess could be the first cancer presentation[68] as well as a postoperative complication[50,69]. In both cases, IR is a reliable minimally invasive alternative to surgery, although the feasibility of this technique depends on the abscess location and the consistency of the contents of collections[70]. In case of deep-seated abscess or abscess located close to vulnerable structures, CT-guided percutaneous drainage is the gold standard (Figure 2). Despite the limit of a non-real-time image, it allowed the best image-depiction of the collection and the adjacent organs[7]. In the case of easily accessible abscesses, US-guided drainage must be preferred and should always be the first procedure in patients with simple abscesses[71]. US and CT can be combined with fluoroscopy to avoid guidewire kinking during the procedure and to monitor the placement of catheters[70]. The abscess can only be aspirated, or a catheter can be left in place for few days, especially when contamination or communication with the bowel or urinary tract is suspected[70]. Deep-seated abscess with interposition of organs can be drained with a surgical approach or the intervening organ can be traversed with a catheter[72]. This approach is not suitable for almost all abdominal organs, except the stomach and the liver[72,73]. Finally, transvaginal and transrectal drainage with US or CT guidance allows access to deep-seated abscesses beside the vagina or rectum, often resulting from gynecological or rectal cancers, and inaccessible with percutaneous methods[74,75]. Percutaneous abscess drain placement for abdominal and pelvic collections could be achieved also with cone-beam CT, with equivalent successful rate and radiation dose of conventional CT positioning and the advantage of reduced procedural time[76].

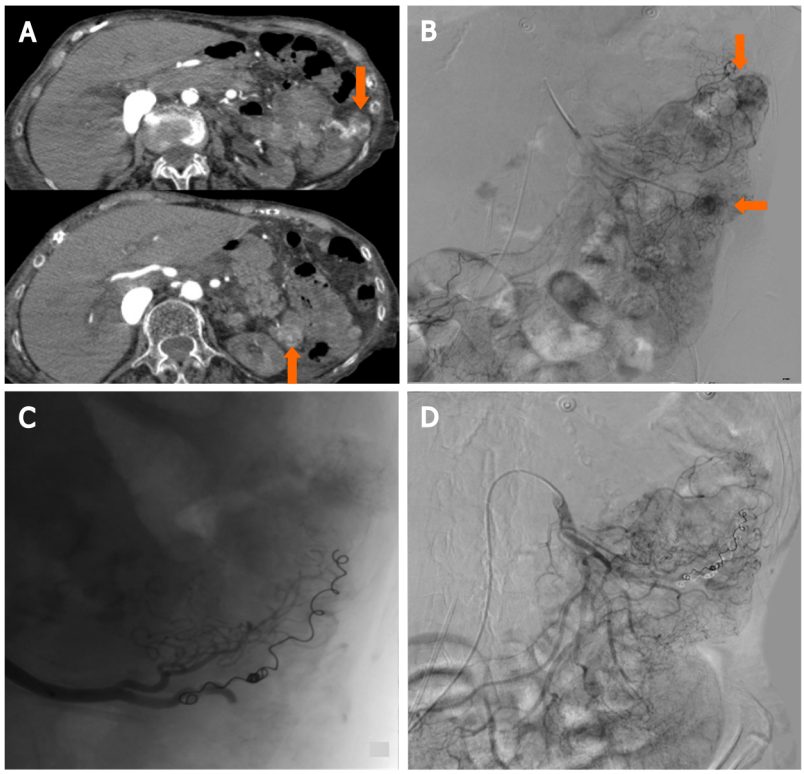


Figure 1 87-year-old female with distal duodenum/proximal jejunum Ca presents with severe recurrent melenas. Endoscopic hemostasis failed in high risk surgical patients with hemodynamic instability and normal coagulation state, requiring embolization after transfusion and hemodynamic stabilization (stabilized blood pressure 90 mmHg with inotropes, HR: 110/min. Hb 6.4). A: Computed tomography-Angio: Two active bleeding sites at proximal jejunum (arrows); B: Selective digital subtraction angiography (DSA) from superior mesenteric artery depicting the bleeding sites (arrows); C: Selective catheterization of the feeding artery with microcatheter and two 3 mm micro coils deployed; D: Lesions are not depicted at final DSA.

GI obstructions

Oesophageal or gastric cancers determining luminal obstruction, dysphagia, or swallowing impairment, are frequently cause of intolerance of the oral intake, requiring nutritional support through a gastrostomy or gastrojejunostomy[77]. The first percutaneous radiologic gastrostomy (PRG) was performed in 1981 using fluoroscopic guidance to avoid bowel and solid organs, without the need for upper endoscopy[10].

IR showed higher technical success and safety rates, with the advantage to be performed in patients not eligible for endoscopy or surgical procedures[10]. PRG complications are similar to the percutaneous endoscopic gastrostomy (PEG), including infections (23%) and the discomfort on feeding (33%)[78,79] and less frequent complications such as haemorrhage, ileus, aspiration of feed, and tube occlusion[10].

The tube dislocation is relatively common, with the possibility of easy tube reinsertion in the same tract if this is established for more than 2 wk. Alternatively, early tube dislodgment requiring repeated gastric puncture[79]. Gastrostomy and gastrojejunostomy can be performed also in small bowel obstruction with a decompression purpose with a success rate higher than 98%[80] (Figure 3). In patients with ascites, a paracentesis must be performed to reduce the peritoneal liquid, to reduce the possibility of complications such as peritonitis or peri-catheter leakage[80,81]. Contraindications for PRG are the same as PEG, including coagulopathy as an absolute contraindication and immunosuppression as a relative one[10]. In the last years, different studies, suggested the positioning of gastroduodenal and colonic self-expanded stent under fluoroscopic-guide as a palliative treatment, in oncologic patients with no indication for surgery[82,83]. Self-expanded stent are extensively used in the palliative treatment of duodenal and rectal occlusions, as given the smallest diameter of these segments, a malignant obstruction can easily occur at these levels [82].

The positioning of the stent under fluoroscopy-guidance allowed to approach the obstruction and the safe placement of the stent, without the need of bowel preparation in case of colonic stents[82]. The use of angiographic catheters with variable head

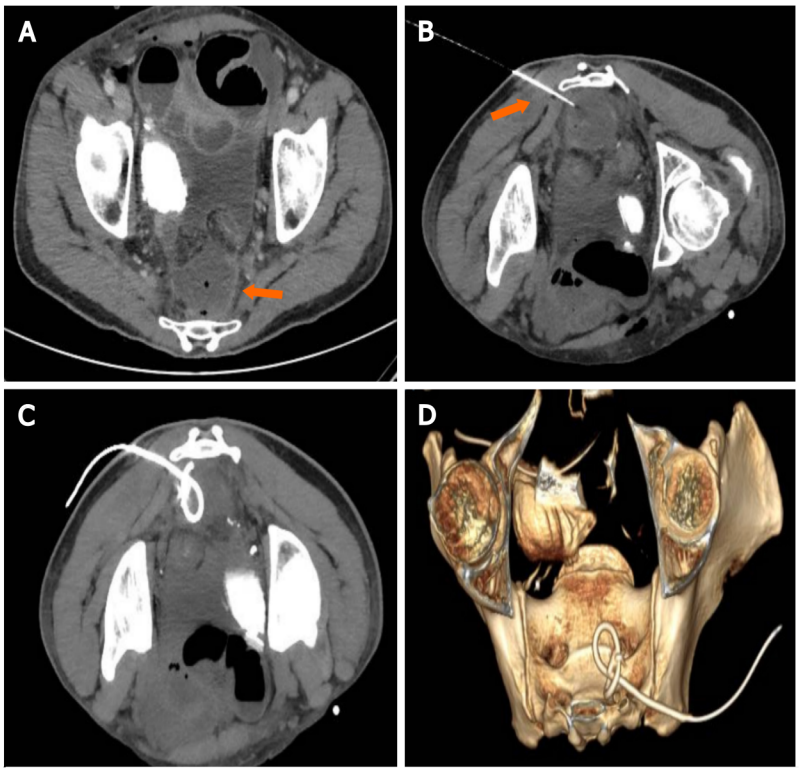


Figure 2 Presacral collection following rectal surgery. A: Axial computed tomography (CT) scan demonstrating a 4 cm × 3 cm presacral fluid collection (arrow), with small air bubbles; B: Patient in prone position, a Chiba needle is inserted with a trans-gluteal approach under CT guidance; C and D: Mip CT images and 3D Volume rendering reconstruction confirming the exact 8Fr drainage positioning.

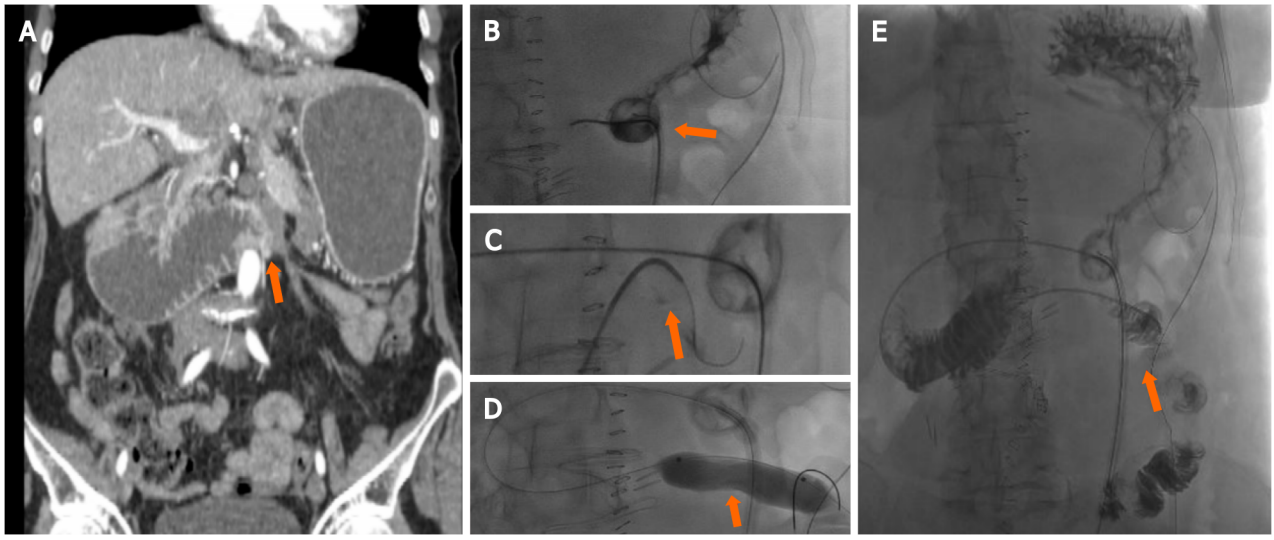


Figure 3 Upper gastrointestinal cancers obstruction. A: A 60 yr female with stage 4 ovarian cancer, with peritoneal carcinomatosis causing occlusion at the Treitz level (arrow); B and C: After percutaneous insertion of a decompressive gastrostomy, an angiografic catheter was advanced at the level of the occlusion and crossed using an hydrophilic guidewire (arrow); D and E: A ballon dilatation (18 mm × 6 cm) was performed (D, arrow) and a 5 fr catheter was left in place to ensure enteral nutrition (E, arrow).

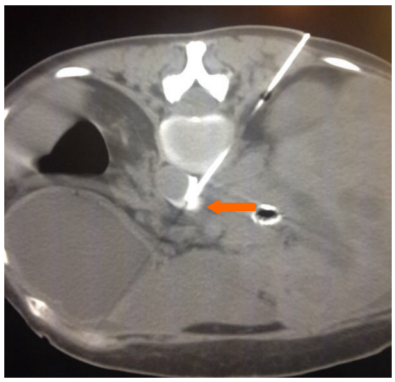


Figure 4 Celiac plexus alcohol neurolysis. In a patient with metastatic pancreatic cancer and non-controlled pain, an 18G Chiba needle (arrow) is inserted under computed tomography-guidance with a paravertebral approach; ethanol (95%–100%) is injected into the antecrural space after confirming the needle position with diluted iodinate contrast medium.

shapes and easily shapable guide-wires can facilitate passing the angulated obstruction, which is the most common cause of endoscopic failure[82,83].

Pain control

Pain represents a significant source of morbidity in oncologic patients, especially in advanced stages, with an incidence ranging from 40% to 90%. According to the World Health Organization, opiates remain the first choice drugs in these patients. However, those patients with non-controlled pain or with intolerable analgesic effects could also benefit from interventional pain control techniques[84,85]. Upper abdominal visceral cancers are often poorly responsive to analgesic therapy. In these cases, nerve block or celiac ganglion neurolysis can reduce pain, especially related to pancreatic, gastric, and oesophageal cancers[86] (Figure 4). The substances most often employed in IR include local alcohol or phenol, which induce permanent nerve destruction, and triamcinolone, which reversibly blocks nocireceptors[87]. CT represents the most commonly used image-modality to guide the celiac axis block, with either an anterior or posterior approach, according to the operator experience[87]. The most frequent complications of these techniques are diarrhea (73%) and orthostatic hypotension (12%)[87].

FUTURE PERSPECTIVES

IR showed an exponential growth in the last years and represents a useful tool in the treatment of oncologic patients. Its role in the context of GI cancers is increasingly relevant, allowing for the diagnosis and treatment of cancer and related complications, with a minimally-invasive approach. The introduction of ablation techniques and monitoring devices contributed to the effectiveness and safety of IR procedures, allowing for the treatment of lesions close to sensitive structures, often difficult to be accessed by other approaches. IR is a very useful tool also in the treatment of GI cancer complications, *e.g.*, bleeding from the digestive tract that cannot be reached by endoscopy[56].

Given the increasing relevance of IR in GI cancers management, the inclusion of interventional radiologists in the multidisciplinary oncologic staff is considered of paramount importance. Specific training programs, also including the use of simulators, are necessary to support the IR learning curve.

CONCLUSION

IR is a medical specialty which uses minimally-invasive technique in GI cancer management. Given its prominent role, the IR specialist should always be considered as an essential player in the multidisciplinary staff responsible for the treatment of the oncologic patient.

ACKNOWLEDGEMENTS

The entire manuscript has been written and amended by a native English speaker (Martin Mariappan MD).

REFERENCES

1 **Arnold M**, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology* 2020; **159**: 335-349.e15 [PMID: 32247694 DOI: 10.1053/j.gastro.2020.02.068]

2 **Rawla P**, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol* 2019; **14**: 26-38 [PMID: 30944675 DOI: 10.5114/pg.2018.80001]

3 **Rawla P**, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol* 2019; **14**: 89-103 [PMID: 31616522 DOI: 10.5114/pg.2018.81072]

4 **Rawla P**, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. *World J Oncol* 2019; **10**: 10-27 [PMID: 30834048 DOI: 10.14740/wjon1166]

5 **GBD 2017 Risk Factor Collaborators**. . Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1923-1994 [PMID: 30496105 DOI: 10.1016/S0140-6736(18)32225-6]

6 **Silverman SG**, Khorasani R, Adams DF, Phillips MD, Sica GT, Mayer RJ. Multidisciplinary gastrointestinal cancer clinic: abdominal radiologist as active participant. *Acad Radiol* 1998; **5**: 694-697 [PMID: 9787840 DOI: 10.1016/S1076-6332(98)80564-3]

7 **Mahnken AH**, Ricke J. CT- and MR-guided interventions in radiology. Berlin: Springer Berlin Heidelberg, 2013: 11-24

8 **Livraghi T**, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology* 2003; **226**: 441-451 [PMID: 12563138 DOI: 10.1148/radiol.2262012198]

9 **Campbell TC**, Roenn JH. Palliative Care for Interventional Radiology: An Oncologist's Perspective. *Semin Intervent Radiol* 2007; **24**: 375-381 [PMID: 21326589 DOI: 10.1055/s-2007-992325]

10 **Lyon SM**, Pascoe DM. Percutaneous gastrostomy and gastrojejunostomy. *Semin Intervent Radiol* 2004; **21**: 181-189 [PMID: 21331127 DOI: 10.1055/s-2004-860876]

11 **Abi-Jaoudeh N**, Duffy AG, Greten TF, Kohn EC, Clark TW, Wood BJ. Personalized oncology in interventional radiology. *J Vasc Interv Radiol* 2013; **24**: 1083-92; quiz 1093 [PMID: 23885909 DOI: 10.1016/j.jvir.2013.04.019]

12 **Tam AL**, Lim HJ, Wistuba II, Tamrazi A, Kuo MD, Ziv E, Wong S, Shih AJ, Webster RJ 3rd, Fischer GS, Nagrath S, Davis SE, White SB, Ahrar K. Image-Guided Biopsy in the Era of Personalized Cancer Care: Proceedings from the Society of Interventional Radiology Research Consensus Panel. *J Vasc Interv Radiol* 2016; **27**: 8-19 [PMID: 26626860 DOI: 10.1016/j.jvir.2015.10.019]

13 **Mihlon F 4th**, Ray CE Jr, Messersmith W. Chemotherapy agents: a primer for the interventional radiologist. *Semin Intervent Radiol* 2010; **27**: 384-390 [PMID: 22550380 DOI: 10.1055/s-0030-1267852]

14 **de Sio I**, Funaro A, Vitale LM, Niosi M, Francica G, Federico A, Sgambato D, Loguercio C, Romano M. Ultrasound-guided percutaneous biopsy for diagnosis of gastrointestinal lesions. *Dig Liver Dis* 2013; **45**: 816-819 [PMID: 23707404 DOI: 10.1016/j.dld.2013.04.003]

15 **Arellano RS**, Maher M, Gervais DA, Hahn PF, Mueller PR. The difficult biopsy: let's make it easier. *Curr Probl Diagn Radiol* 2003; **32**: 218-226 [PMID: 12963868 DOI: 10.1016/S0363-0188(03)00027-6]

16 **Sheafor DH**, Paulson EK, Simmons CM, DeLong DM, Nelson RC. Abdominal percutaneous interventional procedures: comparison of CT and US guidance. *Radiology* 1998; **207**: 705-710 [PMID: 9609893 DOI: 10.1148/radiology.207.3.9609893]

17 **Cerci JJ**, Tabacchi E, Bogoni M, Delbeke D, Pereira CC, Cerci RJ, Krauzer C, Sakamoto DG, Fanti S, Vitola JV. Comparison of CT and PET/CT for biopsy guidance in oncological patients. *Eur J Nucl Med Mol Imaging* 2017; **44**: 1269-1274 [PMID: 28364161 DOI: 10.1007/s00259-017-3658-8]

18 **Paulson EK**, Sheafor DH, Enterline DS, McAdams HP, Yoshizumi TT. CT fluoroscopy--guided interventional procedures: techniques and radiation dose to radiologists. *Radiology* 2001; **220**: 161-167 [PMID: 11425990 DOI: 10.1148/radiology.220.1.r01jl29161]

19 **Hakime A**, Deschamps F, De Carvalho EG, Teriitehau C, Auperin A, De Baere T. Clinical evaluation of spatial accuracy of a fusion imaging technique combining previously acquired computed tomography and real-time ultrasound for imaging of liver metastases. *Cardiovasc Intervent Radiol* 2011; **34**: 338-344 [PMID: 20845039 DOI: 10.1007/s00270-010-9979-7]

20 **Lim HJ**, Park CM, Yoon SH, Bae JS, Goo JM. Cone-Beam CT Virtual Navigation-Guided Percutaneous Needle Biopsy of Suspicious Pleural Metastasis: A Pilot Study. *Korean J Radiol* 2018; **19**: 872-879 [PMID: 30174476 DOI: 10.3348/kjr.2018.19.5.872]

21 **Choi YR**, Chung JW, Kim JH, Kim HC, Jae HJ, Hur S. Cone-Beam Computed Tomography-Hepatic

Arteriography as a Diagnostic Tool for Small Hypervascular Hepatocellular Carcinomas: Method and Clinical Implications. *Korean J Radiol* 2020; **21**: 306-315 [PMID: 32090523 DOI: 10.3348/kjr.2019.0060]

22 **Takaki H**, Litchman T, Covey A, Cornelis F, Maybody M, Getrajdman GI, Sofocleous CT, Brown KT, Solomon SB, Alago W, Erinjeri JP. Hepatic artery embolization for liver metastasis of gastrointestinal stromal tumor following imatinib and sunitinib therapy. *J Gastrointest Cancer* 2014; **45**: 494-499 [PMID: 25358551 DOI: 10.1007/s12029-014-9663-2]

23 **Goldstein HM**, Medellin H, Ben-Menachem Y, Wallace S. Transcatheter arterial embolization in the management of bleeding in the cancer patient. *Radiology* 1975; **115**: 603-608 [PMID: 1079352 DOI: 10.1148/15.3.603]

24 **Eriksson LG**, Ljungdahl M, Sundbom M, Nyman R. Transcatheter arterial embolization *vs* surgery in the treatment of upper gastrointestinal bleeding after therapeutic endoscopy failure. *J Vasc Interv Radiol* 2008; **19**: 1413-1418 [PMID: 18755604 DOI: 10.1016/j.jvir.2008.06.019]

25 **Amesur NB**, Zajko AB, Carr BI. Chemo-embolization for unresectable hepatocellular carcinoma with different sizes of embolization particles. *Dig Dis Sci* 2008; **53**: 1400-1404 [PMID: 18046645 DOI: 10.1007/s10620-007-9995-x]

26 **Katsanos K**, Kitrou P, Spiliopoulos S, Maroulis I, Petsas T, Karnabatidis D. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. *PLoS One* 2017; **12**: e0184597 [PMID: 28934265 DOI: 10.1371/journal.pone.0184597]

27 **Rodríguez Carvajal R**, Orgaz A, Leal JI, Peinado FJ, Vicente S, Gil J, Flores A, Fontcuberta J, Buendia E, Bolufer E, Gómez A, Doblas M. Renal embolization and nephrectomy in a single surgical act in high-risk renal tumor pathology. *Ann Vasc Surg* 2011; **25**: 222-228 [PMID: 20947293 DOI: 10.1016/j.avsg.2010.03.037]

28 **Wörns MA**, Galle PR. Future perspectives in hepatocellular carcinoma. *Dig Liver Dis* 2010; **42** Suppl 3: S302-S309 [PMID: 20547319 DOI: 10.1016/S1590-8658(10)60521-X]

29 **Bruix J**, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014; **63**: 844-855 [PMID: 24531850 DOI: 10.1136/gutjnl-2013-306627]

30 **Fiorentini G**, Sarti D, Nardella M, Inchingolo R, Nestola M, Rebonato A, Guadagni S. Chemoembolization Alone or Associated With Bevacizumab for Therapy of Colorectal Cancer Metastases: Preliminary Results of a Randomized Study. *In Vivo* 2020; **34**: 683-686 [PMID: 32111770 DOI: 10.21873/invivo.11824]

31 **Fiorentini G**, Carandina R, Sarti D, Nardella M, Zoras O, Guadagni S, Inchingolo R, Nestola M, Felicioli A, Barnes Navarro D, Munoz Gomez F, Aliberti C. Polyethylene glycol microspheres loaded with irinotecan for arterially directed embolic therapy of metastatic liver cancer. *World J Gastrointest Oncol* 2017; **9**: 379-384 [PMID: 28979720 DOI: 10.4251/wjgo.v9.i9.379]

32 **Sieghart W**, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. *J Hepatol* 2015; **62**: 1187-1195 [PMID: 25681552 DOI: 10.1016/j.jhep.2015.02.010]

33 **Pereira PL**, Iezzi R, Manfredi R, Carchesio F, Bánsághi Z, Brountzos E, Spiliopoulos S, Echevarria-Uraga JJ, Gonçalves B, Inchingolo R, Nardella M, Pellerin O, Sousa M, Arnold D, de Baère T, Gomez F, Helmberger T, Maleux G, Prenen H, Sangro B, Zeka B, Kaufmann N, Taieb J. The CIREL Cohort: A Prospective Controlled Registry Studying the Real-Life Use of Irinotecan-Loaded Chemoembolisation in Colorectal Cancer Liver Metastases: Interim Analysis. *Cardiovasc Intervent Radiol* 2021; **44**: 50-62 [PMID: 32974773 DOI: 10.1007/s00270-020-02646-8]

34 **Ahmed M**, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, Chen MH, Choi BI, de Baère T, Dodd GD 3rd, Dupuy DE, Gervais DA, Gianfelice D, Gillams AR, Lee FT Jr, Leen E, Lencioni R, Littrup PJ, Livraghi T, Lu DS, McGahan JP, Meloni MF, Nikolic B, Pereira PL, Liang P, Rhim H, Rose SC, Salem R, Sofocleous CT, Solomon SB, Soulen MC, Tanaka M, Vogl TJ, Wood BJ, Goldberg SN; International Working Group on Image-Guided Tumor Ablation; Interventional Oncology Sans Frontières Expert Panel; Technology Assessment Committee of the Society of Interventional Radiology; Standard of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. *J Vasc Interv Radiol* 2014; **25**: 1691-705.e4 [PMID: 25442132 DOI: 10.1016/j.jvir.2014.08.027]

35 **Chen J**, Tang Z, Dong X, Gao S, Fang H, Wu D, Xiang D, Zhang S. Radiofrequency ablation for liver metastasis from gastric cancer. *Eur J Surg Oncol* 2013; **39**: 701-706 [PMID: 23597495 DOI: 10.1016/j.ejso.2013.03.023]

36 **Liu LX**, Zhang WH, Jiang HC. Current treatment for liver metastases from colorectal cancer. *World J Gastroenterol* 2003; **9**: 193-200 [PMID: 12532430 DOI: 10.3748/wjg.v9.i2.193]

37 **Rose SC**, Thistlethwaite PA, Sewell PE, Vance RB. Lung cancer and radiofrequency ablation. *J Vasc Interv Radiol* 2006; **17**: 927-951; quiz 951 [PMID: 16778226 DOI: 10.1097/01.RVI.0000222707.44902.66]

38 **Thanos L**, Mylona S, Galani P, Tzavoulis D, Kalioras V, Tanteles S, Pomoni M. Radiofrequency ablation of osseous metastases for the palliation of pain. *Skeletal Radiol* 2008; **37**: 189-194 [PMID: 18030464 DOI: 10.1007/s00256-007-0404-5]

39 **Iannuccilli JD**, Dupuy DE, Beland MD, Machan JT, Golijanin DJ, Mayo-Smith WW. Effectiveness and safety of computed tomography-guided radiofrequency ablation of renal cancer: a 14-year single

institution experience in 203 patients. *Eur Radiol* 2016; **26**: 1656-1664 [PMID: 26373755 DOI: 10.1007/s00330-015-4006-7]

40 **Beland M**, Mueller PR, Gervais DA. Thermal ablation in interventional oncology. *Semin Roentgenol* 2007; **42**: 175-190 [PMID: 17599551 DOI: 10.1053/j.ro.2007.04.005]

41 **Aarts BM**, Klompenhouwer EG, Rice SL, Imani F, Baetens T, Bex A, Horenblas S, Kok M, Haanen JBAG, Beets-Tan RGH, Gómez FM. Cryoablation and immunotherapy: an overview of evidence on its synergy. *Insights Imaging* 2019; **10**: 53 [PMID: 31111237 DOI: 10.1186/s13244-019-0727-5]

42 **Chu KF**, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer* 2014; **14**: 199-208 [PMID: 24561446 DOI: 10.1038/nrc3672]

43 **Sabel MS**. Cryo-immunology: a review of the literature and proposed mechanisms for stimulatory *vs* suppressive immune responses. *Cryobiology* 2009; **58**: 1-11 [PMID: 19007768 DOI: 10.1016/j.cryobiol.2008.10.126]

44 **Hinshaw JL**, Lubner MG, Ziemlewicz TJ, Lee FT Jr, Brace CL. Percutaneous tumor ablation tools: microwave, radiofrequency, or cryoablation--what should you use and why? *Radiographics* 2014; **34**: 1344-1362 [PMID: 25208284 DOI: 10.1148/rg.345140054]

45 **Galandi D**, Antes G. Radiofrequency thermal ablation *vs* other interventions for hepatocellular carcinoma. *Cochrane Database Syst Rev* 2002; CD003046 [PMID: 12137670 DOI: 10.1002/14651858.CD003046]

46 **Ohmoto K**, Yoshioka N, Tomiyama Y, Shibata N, Kawase T, Yoshida K, Kuboki M, Yamamoto S. Comparison of therapeutic effects between radiofrequency ablation and percutaneous microwave coagulation therapy for small hepatocellular carcinomas. *J Gastroenterol Hepatol* 2009; **24**: 223-227 [PMID: 18823439 DOI: 10.1111/j.1440-1746.2008.05596.x]

47 **Biçeroğlu S**, Memiş A. Gene therapy: applications in interventional radiology. *Diagn Interv Radiol* 2005; **11**: 113-118 [PMID: 15957100]

48 **Yu M**, Chen W, Zhang J. p53 gene therapy for pulmonary metastasis tumor from hepatocellular carcinoma. *Anticancer Drugs* 2010; **21**: 882-884 [PMID: 20679889 DOI: 10.1097/CAD.0b013e32833db1bb]

49 **Mahnken AH**, Pereira PL, de Baère T. Interventional oncologic approaches to liver metastases. *Radiology* 2013; **266**: 407-430 [PMID: 23362094 DOI: 10.1148/radiol.12112544]

50 **Sohn TA**, Yeo CJ, Cameron JL, Geschwind JF, Mitchell SE, Venbrux AC, Lillemoe KD. Pancreaticoduodenectomy: role of interventional radiologists in managing patients and complications. *J Gastrointest Surg* 2003; **7**: 209-219 [PMID: 12600445 DOI: 10.1016/S1091-255X(02)00193-2]

51 **Buss MK**. The Intersection of Palliative Care and Interventional Radiology: Enhancing Understanding and Collaboration. *Semin Intervent Radiol* 2017; **34**: 140-144 [PMID: 28579682 DOI: 10.1055/s-0037-1602756]

52 **Park S**, Shin JH, Gwon DI, Kim HJ, Sung KB, Yoon HK, Ko GY, Ko HK. Transcatheter Arterial Embolization for Gastrointestinal Bleeding Associated with Gastric Carcinoma: Prognostic Factors Predicting Successful Hemostasis and Survival. *J Vasc Interv Radiol* 2017; **28**: 1012-1021 [PMID: 28483303 DOI: 10.1016/j.jvir.2017.03.017]

53 **Del Piano M**, Bianco MA, Cipolletta L, Zambelli A, Chilovi F, Di Matteo G, Pagliarulo M, Ballarè M, Rotondano G; Prometeo study group of the Italian Society of Digestive Endoscopy (SIED). The "Prometeo" study: online collection of clinical data and outcome of Italian patients with acute nonvariceal upper gastrointestinal bleeding. *J Clin Gastroenterol* 2013; **47**: e33-e37 [PMID: 22914349 DOI: 10.1097/MCG.0b013e3182617dcc]

54 **Esrailian E**, Gralnek IM. Nonvariceal upper gastrointestinal bleeding: epidemiology and diagnosis. *Gastroenterol Clin North Am* 2005; **34**: 589-605 [PMID: 16303572 DOI: 10.1016/j.gtc.2005.08.006]

55 **Kim YI**, Choi IJ, Cho SJ, Lee JY, Kim CG, Kim MJ, Ryu KW, Kim YW, Park YI. Outcome of endoscopic therapy for cancer bleeding in patients with unresectable gastric cancer. *J Gastroenterol Hepatol* 2013; **28**: 1489-1495 [PMID: 23662891 DOI: 10.1111/jgh.12262]

56 **Stanley AJ**, Laine L. Management of acute upper gastrointestinal bleeding. *BMJ* 2019; **364**: l536 [PMID: 30910853 DOI: 10.1136/bmj.l536]

57 **Spiliopoulos S**, Inchingolo R, Lucatelli P, Iezzi R, Diamantopoulos A, Posa A, Barry B, Ricci C, Cini M, Konstantos C, Palialexis K, Reppas L, Trikola A, Nardella M, Adam A, Brountzos E. Transcatheter Arterial Embolization for Bleeding Peptic Ulcers: A Multicenter Study. *Cardiovasc Intervent Radiol* 2018; **41**: 1333-1339 [PMID: 29671058 DOI: 10.1007/s00270-018-1966-4]

58 **Lee HJ**, Shin JH, Yoon HK, Ko GY, Gwon DI, Song HY, Sung KB. Transcatheter arterial embolization in gastric cancer patients with acute bleeding. *Eur Radiol* 2009; **19**: 960-965 [PMID: 18987861 DOI: 10.1007/s00330-008-1216-2]

59 **Inchingolo R**, Nestola M, Posa A, Di Costanzo G, Nardella M. Intrastent Pseudoaneurysm following Endoscopic Biliary Stent Insertion. *J Vasc Interv Radiol* 2017; **28**: 1321-1323 [PMID: 28841953 DOI: 10.1016/j.jvir.2017.04.014]

60 **Speir EJ**, Ermentrout RM, Martin JG. Management of Acute Lower Gastrointestinal Bleeding. *Tech Vasc Interv Radiol* 2017; **20**: 258-262 [PMID: 29224658 DOI: 10.1053/j.tvir.2017.10.005]

61 **Hur S**, Jae HJ, Lee M, Kim HC, Chung JW. Safety and efficacy of transcatheter arterial embolization for lower gastrointestinal bleeding: a single-center experience with 112 patients. *J Vasc Interv Radiol* 2014; **25**: 10-19 [PMID: 24286939 DOI: 10.1016/j.jvir.2013.09.012]

62 **Strate LL**, Gralnek IM. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. *Am J Gastroenterol* 2016; **111**: 459-474 [PMID: 26925883 DOI: 10.1038/ajg.2016.41]

63 **Nykänen T**, Peltola E, Kylänpää L, Udd M. Transcatheter Arterial Embolization in Lower Gastrointestinal Bleeding: Ischemia Remains a Concern Even with a Superselective Approach. *J Gastrointest Surg* 2018; **22**: 1394-1403 [PMID: 29549618 DOI: 10.1007/s11605-018-3728-7]

64 **Ierardi AM**, Urbano J, De Marchi G, Micieli C, Duka E, Iacobellis F, Fontana F, Carrafiello G. New advances in lower gastrointestinal bleeding management with embolotherapy. *Br J Radiol* 2016; **89**: 20150934 [PMID: 26764281 DOI: 10.1259/bjr.20150934]

65 **Chatani S**, Inoue A, Ohta S, Takaki K, Sato S, Iwai T, Murakami Y, Watanabe S, Sonoda A, Nitta N, Maehira H, Tani M, Murata K. Transcatheter Arterial Embolization for Postoperative Bleeding Following Abdominal Surgery. *Cardiovasc Intervent Radiol* 2018; **41**: 1346-1355 [PMID: 29955913 DOI: 10.1007/s00270-018-2019-8]

66 **Partovi S**, Trischman T, Sheth RA, Huynh TTT, Davidson JC, Prabhakar AM, Ganguli S. Imaging work-up and endovascular treatment options for aorto-enteric fistula. *Cardiovasc Diagn Ther* 2018; **8**: S200-S207 [PMID: 29850432 DOI: 10.21037/cdt.2017.10.05]

67 **Chiesa R**, Melissano G, Marone EM, Marrocco-Trischitta MM, Kahlberg A. Aorto-oesophageal and aortobronchial fistulae following thoracic endovascular aortic repair: a national survey. *Eur J Vasc Endovasc Surg* 2010; **39**: 273-279 [PMID: 20096612 DOI: 10.1016/j.ejvs.2009.12.007]

68 **Cho J**, Park I, Lee D, Sung K, Baek J, Lee J. Advanced Gastric Cancer Perforation Mimicking Abdominal Wall Abscess. *J Gastric Cancer* 2015; **15**: 214-217 [PMID: 26468420 DOI: 10.5230/jgc.2015.15.3.214]

69 **Connell TR**, Stephens DH, Carlson HC, Brown ML. Upper abdominal abscess: a continuing and deadly problem. *AJR Am J Roentgenol* 1980; **134**: 759-765 [PMID: 6767363 DOI: 10.2214/ajr.134.4.759]

70 **Maher MM**, Gervais DA, Kalra MK, Lucey B, Sahani DV, Arellano R, Hahn PF, Mueller PR. The inaccessible or undrainable abscess: how to drain it. *Radiographics* 2004; **24**: 717-735 [PMID: 15143224 DOI: 10.1148/rg.243035100]

71 **Men S**, Akhan O, Köroğlu M. Percutaneous drainage of abdominal abcess. *Eur J Radiol* 2002; **43**: 204-218 [PMID: 12204403 DOI: 10.1016/S0720-048X(02)00156-0]

72 **Cronin CG**, Gervais DA, Castillo CF, Mueller PR, Arellano RS. Interventional radiology in the management of abdominal collections after distal pancreatectomy: a retrospective review. *AJR Am J Roentgenol* 2011; **197**: 241-246 [PMID: 21701036 DOI: 10.2214/AJR.10.5447]

73 **Hawel J**, McFadgen H, Stewart R, El-Ghazaly T, Alawashez A, Ellsmere J. Interventional radiology-assisted transgastric endoscopic drainage of peripancreatic fluid collections. *Can J Surg* 2020; **63**: E254-E256 [PMID: 32400149 DOI: 10.1503/cjs.003019]

74 **Varghese JC**, O'Neill MJ, Gervais DA, Boland GW, Mueller PR. Transvaginal catheter drainage of tuboovarian abscess using the trocar method: technique and literature review. *AJR Am J Roentgenol* 2001; **177**: 139-144 [PMID: 11418415 DOI: 10.2214/ajr.177.1.1770139]

75 **Martins BC**, Marques CF, Nahas CS, Hondo FY, Pollara W, Nahas SC, Ribeiro Junior U, Cecconello I, Maluf-Filho F. A novel approach for the treatment of pelvic abscess: transrectal endoscopic drainage facilitated by transanal endoscopic microsurgery access. *Surg Endosc* 2012; **26**: 2667-2670 [PMID: 22407154 DOI: 10.1007/s00464-012-2215-6]

76 **Partovi S**, Li X, Moon E, Thompson D. Image guided percutaneous gastrostomy catheter placement: How we do it safely and efficiently. *World J Gastroenterol* 2020; **26**: 383-392 [PMID: 32063687 DOI: 10.3748/wjg.v26.i4.383]

77 **McKay T**, Ingraham CR, Johnson GE, Kogut MJ, Vaidya S, Padia SA. Cone-Beam CT with Fluoroscopic Overlay Versus Conventional CT Guidance for Percutaneous Abdominopelvic Abscess Drain Placement. *J Vasc Interv Radiol* 2016; **27**: 52-57 [PMID: 26573489 DOI: 10.1016/j.jvir.2015.09.016]

78 **Gonçalves F**, Mozes M, Saraiva I, Ramos C. Gastrostomies in palliative care. *Support Care Cancer* 2006; **14**: 1147-1151 [PMID: 16625334 DOI: 10.1007/s00520-006-0045-6]

79 **Silas AM**, Pearce LF, Lestina LS, Grove MR, Tosteson A, Manganiello WD, Bettmann MA, Gordon SR. Percutaneous radiologic gastrostomy *vs* percutaneous endoscopic gastrostomy: a comparison of indications, complications and outcomes in 370 patients. *Eur J Radiol* 2005; **56**: 84-90 [PMID: 16168268 DOI: 10.1016/j.ejrad.2005.02.007]

80 **Ryan JM**, Hahn PF, Mueller PR. Performing radiologic gastrostomy or gastrojejunostomy in patients with malignant ascites. *AJR Am J Roentgenol* 1998; **171**: 1003-1006 [PMID: 9762985 DOI: 10.2214/ajr.171.4.9762985]

81 **Given MF**, Lyon SM, Lee MJ. The role of the interventional radiologist in enteral alimentation. *Eur Radiol* 2004; **14**: 38-47 [PMID: 12736755 DOI: 10.1007/s00330-003-1911-y]

82 **Katsanos K**, Sabharwal T, Adam A. Stenting of the lower gastrointestinal tract: current status. *Cardiovasc Intervent Radiol* 2011; **34**: 462-473 [PMID: 21127865 DOI: 10.1007/s00270-010-0005-x]

83 **Katsanos K**, Sabharwal T, Adam A. Stenting of the upper gastrointestinal tract: current status. *Cardiovasc Intervent Radiol* 2010; **33**: 690-705 [PMID: 20521050 DOI: 10.1007/s00270-010-9862-6]

84 **Caraceni A**, Portenoy RK; a working group of the IASP Task Force on Cancer Pain. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain* 1999; **82**: 263-274 [PMID: 10488677 DOI: 10.1016/S0304-3959(99)00073-1]

85 **Caraceni A**, Martini C, Zecca E, Portenoy RK, Ashby MA, Hawson G, Jackson KA, Lickiss N, Muirden N, Pisasale M, Moulin D, Schulz VN, Rico Pazo MA, Serrano JA, Andersen H, Henriksen HT, Mejholm I, Sjogren P, Heiskanen T, Kalso E, Pere P, Poyhia R, Vuorinen E, Tigerstedt I,

Ruismaki P, Bertolino M, Larue F, Ranchere JY, Hege-Scheuing G, Bowdler I, Helbing F, Kostner E, Radbruch L, Kastrinaki K, Shah S, Vijayaram S, Sharma KS, Devi PS, Jain PN, Ramamani PV, Beny A, Brunelli C, Maltoni M, Mercadante S, Plancarte R, Schug S, Engstrand P, Ovalle AF, Wang X, Alves MF, Abrunhosa MR, Sun WZ, Zhang L, Gazizov A, Vaisman M, Rudoy S, Gomez Sancho M, Vila P, Trelis J, Chaudakshetrin P, Koh ML, Van Dongen RT, Vielvoye-Kerkmeer A, Boswell MV, Elliott T, Hargus E, Lutz L; Working Group of an IASP Task Force on Cancer Pain. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med* 2004; **18**: 177-183 [PMID: 15198130 DOI: 10.1191/0269216304pm890oa]

86 **Midia M**, Dao D. The Utility of Peripheral Nerve Blocks in Interventional Radiology. *AJR Am J Roentgenol* 2016; **207**: 718-730 [PMID: 27385059 DOI: 10.2214/AJR.16.16643]

87 **Akhan O**, Ozmen MN, Basgun N, Akinci D, Oguz O, Koroglu M, Karcaaltincaba M. Long-term results of celiac Ganglia block: correlation of grade of tumoral invasion and pain relief. *AJR Am J Roentgenol* 2004; **182**: 891-896 [PMID: 15039160 DOI: 10.2214/ajr.182.4.1820891]

World Journal of Radiology

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

World J Radiol 2021 October 28; 13(10): 327-343

DOI: 10.4329/wjr.v13.i10.327

ISSN 1949-8470 (online)

MINIREVIEWS

COVID-19 pneumonia: A review of typical radiological characteristics

María Churruca, Elisa Martínez-Besteiro, Felipe Couñago, Pedro Landete

ORCID number: María Churruca 0000-0001-6198-3619; Elisa Martínez-Besteiro 0000-0002-2968-1271; Felipe Couñago 0000-0001-7233-0234; Pedro Landete 0000-0002-9631-9408.

Author contributions: All authors contributed to this paper with conception and design of the manuscript, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Authors declare no potential conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

María Churruca, Elisa Martínez-Besteiro, Pulmonology Department, Hospital Universitario de La Princesa, Madrid 28006, Spain

Felipe Couñago, Department of Radiation Oncology, Hospital Universitario Quirónsalud Madrid, Madrid 28223, Spain

Felipe Couñago, Department of Radiation Oncology, Hospital La Luz, Madrid 28003, Spain

Felipe Couñago, Clinical Department, Faculty of Biomedicine,Universidad Europea de Madrid, Madrid 28670, Spain

Pedro Landete, Department of Pneumology, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid 28006, Spain

Corresponding author: María Churruca, MD, Doctor, Pulmonology Department, Hospital Universitario de La Princesa, Diego de León 62, Madrid 28006, Spain.
mchurrucaarrospide@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) was first discovered after unusual cases of severe pneumonia emerged by the end of 2019 in Wuhan (China) and was declared a global public health emergency by the World Health Organization in January 2020. The new pathogen responsible for the infection, genetically similar to the beta-coronavirus family, is known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the current gold standard diagnostic tool for its detection in respiratory samples is the reverse transcription-polymerase chain reaction test. Imaging findings on COVID-19 have been widely described in studies published throughout last year, 2020. In general, ground-glass opacities and consolidations, with a bilateral and peripheral distribution, are the most typical patterns found in COVID-19 pneumonia. Even though much of the literature focuses on chest computed tomography (CT) and X-ray imaging and their findings, other imaging modalities have also been useful in the assessment of COVID-19 patients. Lung ultrasonography is an emerging technique with a high sensitivity, and thus useful in the initial evaluation of SARS-CoV-2 infection. In addition, combined positron emission tomography-CT enables the identification of affected areas and follow-up treatment responses. This review intends to clarify the role of the imaging modalities available and identify the most common radiological manifestations of COVID-19.

Key Words: COVID-19; Radiology; Chest X-ray; Lung ultrasonography; Computed

Country/Territory of origin: Spain

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

Received: January 25, 2021
Peer-review started: January 25, 2021
First decision: March 1, 2021
Revised: March 8, 2021
Accepted: September 14, 2021
Article in press: September 14, 2021
Published online: October 28, 2021

P-Reviewer: Bhardwaj R, Grassi R
S-Editor: Gong ZM
L-Editor: A
P-Editor: Liu JH

Tomography; Positron emission tomography-computed tomography

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Severe acute respiratory syndrome coronavirus-2 is a single-stranded RNA virus that was first isolated in December 2019. Currently, the reverse transcription-polymerase chain reaction test, performed on respiratory samples collected in suspected coronavirus disease 2019 (COVID-19) patients, is the gold standard diagnostic technique. Chest X-ray or computed tomography (CT) are the main imaging tests used to diagnose COVID-19 pneumonia, with ground-glass opacities and consolidations being the major imaging features encountered. There are other radiological modalities, such as lung ultrasonography and combined positron emission tomography-CT, that can provide further information for initial assessment and follow-up treatment response.

Citation: Churruca M, Martínez-Besteiro E, Couñago F, Landete P. COVID-19 pneumonia: A review of typical radiological characteristics. *World J Radiol* 2021; 13(10): 327-343
URL: https://www.wjgnet.com/1949-8470/full/v13/i10/327.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i10.327

INTRODUCTION

On 31 December 2019, 27 cases of pneumonia of unknown aetiology were identified in the city of Wuhan (Hubei Province, China). A new pathogen, genetically similar to the beta-coronavirus family to which the coronaviruses that caused previous epidemics belong – severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) – was isolated from collected respiratory samples and named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In January 2020, the World Health Organization named the disease Coronavirus disease 2019 (COVID-19) and declared a global public health emergency[1,2]. At the beginning of December 2020, a total of 65.8 million cases had been diagnosed, with 1.5 million confirmed deaths since the start of the pandemic[3].

The clinical presentation and radiological findings of COVID-19, as well as various diagnostic tools for its detection, have been widely described in multiple studies published throughout 2020. Regarding its clinical pattern, it is generally nonspecific and variable between individuals. In approximately 80%-90% of cases, the disease is mild or even asymptomatic. However, in the remaining approximately 10% of cases, generally frail patients with coexisting medical conditions develop a severe course of infection with dyspnoea, hypoxaemia and extensive radiological lung involvement[4] . The current gold standard diagnostic tool for the detection of SARS-CoV-2 RNA in respiratory samples is the reverse transcription-polymerase chain reaction (RT-PCR) test. This test shows a non-negligible rate of false negatives results, which can be attributed to errors in the extraction of nasopharyngeal swab sampling and when the sample is collected[5], since its sensitivity varies depending on the time since exposure. Thus, some studies estimate the sensitivity of the RT-PCR test to be 33% four days after exposure, 62% the day clinical manifestations begin and 80% three days after the onset of symptoms[6]. A combination of the growing and rapid spread of COVID-19 and the lack of RT-PCR testing kits in some affected areas has made new diagnostic and screening methods necessary[7]. Radiological diagnosis constitutes an essential component in the initial assessment of the extension and severity of the infection, as it is a key element to guide treatment and monitor the evolution of the condition[8]. So far, much of the literature has predominantly focused on characterising the radiological findings most frequently seen in chest computed tomography (CT). However, other diagnostic modalities, such as chest X-ray, lung ultrasonography (LUS) and combined positron emission tomography-computed tomography (PET-CT), have also been useful in the assessment and management of COVID-19 patients[5].

Ultimately, clinicians will choose an imaging modality based on its advantages, the experience gathered with each diagnostic method and the local resources available[9]. This review aims to clarify the diagnostic value of the different imaging modalities

available and describe the most common radiological findings in COVID-19.

CHEST X-RAY

Chest X-ray is a frequently used method due to its low cost and wide availability, allowing various conditions to be studied in a simple and fast manner.

Furthermore, the existence of portable X-ray devices has enabled its use in intensive care units (ICUs). It is important that clinicians understand both the advantages and limitations of this imaging technique in terms of diagnosing COVID-19 pneumonia [10].

Some studies have proposed that chest radiography is a useful method both for the diagnosis and follow-up of the lung pathology generated by SARS-CoV-2 infection. The American College of Radiology (ACR) defends the application of portable X-rays in order to avoid collapses in imaging departments and minimise the risk of contamination associated with the intra-hospital mobilisation of COVID-19 patients and thus the spread of the disease[11].

Studies published during 2020 report a low sensitivity of chest X-rays in detecting pulmonary infiltrates during the initial phases of COVID-19 infection, as well as in mild forms of the disease (Table 1)[12]. In this regard, in a retrospective study of 64 patients, Wong *et al*[13] noted a chest radiography sensitivity of just 69%, compared to 91% for the RT-PCR test, and highlighted that 9% of cases in which X-ray detected abnormalities were initially RT-PCR negative. Both Ng *et al*[14] and Kim *et al*[15] found that chest X-ray has a low sensitivity when it comes to identifying lung alterations caused by SARS-CoV-2 infection. However, at the beginning of February, Chen *et al*[16] published a study which found a sensitivity of 100% with the use of chest radiography, with 74/99 patients presenting bilateral pneumonia and 25/99 unilateral involvement. However, these results can be explained by the overload that the health system was experiencing at that time, when the radiological screening of positive COVID-19 patients was limited to severe and advanced cases. For these reasons, the European Society of Radiology and the European Society of Thoracic Imaging recommend avoiding its use as a first-line technique in the diagnosis of COVID-19 pneumonia, restricting its use to the follow-up of patients admitted to the ICU, whose fragility would make it difficult to transfer them for a chest CT scan[11].

The severity of COVID-19 pneumonia cannot be determined by a SARS-CoV-2-positive nasopharyngeal swab; therefore, it is necessary to conduct a complementary radiological study. Recently, Cellina *et al*[17] retrospectively studied the prognostic predictive value of radiographic imaging performed in the initial stages of the disease in 246 COVID-19 patients, establishing a significant correlation between lung parenchymal involvement – valued by a percentage of the areas affected by ground-glass opacities (GGOs) or consolidation – and the severity of the disease.

The most common manifestations found in the chest radiographs of COVID-19 patients are GGOs – sometimes accompanied by reticular opacities – and lung consolidation, which, as in other atypical viral pneumonias, are typically multilobar and bilateral, generally involving the lower lobes (Table 2). One of the most specific signs of COVID-19 pneumonia is the peripheral and multifocal location of pulmonary infiltrates (Figure 1). Radiological impairments can rapidly evolve into a consolidative pattern, frequently reaching the peak of maximum severity and the worst pulmonary parenchymal involvement between 6-12 d after the onset of symptoms (Figure 2). Pleural effusion is extremely rare in patients infected by SARS-CoV-2, but if detected, is normally identified in the late stages of the disease. Lung cavitation images and pneumothorax are also unusual but can occur in some COVID-19 cases (Figure 3)[18]. Lomoro *et al*[19] retrospectively studied the chest X-rays of 32 patients, describing consolidations in 46.9% of the cases and GGOs in 37.5%, without identifying pleural effusion in any of them. The distribution of these findings was predominately bilateral (78.1%) and unilateral only in 6.2% of the cases. Furthermore, the lower lobes were the most frequently affected (52%), followed by 34.4% of patients who presented similar involvement of both the upper and lower lobes, while just 3.1% presented involvement in the upper lobes.

The impact of pneumomediastinum and subcutaneous emphysema during the COVID-19 pandemic has been described by Lemmers *et al*[20], who detected these conditions in 13% of the patients in their study. While at the outset this was considered to be a consequence of the barotrauma produced by mechanical ventilation in critically ill respiratory patients, it is nevertheless believed that these findings could be attributed to the Macklin effect, characterised by the rupture of the pulmonary alveoli

Table 1 Adapted from Chen *et al*[21] chest X-ray sensitivity in coronavirus disease 2019 pneumonia

Ref.	Cases	Initial RT-PCR	RT-PCR	Abnormal	Bilateral
Wong *et al*[13], 2020	64	Positive 58/64 (91%); Negative 6/64 (9%)	64 positive/0 negative	21/64 (33%)	32/64 (50%)
Chen *et al*[21], 2020	99	–	99 positive/0 negative	99/99 (100%)	74/99 (75%)
Kim *et al*[15], 2020	28	–	28 positive/ 0 negative	13/28 (46.4%)	6 (21.4%)
Ng *et al*[14], 2020	21	–	21 positive/0 negative	3/5 (60%)	2/5 (40%)

RT-PCR: Reverse transcription-polymerase chain reaction.

Table 2 Most common findings of chest X-rays

Main distribution	
Bilateral	+++
Unilateral	+
Imaging findings	
Ground-glass opacities	++++
Consolidation	+++
Reticular opacities	+++
Pneumothorax/pneumomediastinum	++
Pleural effusion	+
Lung cavitation	+

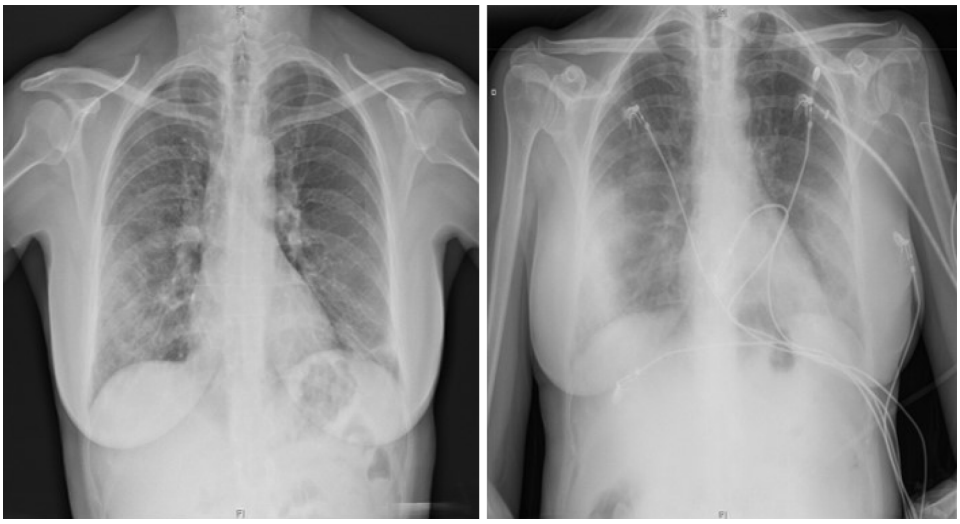


Figure 1 Chest X-ray findings in a 60-year-old woman with confirmed severe acute respiratory syndrome coronavirus-2 pneumonia (positive RT-PCR test). PA X-ray (left) with patchy right mid-to-lower and left lower lung opacities. AP X-ray (right) with peripherally distributed bilateral lung opacities.

– fragile in these patients – which releases air that centripetally dissects through the pulmonary interstitium, reaching the mediastinum.

Ultimately, the published data suggest that chest radiography has a high utility in patients with SARS-CoV-2 infection, especially in those with moderate to severe pulmonary involvement and in the advanced stages of the disease. Moreover, it can serve as a first-line imaging tool when resources are limited, playing a key role in the monitoring of patients and the evaluation of eventual associated complications[21].

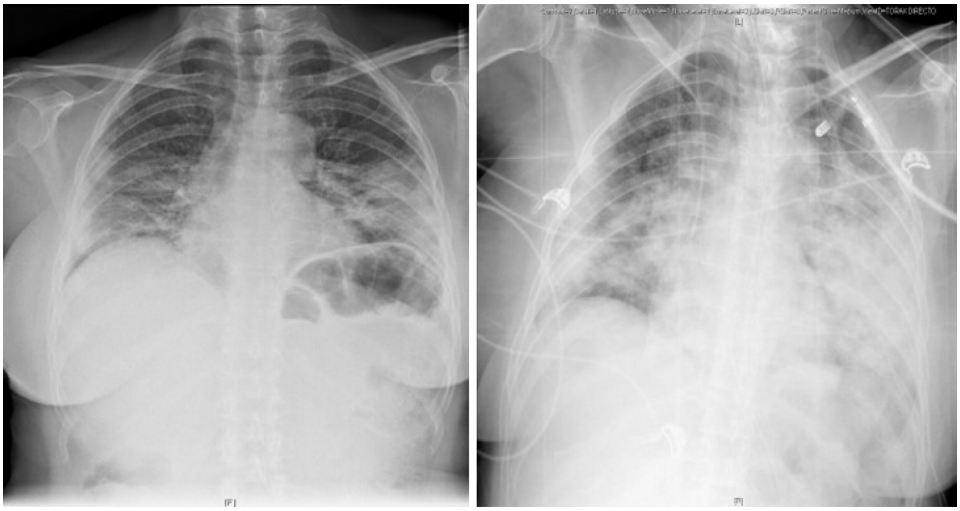


Figure 2 PA Chest X-ray findings in a 55-year-old woman with varying degrees of coronavirus disease 2019 pneumonia defined by diffuse ground-glass and consolidative opacities, predominantly involving the lower zone in both lungs.

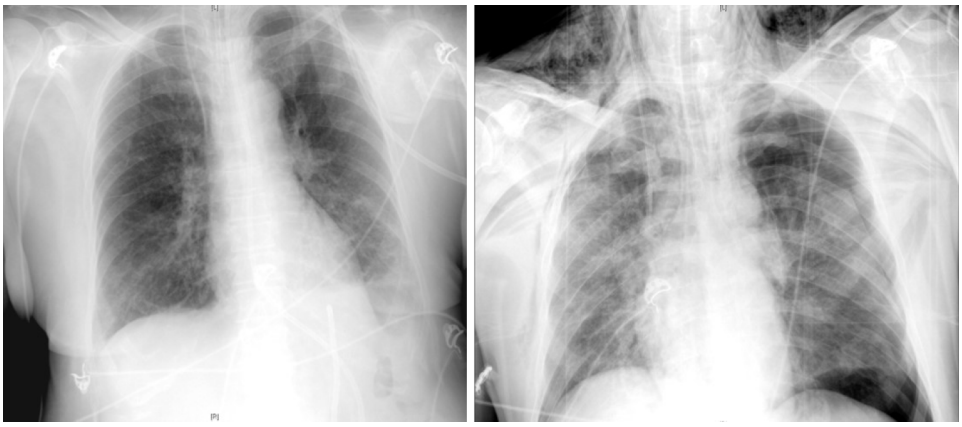


Figure 3 AP chest X-ray findings. AP chest X-ray findings (left) in an 80-year-old man with bilateral COVID-19 pneumonia and associated left pleural effusion. AP chest X-ray findings (right) in an 84-year-old man with bilateral alveolar infiltrates, diffusely distributed and left tension pneumothorax with subcutaneous emphysema.

LUNG ULTRASONOGRAPHY IN THE COVID-19 ERA

Since the influenza A pandemic (H1N1) in 2009 and the avian influenza epidemic (H7N9) in 2013, LUS has become a significant diagnostic tool for the early detection of interstitial lung disease[22,23]. The current data published on COVID-19 support it as a safe and accessible emerging technique that can be applied to patients with either suspected or confirmed SARS-CoV-2 infection, both in the initial evaluation and the subsequent follow-up.

Traditionally, a healthy lung is considered invisible to ultrasonography. Since it is an aerated organ, it does not transmit ultrasound and therefore does not provide anatomical images. However, when lung tissue is occupied by fluid or cellular elements, its impedance varies resulting in artifacts that permit the identification of pathological findings.

The most basic of these artifacts are *A lines* – transversal hyperechoic lines parallel to the pleural line – separated by a distance equal to that between the pleural line and the skin. They are the result of the reverberation of the pleural line in a healthy lung, representing normal lung aeration.

An additional and significant artifact in LUS are *B lines*, which are described as vertical hyperechogenic artifacts that arise from the pleural line. They extend like a comet tail towards the deep parenchyma, hiding *A lines* on their way and moving synchronously with pleural sliding[24]. They are considered to be the main ultrasound sign of interstitial lung disease, and their quantity increases as air content decreases and lung density intensifies. The presence of more than three *B lines* per intercostal

space is considered pathological.

In normal conditions, the pleural line is hyperechogenic, thin and regular. However, in the presence of inflammation, thickening and/or fragmentation may occur if there are adjacent pulmonary consolidations. Additionally, there may be a decrease in pleural sliding.

One of the great advantages of LUS is its accessibility and immediacy, since it generates bedside and real-time images. Additionally, it is a non-invasive and innocuous technique that can be applied safely in certain population groups, such as pregnant women and paediatric patients.

Furthermore, LUS has a high sensitivity and outperforms chest X-rays in detecting the early stages of interstitial lung disease[25].

The main limitation of LUS is its operator-dependent nature, as its reliability is closely related to clinicians' experience and ability. However, in experienced hands, the whole exploration can be performed in a few minutes, thus providing results faster in comparison with other imaging tests.

Lung ultrasound patterns in COVID-19

Before the outbreak of the COVID-19 pandemic, previous studies reported that LUS findings were highly consistent with chest CTs in patients with viral pneumonia[26]. Similarly, in patients with SARS-CoV-2 pneumonia, there is a good correlation between both imaging techniques[27-31].

The common ultrasound findings described in patients with SARS-CoV-2 infection are summarised in Table 3 and Figure 4[32,33].

Gattinoni *et al*[34] describe two different ultrasound patterns in the hyperinflammatory phase of COVID-19: One phenotype of diffuse pulmonary infiltrates (type L), with normal or minimally decreased lung compliance, and therefore limited scope for alveolar recruitment, and a second phenotype of extensive consolidations (type H), with a low or very low compliance and with a clinical and prognostic behaviour analogous to the common acute respiratory distress syndrome (ARDS).

None of the findings described so far are pathognomonic for COVID-19; therefore, LUS cannot provide a confirmatory diagnosis. As such, it is essential to integrate the images with a clinical assessment and nasopharyngeal swab result.

Recently, some authors have discovered an unusual finding that could be more specific to COVID-19: The '*light beam*'[35]. This is a thick hyperechogenic band of confluent *B lines* that originates from a portion of the pleural line that is apparently preserved. It is usually found in the early stages of the disease and correlates with incipient GGOs on chest CT scan.

LUS findings vary depending on the stage of the disease (Figure 5)[36]. Thus, in the first days after the onset of symptoms, it is common to observe unilateral or bilateral focal *B lines*. As the disorder progresses, the density of lung parenchyma increases along with the number of *B lines*; diffuse and bilateral *B lines* appear, starting from a pleural line that begins to thicken and becomes irregular, with small subpleural consolidations. Finally, *B lines* may coalesce, creating a 'white lung' pattern of consolidation or hepatisation of the lung parenchyma – particularly in declining areas – with the respiratory failure that this implies.

Given its high sensitivity, LUS allows the detection of both deterioration and recovery in lung lesions during the final stage of the disease. Consequently, during the convalescent stage, there is a progressive regression of *B lines* and consolidations. Additionally, *A lines* appear one again, in accordance with aeration improvement[31].

LUS is also efficient for the assessment of other events that, although not common, can occur in the course of SARS-CoV-2 pneumonia. These events include pleural effusion, pneumothorax – associated with mechanical ventilation or the insertion of a central venous catheter, among other causes – or a pulmonary embolism (PE). CT pulmonary angiogram remains the gold standard technique for the diagnosis of PE, but in critical, unstable patients with a suspected diagnosis, ultrasounds can provide valuable information on the presence of right ventricular dysfunction, acute pulmonary hypertension or deep vein thrombosis in the lower limbs.

Ultrasound scanning protocol

Evaluation of patients with acute respiratory failure using the Bedside Lung Ultrasound in Emergency Protocol (BLUE protocol), is one of the best-known applications of LUS[37]. In the particular case of COVID-19, one of its main challenges lies in standardising the technique to allow comparisons between study groups.

In clinical practice – and especially in ICUs – certain specific scanning protocols have been designed to quantify the extent of lung involvement by COVID-19[29,38-40]. We highlight the proposal of Soldati *et al*[38], which delimits seven exploration

Table 3 Common ultrasound findings in coronavirus disease 2019

B pattern: Presence of multifocal and separated B-lines ("*waterfall sign*") or confluent B-lines ("*white lung*"). The distribution is predominantly posteroinferior and bilateral, and varies depending on the severity of the disease
Patchy involvement: Pathological areas of lung parenchyma alternating with well-aerated and preserved areas
Thickening or interruption of pleural line, and reduced pleural sliding
Small subpleural consolidations in any region of the lung, more common at bases. Less frequently, larger consolidations may be found, with or without dynamic air bronchogram
Decrease in blood flow (within doppler mode) related to subpleural consolidations
Small or absent pleural effusion

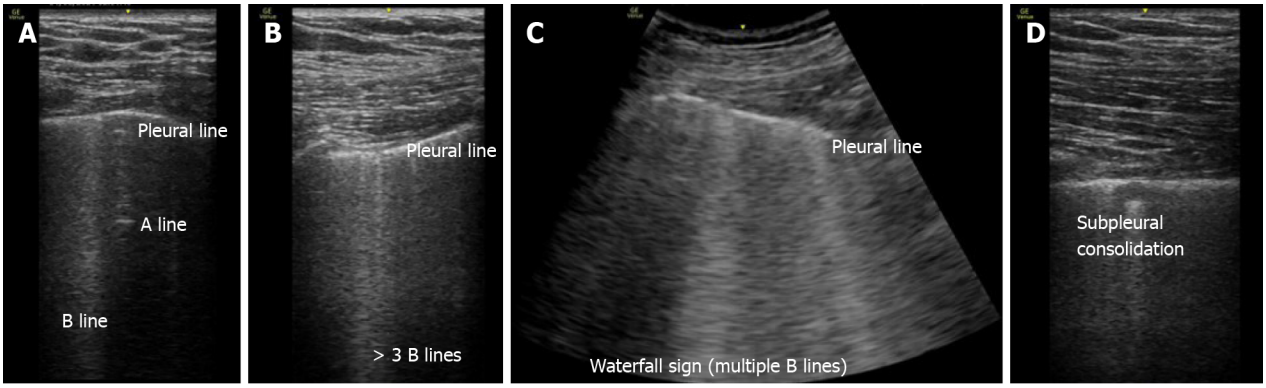


Figure 4 Images demonstrating the main changes in lung ultrasonography in coronavirus disease 2019 patients. A: Normal A-pattern with presence of 1 B line. B: Normal pleural line with presence of > 3 B lines. C: Irregular pleural line with coalescent B lines. D: Pleural involvement as sign of poor areation.

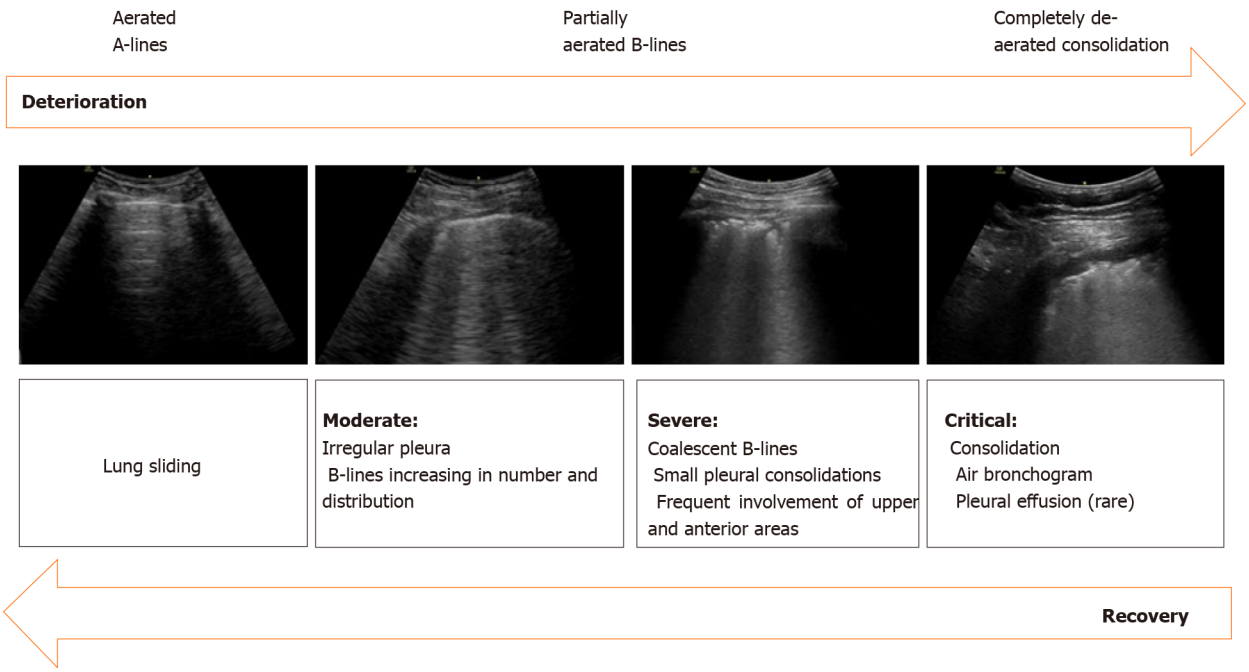


Figure 5 Sonographic characteristics of moderate, severe and critical pleural and parenchymal changes in patients with coronavirus disease 2019.

areas in each hemithorax, 14 zones in total. Each hemithorax is divided by three longitudinal lines – at the sternal, anterior and posterior axillary lines – and a transverse line at the nipple level, which separates a superior and an inferior area. Each one of the segments described receives a score between 0–3, according to the predominant

findings in them, defining four different patterns (Table 4, Figure 4)[40].

At the end of the exploration, the score assigned to every explored area is accumulated, obtaining the final score. In the case of patterns B1 and B2, special attention must be paid to the pleural line, since the presence of pleural lesions is a severity sign that should be indicated by adding the letter 'p' to the score.

Ultimately, this scale allows the estimation of the extent of lung involvement in COVID-19 and provides clinical and prognostic information. Therefore, it could contribute to identifying those patients who require hospital admission, as well as to predict their response to certain therapies, such as prone positioning or mechanical ventilation. For example, the progressive reduction in the number of *B lines*, the reappearance of *A lines* or the regression of consolidations could suggest a favourable clinical evolution and support the decision to progress in the de-escalation of care.

A summary of the potential applications of LUS in COVID-19 pandemic is outlined below: (1) At triage: For risk stratification and initial screening of lung involvement in patients with suspected or confirmed SARS-CoV-2 infection; (2) In patients with symptoms consistent with COVID-19, but a negative nasopharyngeal swab (RT-PCR) and indeterminate chest X-ray: The presence of suggestive ultrasound findings could support the idea that the RT-PCR may represent a false-negative result; and (3) During hospital admission, to monitor the progression or regression of pulmonary lesions: Successive ultrasound explorations might result in accurate information that could be used to determine ventilation strategies and assess patients' response to them. For example, those with posterolateral consolidations could benefit from early prone positioning[41,42], or lung aeration could be improved in those with coalescent *B lines* by titrating positive end-expiratory pressure (PEEP). In addition, in critically-ill patients – respiratory or hemodynamically unstable – LUS could play a remarkable role in the early detection of complications, including superimposed bacterial pneumonia and pneumothorax, and as a guide for clinical decisions.

Therefore, LUS is becoming an increasingly valuable diagnostic tool due to its high sensitivity, safety, immediacy and accuracy. On this basis, it may play a key role in the management of patients with COVID-19. However, its low specificity for this pathology does not allow clinicians to distinguish COVID-19 from other viral infections. Therefore, LUS images must be evaluated in conjunction with clinical and microbiological data.

ROLE OF CHEST CT SCAN IN THE EVALUATION OF COVID-19 PNEUMONIA

Chest CT scan is a key element in the management of SARS-CoV-2 infection. It allows the detection of distinctive pulmonary manifestations, establishes their severity and enables the follow-up of their progression, differentiating early stages from more advanced ones based on the radiological findings identified. However, its role as a screening tool in COVID-19 pneumonia has yet to be fully defined[43].

Recent studies concerning COVID-19 pneumonia propose that chest CT is a more sensitive, practical and rapid diagnostic technique compared to the RT-PCR test, especially in the early stages of the disease (Table 5). Ai *et al*[44] reported a sensitivity for chest CT of 97%, taking RT-PCR as a reference, compared to 59% of RT-PCR performed in patients with suspected SARS-CoV-2 infection. However, chest CT specificity was only 25%. Furthermore, a meta-analysis conducted by Kim *et al*[45] produced similar results, with a higher chest CT sensitivity than the one found for RT-PCR, 94% and 89%, respectively. However, a low specificity (37%) was encountered, which could be due to the fact that the nonspecific findings of COVID-19 pneumonia may overlap with those found in other viral pneumonias, so a high rate of false positives can be detected in chest CTs, especially in areas of low prevalence of the disease.

Supporting these results, the Society of Thoracic Radiology, the ACR and the Radiological Society of North America recommend avoiding using chest CT as a routine screening test in patients with suspected SARS-CoV-2 infection[46]. Instead it should be saved for the assessment of symptomatic patients or those with a negative RT-PCR but high clinical suspicion, as it can help to characterise the disease by detecting typical pulmonary manifestations[47].

Thus, chest CT findings suggesting viral pneumonia, accompanied by a typical clinical presentation and compatible epidemiological data, should strongly indicate SARS-CoV-2 infection even though the RT-PCR may be negative[48].

Table 4 Adapted from Vetrugno *et al*[39] proposal of lung ultrasonography score system in coronavirus disease 2019

Class	Score	Definition
A	0 point	Normal aeration pattern. Presence of *A lines*, pleural sliding, and ≤ 3 well-spaced *B lines*
B1	1 point	More than 3 *B lines* per intercostal space
B2	2 points	Confluent *B lines* (with or without small consolidations). This pattern corresponds to the presence of GGO on chest CT scan
C	3 points	Large consolidations, parenchymal hepatization (with or without air bronchogram)

CT: Computed tomography; GGO: Ground-glass opacity.

Table 5 Chest computed tomography and reverse transcription-polymerase chain reaction sensitivity in coronavirus disease 2019 pneumonia

Ref.	Number of patients	Symptoms	Positive RT-PCR	RT-PCR sensitivity	Chest CT abnormalities	Chest CT sensitivity
Fang *et al*[76], 2020	51	Fever/acute respiratory symptoms	36/51 patients	71%	50/51 patients	98%
Xie *et al*[48], 2020	167	Fever	162/167 patients	97%	160/167 patients	95.8%
Yang *et al*[77], 2020	149	Fever, cough and sputum	149/149	100%	132/149	88.6%
Ai *et al*[44], 2020	1014	–	601/1014	59%	888/1014	88%
Kim *et al*[45], 2020	7720	–	1336/1502	89%	5845/6218	94%

RT-PCR: Reverse transcription-polymerase chain reaction; CT: Computed tomography.

There are currently few works on the use of artificial intelligence in the diagnosis of SARS-CoV-2. Although this technique could be useful in diagnosing COVID-19 pneumonia, there is little evidence so far to recommend it as a routine diagnostic approach[49].

Chest CT imaging features of COVID-19

SARS-CoV-2 infection causes direct lung damage through the angiotensin-converting enzyme. Interstitial pneumonia with alveolar edema in the early stages and diffuse alveolar damage in the most severe stages are the underlying pathological mechanisms responsible for the typical radiological images of COVID-19 pneumonia and its rapid progression[50,51].

A wide range of radiological findings have been reported in the multiple published studies (Table 6); however, the images may differ depending on the evolutionary stage of the disease. The main and most frequent finding of COVID-19 pneumonia is the presence of GGOs, typically subpleural (Figure 6)[52,53]. GGOs are defined as areas of slightly increased density without obscuration of bronchial and vascular structures, caused by a partial filling of the alveolar spaces and interstitial thickening. In an investigation conducted by Chung *et al*[53] with 21 COVID-19 patients, GGOs – being the most characteristic radiological finding in the early stages of the disease – were found in 57% of cases[54]. In accordance with these results, Pan *et al*[55] predominantly observed subpleural GGOs at the onset of the disease, with the subsequent development of a 'crazy paving' pattern and consolidations at two weeks of evolution.

Regarding the distribution of the radiological images encountered, a retrospective study of 101 patients[56] classified them as either bilateal (82.2%), peripheral (87.1%) or multifocal (54.5%), principally involving the lower lobes (54.5%) of the patients. These results are broadly in line with other published studies. In a study conducted by Salehi *et al*[57], pulmonary changes were bilateral (87.5%), with a peripheral distribution (76.0%) and a predominantly multilobar (78.8%) and posterior (80.4%) pulmonary infiltration.

Table 6 Adapted from Carotti *et al*[57] average percentage of chest computed tomography manifestations of coronavirus disease 2019

Average percentage of chest computed tomography manifestations of coronavirus		
Ground-glass opacities	66%	+++++
Ground-glass opacities + consolidation	47%	++++
Consolidation	41%	++++
Interlobular septal thickening	53%	++++
Reticular pattern	27%	++
Crazy paving pattern	20%	++
Air bronchogram sign	50%	++++
Bronchial wall thickening	17%	++
Pleural effusion	10%	+
Nodules	15%	++
Reverse halo sign	3%	+
Lymphadenopathies	8%	+
Pericardial effusion	4%	+

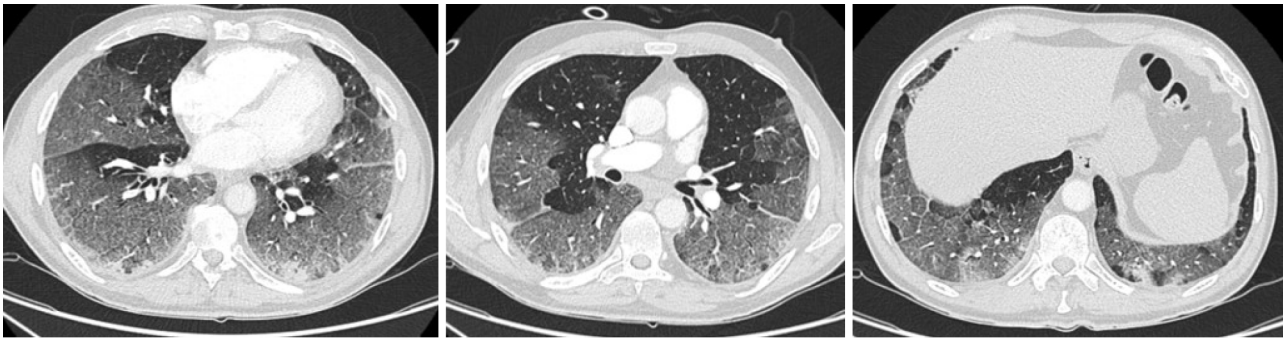


Figure 6 59-year-old man with no clinical background and confirmed severe acute respiratory syndrome coronavirus-2 infection. Chest computed tomography imaging with peripherally distributed bilateral and multilobar ground-glass opacities.

Consolidation images have been described as the second most prevalent finding, reported in 2%-63% of cases. The involvement may be multifocal, patchy, or segmental, with a subpleural or peribronchovascular distribution. The development of this consolidation pattern may be in relation to the progression of the disease and can either coexist alongside or replace GGOs between week one to three of the clinical course, which could alert to the severity of the disease[55,58] (Figure 7).

Recent investigations have reported 5%-36% of COVID-19 patients with a crazy paving pattern on their imaging studies. This pattern refers to the appearance of GGOs with superimposed interlobular and intralobular septal thickening. While not observed as frequently as GGOs and consolidation, this pattern may be a sign that the disease is reaching its peak of maximum severity[54], which is described by Pan *et al*[55] as occurring 10 d after the onset of symptoms.

Other findings, such as the reverse halo sign (11.0%), the air bronchogram sign (14%), pleural thickening (15.0%), pleural effusion (4.0%) and the appearance of lymphadenopathies (2.7%), have been less frequently described[59]. Bronchial wall thickening and the presence of extrapulmonary lesions suggest severe inflammation and are characteristic of critical COVID-19 pneumonia (Figure 8)[60].

A reticular pattern associated with bronchiolectasis and irregular thickening of the interlobular septa has been identified with the progression of the disease, usually after the second week of evolution (Figure 9). These interstitial changes suggest the development of fibrosis. Pulmonary fibrosis is a relatively common consequence of ARDS. Approximately 40% of patients diagnosed with COVID-19 pneumonia are believed to develop ARDS, 20% of them severe. Although long-term studies have shown the existence of persistent interstitial alterations in patients who have suffered

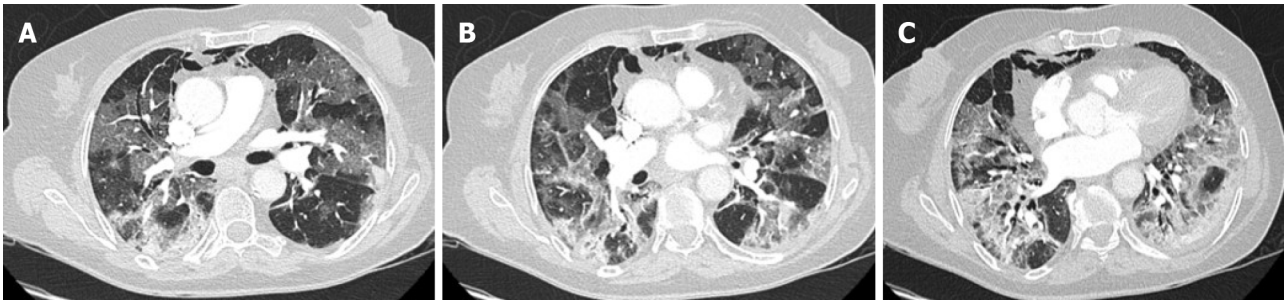


Figure 7 45-year-old woman with coronavirus disease 2019-confirmed pneumonia. Chest computed tomography imaging. A: Bilateral and patchy ground-glass opacities involving upper and lower lobes. B: Crazy paving pattern involving upper and lower lobes. C: Alveolar consolidation mainly involving the lower lobes, with fibrous stripes associated.

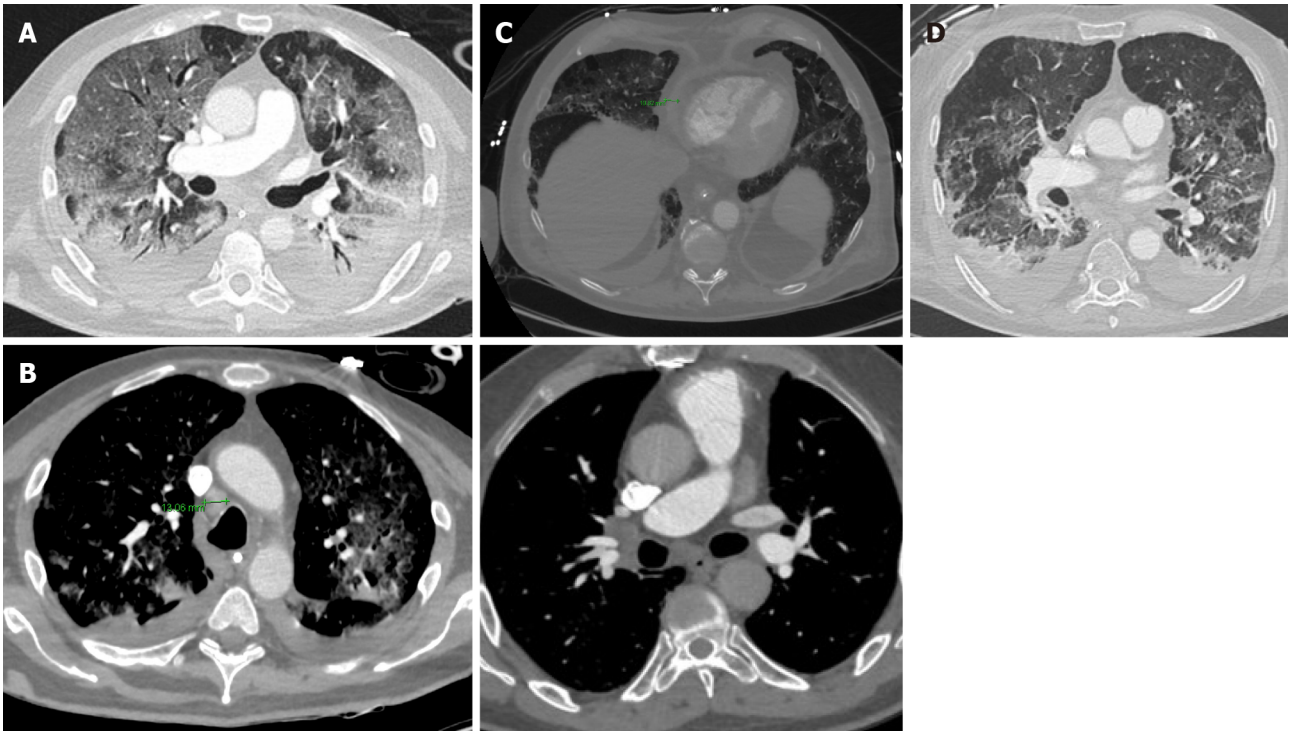


Figure 8 Unusual chest computed tomography findings in coronavirus disease 2019 pneumonia. A: Air bronchogram sign; B: Right paratracheal lymphadenopathy (marked) and right hilar lymphadenopathy; C: Pericardial effusion; D: Pleural effusion.

pneumonia due to other coronaviruses genetically similar to SARS-CoV-2 – SARS-CoV and MERS-CoV, first identified in 2002 and 2012 respectively[61,62], – the natural history of COVID-19 pneumonia has not yet been fully defined. Therefore, it is too early to classify these pulmonary changes as irreversible fibrotic changes, meaning that future prospective studies are necessary to confirm these preliminary results.

FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY IN COVID-19

PET-CT imaging with fluorodeoxyglucose (FDG) is a relevant and well-established diagnostic tool in tumoral pathology; in combination with CT, it provides anatomical and functional information that facilitates the study of tumoral extension and the evaluation of therapeutic response. This technique has also recently been gaining a certain importance in inflammatory and infectious pathologies. However, it has not yet been validated in this field and its use is not routinely recommended[63].

Several studies have suggested that PET-CT may be useful to evaluate the immune response to viral infections and their progression[64,65], since FDG uptake increases in

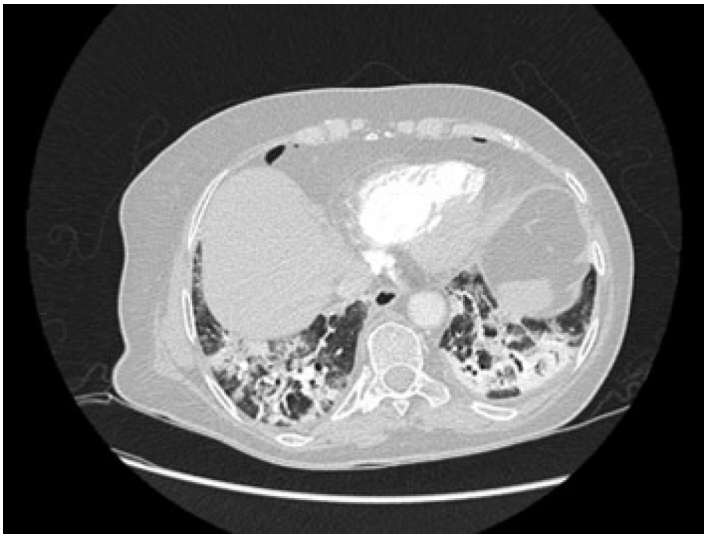


Figure 9 Reticular pattern and fibrous stripes showing coronavirus disease 2019 pneumonia in evolution (> 2 wk after the onset of symptoms).

neutrophils, lymphocytes, activated macrophages and granulocytes where there is inflammation. Therefore, it enables the localisation of where the immune response starts and how it develops.

Some authors have used PET-CT in animal models to study the development of viral infections, including MERS-CoV, H1N1, and HIV[66-68]. After exposure to the virus, in the absence of symptoms or abnormalities in chest CT scans, PET-CT is able to detect increased cellular metabolism in the lymph node stations directly involved in the lymphatic drainage of the lung tissue: the mediastinal and axillary nodes[66]. Furthermore, this increase in FDG uptake is observed before massive viral replication occurs[68]; therefore, PET-CT could have a significant utility in early stages of infection.

In line with other inflammatory processes, the lung areas affected by COVID-19 show an increased FDG uptake (Figure 10)[69]. It has been postulated that there could be a correlation between greater FDG uptake and a slower progression towards improvement, as well as a higher erythrocyte sedimentation rate[70]. Various studies – which compare the findings of PET-CT and chest CT scans in COVID-19 patients – have also reported that despite the absence of lymphadenopathy in CT, PET-CT does detect an increased FDG uptake at the mediastinal and subclavicular lymph nodes[70-73]. Additionally, in some patients infected by SARS-CoV-2, mild inflammatory activity has been observed in the spleen and bone marrow, possibly in relation to a systemic inflammatory state. Finally, Lutje *et al*[74] proposed that PET-CT with FDG might help in detecting changes in other organs, including the heart, kidneys and gastrointestinal tract. However, all of the data published so far agree that the inflammatory process triggered by COVID-19 has a particular tropism for the lower respiratory tract.

Preliminary studies have suggested that there is a certain correlation between the metabolic information provided by PET-CT and the degree of ventilation in different areas of the lung[75]. The collected data indicate that poorly ventilated areas of lung parenchyma show a greater FDG uptake than non-ventilated areas. This might mean that, within inflammatory processes, the better ventilated areas of the lung probably present higher infiltration by inflammatory cells[76].

PET-CT is not recommended as an initial test for diagnosing SARS-CoV-2 infection, as it involves greater irradiation to the patient than chest X-ray or chest CT scan, and the image acquisition periods are longer. Nonetheless, the structural and metabolic image that it provides could have an application in COVID-19 in the following situations[77]: (1) As a diagnostic tool for differential diagnosis in asymptomatic patients and in already diagnosed patients with a normal CT scan; (2) For monitoring responses to therapy, in combination with chest CT scan; (3) As a potential prognostic factor in the recovery stage of the disease; and (4) To evaluate extrapulmonary systemic involvement.

In conclusion, the studies published to date on the potential role of PET-CT in COVID-19 are limited. However, the existing data suggest that it may provide

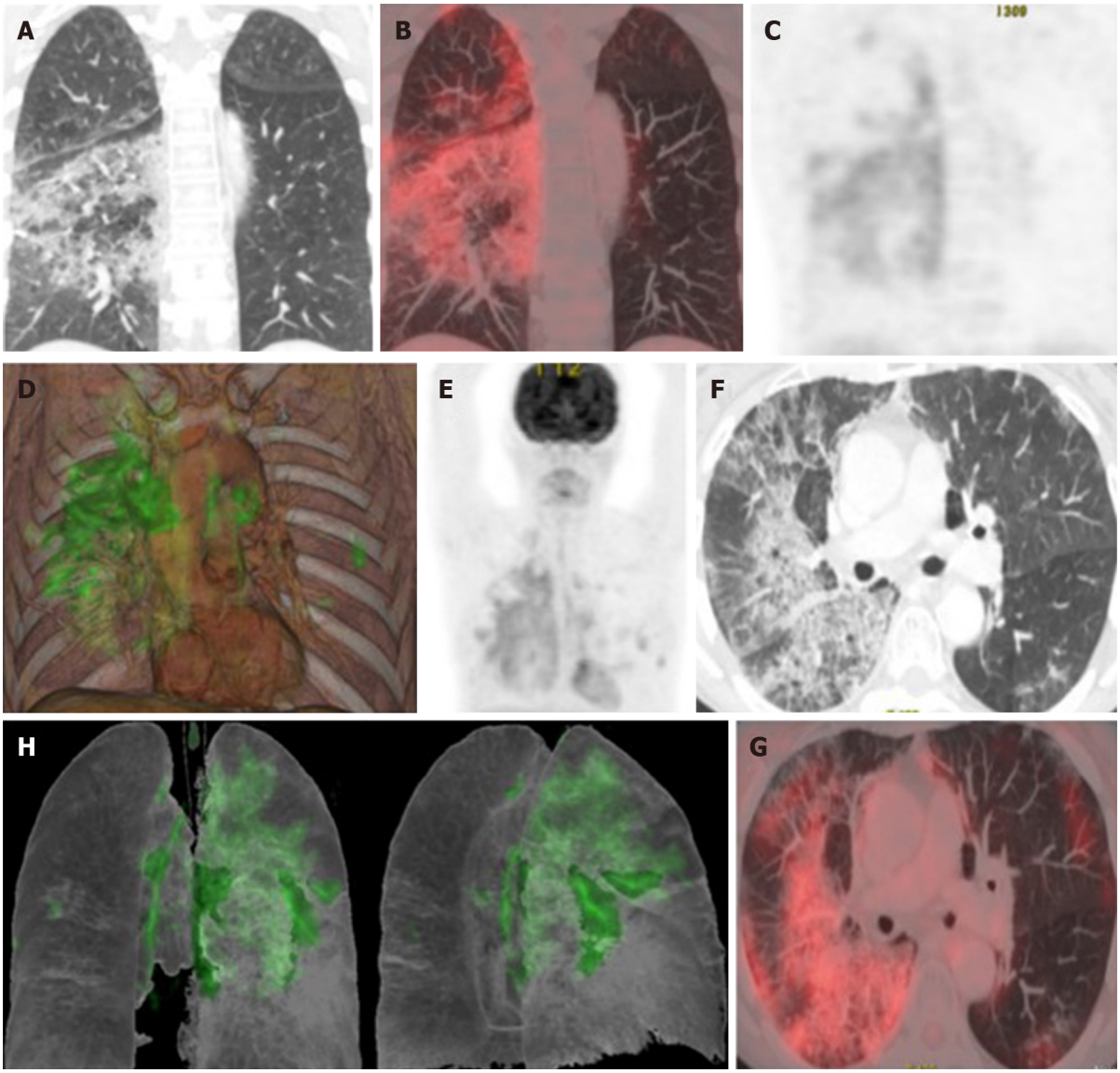


Figure 10 Taken from Landete *et al*[12], A 65-year-old patient with a history of invasive lepidic-predominant adenocarcinoma (stage pT1bNxM0) treated with surgery, chemotherapy and radiotherapy. A: Coronal computed tomography (CT) showing the crazy paving pattern with a markedly asymmetric bilateral distribution, mainly affecting the right side. B: Positron emission tomography-CT (PET-CT) coronal section. C: Metabolic PET. D: Volume rendering 3D PET-CT. E: MIP, PET. Images B–E reveal an increased cellular activity [standard uptake value (SUV) 4-6] related to the associated inflammatory process and a PET-CT pattern of bilateral coronavirus disease 2019 (COVID-19) with viral pneumonitis, predominantly right-sided. F: Axial CT showing crazy paving pattern with a bilateral, yet markedly asymmetric distribution, predominant right-sided. G and H: Axial section and 3D volume rendering from PET-CT metabolic imaging revealing increased cellular activity (SUV 4-6) related to the associated inflammatory process. PET-CT pattern of bilateral, predominantly right-sided, COVID-19 viral pneumonitis. Citation: Landete P, Quezada Loaiza CA, Aldave-Orzaiz B, Muñiz SH, Maldonado A, Zamora E, Sam Cerna AC, Del Cerro E, Alonso RC, Couñago F. Clinical features and radiological manifestations of COVID-19 disease. *World J Radiol* 2020; 12(11): 247-260. Copyright ©The Author(s) 2020. Published by Baishideng Publishing Group Inc[12]".

valuable information – complementary to the other imaging tests mentioned in this review – which helps to understand the pathophysiology of SARS-CoV-2 infection, define therapeutic strategies and assess the response to them.

CONCLUSION

Chest X-ray and CT play an important role in detecting abnormal lung changes, being the main imaging tests used to diagnose COVID-19 pneumonia. Other radiological modalities, such as lung ultrasonography and PET-CT, can provide further information for initial assessment and follow-up treatment response. Moreover, as we move through the pandemic, we believe that radiological findings of COVID-19 will be further explored, helping in determining diagnostic imaging features and guiding

treatment.

REFERENCES

1 **Sohrabi C**, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 2020; **76**: 71-76 [PMID: 32112977 DOI: 10.1016/j.ijsu.2020.02.034]

2 **Udugama B**, Kadhiresan P, Kozlowski HN, Malekjahani A, Osborne M, Li VYC, Chen H, Mubareka S, Gubbay JB, Chan WCW. Diagnosing COVID-19: The Disease and Tools for Detection. *ACS Nano* 2020; **14**: 3822-3835 [PMID: 32223179 DOI: 10.1021/acsnano.0c02624]

3 **World Health Organization**. COVID-19 Weekly epidemiological update-8 December 2020. [cited 20 January 2021] Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-8-december-2020

4 **Pascarella G**, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 2020; **288**: 192-206 [PMID: 32348588 DOI: 10.1111/joim.13091]

5 **Aljondi R**, Alghamdi S. Diagnostic Value of Imaging Modalities for COVID-19: Scoping Review. *J Med Internet Res* 2020; **22**: e19673 [PMID: 32716893 DOI: 10.2196/19673]

6 **Wiersinga WJ**, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; **324**: 782-793 [PMID: 32648899 DOI: 10.1001/jama.2020.12839]

7 **Araujo-Filho JAB**, Sawamura MVY, Costa AN, Cerri GG, Nomura CH. COVID-19 pneumonia: what is the role of imaging in diagnosis? *J Bras Pneumol* 2020; **46**: e20200114 [PMID: 32236303 DOI: 10.36416/1806-3756/e20200114]

8 **Gandhi D**, Ahuja K, Grover H, Sharma P, Solanki S, Gupta N, Patel L. Review of X-ray and computed tomography scan findings with a promising role of point of care ultrasound in COVID-19 pandemic. *World J Radiol* 2020; **12**: 195-203 [PMID: 33033574 DOI: 10.4329/wjr.v12.i9.195]

9 **Rubin GD**, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin J, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest* 2020; **158**: 106-116 [PMID: 32275978 DOI: 10.1016/j.chest.2020.04.003]

10 **Farias LPG**, Fonseca EKUN, Strabelli DG, Loureiro BMC, Neves YCS, Rodrigues TP, Chate RC, Nomura CH, Sawamura MVY, Cerri GG. Imaging findings in COVID-19 pneumonia. *Clinics (Sao Paulo)* 2020; **75**: e2027 [PMID: 32578826 DOI: 10.6061/clinics/2020/e2027]

11 **Revel MP**, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A; European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020; **30**: 4903-4909 [PMID: 32314058 DOI: 10.1007/s00330-020-06865-y]

12 **Landete P**, Quezada Loaiza CA, Aldave-Orzaiz B, Muñiz SH, Maldonado A, Zamora E, Sam Cerna AC, Del Cerro E, Alonso RC, Couñago F. Clinical features and radiological manifestations of COVID-19 disease. *World J Radiol* 2020; **12**: 247-260 [PMID: 33362916 DOI: 10.4329/wjr.v12.i11.247]

13 **Wong HYF**, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* 2020; **296**: E72-E78 [PMID: 32216717 DOI: 10.1148/radiol.2020201160]

14 **Ng MY**, Lee EYP, Yang J, Yang F, Li X, Wang H, Lui MM, Lo CS, Leung B, Khong PL, Hui CK, Yuen KY, Kuo MD. Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review. *Radiol Cardiothorac Imaging* 2020; **2**: e200034 [PMID: 33778547 DOI: 10.1148/ryct.2020200034]

15 **Kim ES**, Chin BS, Kang CK, Kim NJ, Kang YM, Choi JP, Oh DH, Kim JH, Koh B, Kim SE, Yun NR, Lee JH, Kim JY, Kim Y, Bang JH, Song KH, Kim HB, Chung KH, Oh MD; Korea National Committee for Clinical Management of COVID-19. Clinical Course and Outcomes of Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection: a Preliminary Report of the First 28 Patients from the Korean Cohort Study on COVID-19. *J Korean Med Sci* 2020; **35**: e142 [PMID: 32242348 DOI: 10.3346/jkms.2020.35.e142]

16 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

17 **Cellina M**, Panzeri M, Oliva G. Chest Radiography Features Help to Predict a Favorable Outcome in Patients with Coronavirus Disease 2019. *Radiology* 2020; **297**: E238 [PMID: 32484419 DOI: 10.1148/radiol.2020202326]

18 **Jacobi A**, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-

19): A pictorial review. *Clin Imaging* 2020; **64**: 35-42 [PMID: 32302927 DOI: 10.1016/j.clinimag.2020.04.001]

19 **Lomoro P**, Verde F, Zerboni F, Simonetti I, Borghi C, Fachinetti C, Natalizi A, Martegani A. COVID-19 pneumonia manifestations at the admission on chest ultrasound, radiographs, and CT: single-center study and comprehensive radiologic literature review. *Eur J Radiol Open* 2020; **7**: 100231 [PMID: 32289051 DOI: 10.1016/j.ejro.2020.100231]

20 **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]

21 **Chen SG**, Chen JY, Yang YP, Chien CS, Wang ML, Lin LT. Use of radiographic features in COVID-19 diagnosis: Challenges and perspectives. *J Chin Med Assoc* 2020; **83**: 644-647 [PMID: 32349032 DOI: 10.1097/JCMA.0000000000000336]

22 **Zhang YK**, Li J, Yang JP, Zhan Y, Chen J. Lung ultrasonography for the diagnosis of 11 patients with acute respiratory distress syndrome due to bird flu H7N9 infection. *Virol J* 2015; **12**: 176 [PMID: 26503117 DOI: 10.1186/s12985-015-0406-1]

23 **Tsai NW**, Ngai CW, Mok KL, Tsung JW. Lung ultrasound imaging in avian influenza A (H7N9) respiratory failure. *Crit Ultrasound J* 2014; **6**: 6 [PMID: 24949191 DOI: 10.1186/2036-7902-6-6]

24 **Volpicelli G**, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, Dean A, Tsung JW, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby JJ, Arbelot C, Liteplo A, Sargsyan A, Silva F, Hoppmann R, Breitkreutz R, Seibel A, Neri L, Storti E, Petrovic T; International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* 2012; **38**: 577-591 [PMID: 22392031 DOI: 10.1007/s00134-012-2513-4]

25 **Mojoli F**, Bouhemad B, Mongodi S, Lichtenstein D. Lung Ultrasound for Critically Ill Patients. *Am J Respir Crit Care Med* 2019; **199**: 701-714 [PMID: 30372119 DOI: 10.1164/rccm.201802-0236CI]

26 **Alzahrani SA**, Al-Salamah MA, Al-Madani WH, Elbarbary MA. Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. *Crit Ultrasound J* 2017; **9**: 6 [PMID: 28244009 DOI: 10.1186/s13089-017-0059-y]

27 **Tung-Chen Y**, Martí de Gracia M, Díez-Tascón A, Alonso-González R, Agudo-Fernández S, Parra-Gordo ML, Ossaba-Vélez S, Rodríguez-Fuertes P, Llamas-Fuentes R. Correlation between Chest Computed Tomography and Lung Ultrasonography in Patients with Coronavirus Disease 2019 (COVID-19). *Ultrasound Med Biol* 2020; **46**: 2918-2926 [PMID: 32771222 DOI: 10.1016/j.ultrasmedbio.2020.07.003]

28 **Poggiali E**, Dacrema A, Bastoni D, Tinelli V, Demichele E, Mateo Ramos P, Marcianò T, Silva M, Vercelli A, Magnacavallo A. Can Lung US Help Critical Care Clinicians in the Early Diagnosis of Novel Coronavirus (COVID-19) Pneumonia? *Radiology* 2020; **295**: E6 [PMID: 32167853 DOI: 10.1148/radiol.2020200847]

29 **Huang Y**, Wang S, Liu Y, Zhang Y, Zheng C, Zheng Y, Zhang C, Min W, Yu M, Hu M. A Preliminary Study on the Ultrasonic Manifestations of Peripulmonary Lesions of Non-Critical Novel Coronavirus Pneumonia (COVID-19) (February 26, 2020). [DOI: 10.2139/ssrn.3544750]

30 **Nouvenne A**, Zani MD, Milanese G, Parise A, Baciarello M, Bignami EG, Odone A, Sverzellati N, Meschi T, Ticinesi A. Lung Ultrasound in COVID-19 Pneumonia: Correlations with Chest CT on Hospital admission. *Respiration* 2020; **99**: 617-624 [PMID: 32570265 DOI: 10.1159/000509223]

31 **Peng QY**, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; **46**: 849-850 [PMID: 32166346 DOI: 10.1007/s00134-020-05996-6]

32 **Volpicelli G**, Gargani L. Sonographic signs and patterns of COVID-19 pneumonia. *Ultrasound J* 2020; **12**: 22 [PMID: 32318891 DOI: 10.1186/s13089-020-00171-w]

33 **Millington SJ**, Koenig S, Mayo P, Volpicelli G. Lung Ultrasound for Patients With Coronavirus Disease 2019 Pulmonary Disease. *Chest* 2021; **159**: 205-211 [PMID: 32835709 DOI: 10.1016/j.chest.2020.08.2054]

34 **Gattinoni L**, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; **46**: 1099-1102 [PMID: 32291463 DOI: 10.1007/s00134-020-06033-2]

35 **Volpicelli G**, Lamorte A, Villén T. What's new in lung ultrasound during the COVID-19 pandemic. *Intensive Care Med* 2020; **46**: 1445-1448 [PMID: 32367169 DOI: 10.1007/s00134-020-06048-9]

36 **Smith MJ**, Hayward SA, Innes SM, Miller ASC. Point-of-care lung ultrasound in patients with COVID-19 - a narrative review. *Anaesthesia* 2020; **75**: 1096-1104 [PMID: 32275766 DOI: 10.1111/anae.15082]

37 **Lichtenstein DA**. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest* 2015; **147**: 1659-1670 [PMID: 26033127 DOI: 10.1378/chest.14-1313]

38 **Soldati G**, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani A, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for International Standardization of the Use of Lung Ultrasound for Patients With COVID-19: A Simple, Quantitative, Reproducible Method. *J Ultrasound Med* 2020; **39**: 1413-1419 [PMID: 32227492 DOI: 10.1002/jum.15285]

39 **Vetrugno L**, Bove T, Orso D, Barbariol F, Bassi F, Boero E, Ferrari G, Kong R. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. *Echocardiography* 2020; **37**: 625-627

[PMID: 32239532 DOI: 10.1111/echo.14664]
40 **Istvan-Adorjan S**, Ágoston G, Varga A, Cotoi OS, Frigy A. Pathophysiological background and clinical practice of lung ultrasound in COVID-19 patients: A short review. *Anatol J Cardiol* 2020; **24**: 76-80 [PMID: 32749247 DOI: 10.14744/AnatolJCardiol.2020.33645]
41 **Prat G**, Guinard S, Bizien N, Nowak E, Tonnelier JM, Alavi Z, Renault A, Boles JM, L'Her E. Can lung ultrasonography predict prone positioning response in acute respiratory distress syndrome patients? *J Crit Care* 2016; **32**: 36-41 [PMID: 26806842 DOI: 10.1016/j.jcrc.2015.12.015]
42 **Wang XT**, Ding X, Zhang HM, Chen H, Su LX, Liu DW; Chinese Critical Ultrasound Study Group (CCUSG). Lung ultrasound can be used to predict the potential of prone positioning and assess prognosis in patients with acute respiratory distress syndrome. *Crit Care* 2016; **20**: 385 [PMID: 27899151 DOI: 10.1186/s13054-016-1558-0]
43 **Sun Z**, Zhang N, Li Y, Xu X. A systematic review of chest imaging findings in COVID-19. *Quant Imaging Med Surg* 2020; **10**: 1058-1079 [PMID: 32489929 DOI: 10.21037/qims-20-564]
44 **Ai T**, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296**: E32-E40 [PMID: 32101510 DOI: 10.1148/radiol.2020200642]
45 **Kim H**, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse Transcriptase Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. *Radiology* 2020; **296**: E145-E155 [PMID: 32301646 DOI: 10.1148/radiol.2020201343]
46 **Simpson S**, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, Litt H. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging* 2020; **35**: 219-227 [PMID: 32324653 DOI: 10.1097/RTI.0000000000000524]
47 **Waller JV**, Kaur P, Tucker A, Lin KK, Diaz MJ, Henry TS, Hope M. Diagnostic Tools for Coronavirus Disease (COVID-19): Comparing CT and RT-PCR Viral Nucleic Acid Testing. *AJR Am J Roentgenol* 2020; **215**: 834-838 [PMID: 32412790 DOI: 10.2214/AJR.20.23418]
48 **Xie X**, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* 2020; **296**: E41-E45 [PMID: 32049601 DOI: 10.1148/radiol.2020200343]
49 **Neri E**, Miele V, Coppola F, Grassi R. Use of CT and artificial intelligence in suspected or COVID-19 positive patients: statement of the Italian Society of Medical and Interventional Radiology. *Radiol Med* 2020; **125**: 505-508 [PMID: 32350794 DOI: 10.1007/s11547-020-01197-9]
50 **Li Y**, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. *AJR Am J Roentgenol* 2020; **214**: 1280-1286 [PMID: 32130038 DOI: 10.2214/AJR.20.22954]
51 **Li M**. Chest CT features and their role in COVID-19. *Radiol Infect Dis* 2020; **7**: 51-54 [PMID: 32309528 DOI: 10.1016/j.jrid.2020.04.001]
52 **Hani C**, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, Revel MP. COVID-19 pneumonia: A review of typical CT findings and differential diagnosis. *Diagn Interv Imaging* 2020; **101**: 263-268 [PMID: 32291197 DOI: 10.1016/j.diii.2020.03.014]
53 **Chung M**, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A, Li K, Li S, Shan H. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020; **295**: 202-207 [PMID: 32017661 DOI: 10.1148/radiol.2020200230]
54 **Ye Z**, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* 2020; **30**: 4381-4389 [PMID: 32193638 DOI: 10.1007/s00330-020-06801-0]
55 **Pan F**, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715-721 [PMID: 32053470 DOI: 10.1148/radiol.2020200370]
56 **Zhao W**, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol* 2020; **214**: 1072-1077 [PMID: 32125873 DOI: 10.2214/AJR.20.22976]
57 **Salehi S**, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *AJR Am J Roentgenol* 2020; **215**: 87-93 [PMID: 32174129 DOI: 10.2214/AJR.20.23034]
58 **Carotti M**, Salaffi F, Sarzi-Puttini P, Agostini A, Borgheresi A, Minorati D, Galli M, Marotto D, Giovagnoni A. Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med* 2020; **125**: 636-646 [PMID: 32500509 DOI: 10.1007/s11547-020-01237-4]
59 **Bai HX**, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, Pan I, Shi LB, Wang DC, Mei J, Jiang XL, Zeng QH, Egglin TK, Hu PF, Agarwal S, Xie FF, Li S, Healey T, Atalay MK, Liao WH. Performance of Radiologists in Differentiating COVID-19 from Non-COVID-19 Viral Pneumonia at Chest CT. *Radiology* 2020; **296**: E46-E54 [PMID: 32155105 DOI: 10.1148/radiol.2020200823]
60 **Li K**, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. *Invest Radiol* 2020; **55**: 327-331 [PMID: 32118615 DOI: 10.1097/RLI.0000000000000672]
61 **Shi H**, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;

20: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]

62 **Spagnolo P**, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Casa GD, Sverzellati N, Maher TM. Pulmonary fibrosis secondary to COVID-19: a call to arms? *Lancet Respir Med* 2020; **8**: 750-752 [PMID: 32422177 DOI: 10.1016/S2213-2600(20)30222-8]

63 **Capitanio S**, Nordin AJ, Noraini AR, Rossetti C. PET/CT in nononcological lung diseases: current applications and future perspectives. *Eur Respir Rev* 2016; **25**: 247-258 [PMID: 27581824 DOI: 10.1183/16000617.0051-2016]

64 **de Prost N**, Tucci MR, Melo MF. Assessment of lung inflammation with 18F-FDG PET during acute lung injury. *AJR Am J Roentgenol* 2010; **195**: 292-300 [PMID: 20651183 DOI: 10.2214/AJR.10.4499]

65 **Brust D**, Polis M, Davey R, Hahn B, Bacharach S, Whatley M, Fauci AS, Carrasquillo JA. Fluorodeoxyglucose imaging in healthy subjects with HIV infection: impact of disease stage and therapy on pattern of nodal activation. *AIDS* 2006; **20**: 495-503 [PMID: 16470113 DOI: 10.1097/01.aids.0000210603.40267.29]

66 **Chefer S**, Thomasson D, Seidel J, Reba RC, Bohannon JK, Lackemeyer MG, Bartos C, Sayre PJ, Bollinger L, Hensley LE, Jahrling PB, Johnson RF. Modeling [(18)F]-FDG lymphoid tissue kinetics to characterize nonhuman primate immune response to Middle East respiratory syndrome-coronavirus aerosol challenge. *EJNMMI Res* 2015; **5**: 65 [PMID: 26573211 DOI: 10.1186/s13550-015-0143-x]

67 **Jonsson CB**, Camp JV, Wu A, Zheng H, Kraenzle JL, Biller AE, Vanover CD, Chu YK, Ng CK, Proctor M, Sherwood L, Steffen MC, Mollura DJ. Molecular imaging reveals a progressive pulmonary inflammation in lower airways in ferrets infected with 2009 H1N1 pandemic influenza virus. *PLoS One* 2012; **7**: e40094 [PMID: 22911695 DOI: 10.1371/journal.pone.0040094]

68 **Wallace M**, Pyzalski R, Horejsh D, Brown C, Djavani M, Lu Y, Hanson JM, Mitchen JL, Perlman SB, Pauza CD. Whole body positron emission tomography imaging of activated lymphoid tissues during acute simian-human immunodeficiency virus 89.6PD infection in rhesus macaques. *Virology* 2000; **274**: 255-261 [PMID: 10964769 DOI: 10.1006/viro.2000.0479]

69 **Dietz M**, Chironi G, Claessens YE, Farhad RL, Rouquette I, Serrano B, Nataf V, Hugonnet F, Paulmier B, Berthier F, Keita-Perse O, Giammarile F, Perrin C, Faraggi M; MONACOVID Group. COVID-19 pneumonia: relationship between inflammation assessed by whole-body FDG PET/CT and short-term clinical outcome. *Eur J Nucl Med Mol Imaging* 2021; **48**: 260-268 [PMID: 32712702 DOI: 10.1007/s00259-020-04968-8]

70 **Qin C**, Liu F, Yen TC, Lan X. ^{18}F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1281-1286 [PMID: 32088847 DOI: 10.1007/s00259-020-04734-w]

71 **Setti L**, Kirienko M, Dalto SC, Bonacina M, Bombardieri E. FDG-PET/CT findings highly suspicious for COVID-19 in an Italian case series of asymptomatic patients. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1649-1656 [PMID: 32342191 DOI: 10.1007/s00259-020-04819-6]

72 **Zou S**, Zhu X. FDG PET/CT of COVID-19. *Radiology* 2020; **296**: E118 [PMID: 32142399 DOI: 10.1148/radiol.2020200770]

73 **Polverari G**, Arena V, Ceci F, Pelosi E, Ianniello A, Poli E, Sandri A, Penna D. ^{18}F-Fluorodeoxyglucose Uptake in Patient With Asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus Disease 2019) Referred to Positron Emission Tomography/Computed Tomography for NSCLC Restaging. *J Thorac Oncol* 2020; **15**: 1078-1080 [PMID: 32243920 DOI: 10.1016/j.jtho.2020.03.022]

74 **Lütje S**, Marinova M, Kütting D, Attenberger U, Essler M, Bundschuh RA. Nuclear medicine in SARS-CoV-2 pandemia: 18F-FDG-PET/CT to visualize COVID-19. *Nuklearmedizin* 2020; **59**: 276-280 [PMID: 32259853 DOI: 10.1055/a-1152-2341]

75 **Bellani G**, Messa C, Guerra L, Spagnolli E, Foti G, Patroniti N, Fumagalli R, Musch G, Fazio F, Pesenti A. Lungs of patients with acute respiratory distress syndrome show diffuse inflammation in normally aerated regions: a [18F]-fluoro-2-deoxy-D-glucose PET/CT study. *Crit Care Med* 2009; **37**: 2216-2222 [PMID: 19487931 DOI: 10.1097/CCM.0b013e3181aab31f]

76 **Fang Y**, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296**: E115-E117 [PMID: 32073353 DOI: 10.1148/radiol.2020200432]

77 **Yang W**, Cao Q, Qin L, Wang X, Cheng Z, Pan A, Dai J, Sun Q, Zhao F, Qu J, Yan F. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020; **80**: 388-393 [PMID: 32112884 DOI: 10.1016/j.jinf.2020.02.016]

World Journal of Radiology

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

World J Radiol 2021 October 28; 13(10): 344-353

DOI: 10.4329/wjr.v13.i10.344

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Prospective Study

Shoulder adhesive capsulitis in cancer patients undergoing positron emission tomography - computed tomography and the association with shoulder pain

Daichi Hayashi, Elaine Gould, Robert Shroyer, Eric van Staalduinen, Jie Yang, Musa Mufti, Mingqian Huang

ORCID number: Daichi Hayashi 0000-0002-2067-5780; Elaine Gould 0000-0002-2674-1785; Robert Shroyer 0000-0002-2493-1710; Eric van Staalduinen 0000-0001-9786-2712; Jie Yang 0000-0003-3469-5931; Musa Mufti 0000-0002-4958-6298; Mingqian Huang 0000-0002-5734-0191.

Author contributions: Hayashi D, Gould E and Huang M designed the research study; Hayashi D, Gould E, Shroyer R, van Staalduinen E, Mufti M and Huang M performed the research including data collection and electronic medical record review; Gould E, Shroyer R and Huang M interpreted positron emission tomography - computed tomography images; Yang J performed the statistical analyses; Hayashi D analyzed results and wrote the manuscript; all authors have read, edited and approved the final manuscript.

Institutional review board statement: Our prospective study received Institutional Review Board approval at our institution (Protocol# 2015-3396-R2).

Clinical trial registration statement: Our study is not a clinical trial. Therefore, there is no Clinical Trial

Daichi Hayashi, Elaine Gould, Robert Shroyer, Eric van Staalduinen, Musa Mufti, Mingqian Huang, Department of Radiology, State University of New York at Stony Brook, Stony Brook, NY 11794, United States

Jie Yang, Department of Family, Population and Preventive Medicine, Stony Brook Medicine, Stony Brook, NY 11794, United States

Corresponding author: Daichi Hayashi, MD, PhD, Associate Professor, Department of Radiology, State University of New York at Stony Brook, HSC Level 4, Room 120, Stony Brook, NY 11794, United States. daichi.hayashi@stonybrookmedicine.edu

Abstract

BACKGROUND

Adhesive capsulitis is a relatively common condition that can develop in cancer patients during treatment. Positron emission tomography - computed tomography (PET-CT) is routinely performed as a follow-up study in cancer patients after therapy. Being aware of PET-CT findings to suggest shoulder adhesive capsulitis may help to alert clinicians for the diagnosis of unsuspected shoulder capsulitis.

AIM

To assess the association of shoulder adhesive capsulitis with cancer/therapy type and symptoms in cancer patients undergoing PET-CT.

METHODS

Our prospective study received Institutional Review Board approval. Written informed consent was obtained from all patients, who answered a questionnaire regarding shoulder pain/stiffness at the time of PET-CT study, between March 2015 and April 2019. Patients with advanced glenohumeral arthrosis, metastatic disease or other mass in the shoulder, or shoulder arthroplasty were excluded. Patterns of shoulder capsule 18F-fluorodeoxyglucose (FDG) uptake were noted. Standard Uptake Value (SUV)max and SUVmean values were measured at rotator interval (RI) and deltoid muscle in bilateral shoulders. Normalized SUV (SUV of RI/SUV of deltoid muscle) was also calculated. We assessed if SUV values are different between symptomatic and asymptomatic patients in both shoulders. Covariates were age, gender, and therapy type (surgery, chemotherapy, radi-

Registration Statement applicable to this submission.

Informed consent statement: Written informed consent was obtained from all patients.

Conflict-of-interest statement: All authors have nothing to disclose.

Data sharing statement: Patient data are not available for sharing for protection of patient confidentiality and anonymity. No additional data are available.

CONSORT 2010 statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Specialty type: Radiology, Nuclear Medicine and Medical Imaging

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: March 13, 2021
Peer-review started: March 13, 2021
First decision: July 31, 2021
Revised: August 3, 2021
Accepted: September 14, 2021

ation). Wilcoxon rank sum tests were used to compare unadjusted marginal differences for age, SUV measurements between symptomatic and asymptomatic patients. Multiple linear regression models were used to examine the relationship between right or left shoulder SUV measurements and symptom status, after adjusting for covariates. Statistical significance level was set at $P < 0.05$.

RESULTS

Of 252 patients initially enrolled for the study (mean age 66 years, 67 symptomatic), shoulder PET-CT data were obtained in 200 patients (52 were excluded due to exclusion criteria above). The most common cancer types were lymphoma ($n = 61$), lung ($n = 54$) and breast ($n = 53$). No significant difference was noted between symptomatic and asymptomatic patients in terms of age, gender, proportion of patients who had surgical therapy and radiation therapy. A proportion of patients who received chemotherapy was higher in patients who were asymptomatic in the right shoulder compared to those symptomatic in the right shoulder (65% *vs* 48%, $P = 0.012$). No such difference was seen for the left shoulder. In both shoulders, SUVmax and SUVmean were higher in symptomatic shoulders than asymptomatic shoulders (Left SUVmax 2.0 *vs* 1.6, SUVmean 1.6 *vs* 1.3, both $P < 0.002$; Right SUVmax 2.2 *vs* 1.8, SUVmean 1.8 *vs* 1.5, both $P < 0.01$). For lung cancer patients, bilateral RI SUVmax and SUVmean values were higher in symptomatic shoulders than asymptomatic shoulders. For other cancer patients, symptomatic patients had higher left RI SUVmax/mean than asymptomatic patients after adjustment.

CONCLUSION

In symptomatic patients metabolic activities in RI were higher than asymptomatic patients. Adhesive capsulitis should be considered in cancer patients with shoulder symptoms and positive FDG uptake in RI.

Key Words: Adhesive capsulitis; Positron emission tomography - computed tomography; Cancer; Shoulder; Pain; Imaging

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Adhesive capsulitis is a relatively common condition that can develop in cancer patients during treatment. However, there has been relatively scant literature evidence on Positron emission tomography - computed tomography (PET-CT) findings specific to adhesive capsulitis. Our study showed that, in symptomatic cancer patients, metabolic activities in the rotator interval were higher than asymptomatic patients overall, and also specifically for lung cancer patients. Presence of adhesive capsulitis may explain shoulder pain or stiffness in cancer patients, which can be incidentally diagnosed on PET-CT. Demographic characteristics, treatment regimen, and cancer type did not appear to be an independent risk factor.

Citation: Hayashi D, Gould E, Shroyer R, van Staalduinen E, Yang J, Mufti M, Huang M. Shoulder adhesive capsulitis in cancer patients undergoing positron emission tomography - computed tomography and the association with shoulder pain. *World J Radiol* 2021; 13(10): 344-353
URL: https://www.wjgnet.com/1949-8470/full/v13/i10/344.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i10.344

INTRODUCTION

Adhesive capsulitis is a relatively common and potentially debilitating disorder of the shoulder joint, with most common onset in the 5th to 6th decades. Typical clinical presentation include shoulder pain, stiffness, and loss of range of motion, and can persist for extended periods of time if not adequately addressed clinically[1-4]. While adhesive capsulitis is a clinical diagnosis, magnetic resonance imaging (MRI) is

Article in press: September 14, 2021
Published online: October 28, 2021

P-Reviewer: Dikaios N
S-Editor: Wang LL
L-Editor: A
P-Editor: Liu JH

currently the most commonly used imaging tool for its diagnosis[5-7], however not all cancer patients undergo MRI of the shoulder unless there is specific clinical suspicion for adhesive capsulitis or other shoulder-specific pathology. Positron emission tomography - computed tomography (PET-CT) is a useful imaging modality for cancer diagnosis, particularly for the purpose of staging and follow-up of malignancy. PET-CT is also useful in monitoring inflammatory disorders, and the shoulder joint can be hypermetabolic on PET-CT when there is active inflammation such as osteoarthritis, inflammatory and infectious arthritis, bursitis, rotator cuff injury, and adhesive capsulitis[8,9]. However, there has been relatively scant literature evidence on PET-CT findings specific to adhesive capsulitis. One study demonstrated radiotracer uptake in the joint capsule of the glenohumeral joint connecting the rotator interval, anterior joint capsule, and axillary recess is related to adhesive capsulitis[10]. Another study found secondary adhesive capsulitis (depicted by PET-CT) after modified radical mastectomy for breast cancer was common (9.6%) and differed in severity and the progression pattern depending on whether the range of motion in the shoulder was mildly or severely limited[11]. Given the fact that PET-CT imaging is routinely performed as a follow-up study in cancer patients after therapy, being aware of PET-CT findings to suggest shoulder adhesive capsulitis may help to alert clinicians for the diagnosis of unsuspected shoulder capsulitis and avoid potential misdiagnosis of cancer progression, while simultaneously allowing for earlier initiation of appropriate therapy of capsulitis to potentially improve outcomes. Therefore, the aims of our study were to: (1) Evaluate the frequency of shoulder capsulitis in cancer patients undergoing PET-CT; (2) Determine if there is correlation between cancer type/treatment regimen and frequency of adhesive capsulitis; and (3) Evaluate if metabolic activities in the rotator interval (RI) are different between symptomatic and asymptomatic patients.

MATERIALS AND METHODS

Data collection

Our prospective study received Institutional Review Board approval at our institution (Protocol# 2015-3396-R2). Written informed consent was obtained from all patients. All participants (cancer patients) answered a questionnaire regarding shoulder pain or stiffness and its duration at the time of presentation to an imaging study at our institution (outpatient cancer center) between March 2015 and April 2019. Questions included: Do you have shoulder pain or stiffness (yes/no, if yes, which side); if yes, how long have you had shoulder pain? Have you noticed decreased range of motion in the affected shoulder (yes/no)? Is the symptom worse at any particular time of day? Do you have difficulty raising arms above your head or moving your arms behind back (yes/no)? Electronic medical chart review was performed to collect demographic information (age and gender) as well as details of cancer type and treatment regimen (type and date of surgery, type and date/duration of chemotherapy, and type and date/duration of radiation therapy). All eligible cancer patients who presented to our outpatient imaging center for PET-CT imaging within the recruitment period and were willing to participate in the study were included in our study. Patients with advanced glenohumeral arthrosis, metastatic disease or other mass lesion in the shoulder (all of which could give positive FDG uptake without adhesive capsulitis), or history of shoulder arthroplasty were excluded.

PET-CT image acquisition and interpretation

All patients fasted for at least 6 hours prior to the PET-CT scan. Blood glucose levels were measured before the injection of 18F-fluorodeoxyglucose (FDG) and were lower than 200 mg/dL in all patients. PET-CT was performed using a Siemens Biograph LSO (Siemens Healthineers, Erlangen, Germany). Whole-body CT from the basal skull to the thigh was performed with a continuous spiral technique on a 40-slice helical CT scanner (120 kV; 65 mAs, slice thickness of 4 mm) in the supine position with the arms down. Next, an emission scan was performed from head to thigh at 3 min per frame at 60 min after the intravenous injection of 0.14 mCi/kg of 18F-FDG. CT data were used for attenuation correction and PET images were reconstructed with a three-dimensional (3D) ordered-subsets expectation maximization algorithm (20 subsets, two iterations). CT and PET scan data were accurately coregistered on a dedicated workstation.

We evaluated the intensity of 18F-FDG accumulation as standardized uptake values (SUVs), defined as the tissue concentration divided by the activity injected per body weight. A region of interest was drawn in transaxial images showing FDG uptake within the RI and also low grade FDG uptake at the deltoid muscle. SUVs were measured at the RI and the deltoid muscle from attenuation-corrected axial images. Maximum SUV (SUVmax) at a pixel with the highest uptake of 18F-FDG within each region of interest (ROI) as well as the mean SUV (SUVmean) of each ROI were recorded in bilateral shoulders. Normalized SUV (SUV of RI/SUV of deltoid muscle) was also calculated. None of the ROIs included osseous structures or muscles other than deltoid to exclude the effect of the tracer uptake at the bone marrow and other muscles.

Patterns of shoulder capsule 18F-FDG uptake were recorded on PET-CT scan by two experienced board-certified musculoskeletal radiologists and a Musculoskeletal Radiology Fellow, blinded to clinical information. FDG uptake was considered positive and suggestive of adhesive capsulitis if there was hypermetabolism corresponding to the location of RI on fused PET-CT images.

Statistical analyses

Statistical analyses were performed using SAS9.4 (SAS Institute Inc., Cary, NC) to assess if SUV values are different between patients with and without symptoms in both shoulders. Covariates were age, gender, history of therapy (surgery, chemotherapy, and radiation). Wilcoxon rank sum tests were used to compare unadjusted marginal differences for age, SUV measurements between patients with and without shoulder symptoms. Multiple linear regression models were used to examine the relationship between right or left shoulder SUV measurements and symptom status, after adjusting for cancer type, therapy status, gender and age. To enable meaningful statistical analyses, cancer types were classified into the following 5 categories; Breast, lung, lymphoma, "multiple" (= patients who had two or more cancers), and "other" (= includes the rest of patients with only one cancer that is other than breast cancer, lung cancer or lymphoma). Interaction of shoulder symptom status and cancer type was also included in the models to model the differences within each specific cancer types. Statistical significance level was set at $P < 0.05$.

RESULTS

252 patients were initially enrolled (143 women, 109 men, mean age 66 years, 67 symptomatic). Of these, two patients had right sided shoulder arthroplasty and one patient had left sided shoulder arthroplasty, and these affected shoulders were excluded from analyses. One patient had a large mass in the left proximal humerus, and was also excluded from analysis. Other patients who did not have PET-CT imaging of shoulders (*e.g.*, patients who had brain PET-CT only, or bilateral shoulders being outside the field of view) or other applicable exclusion criteria described earlier were also excluded. In the end, there were 200 right shoulder PET-CT imaging, and 200 Left shoulder PET-CT imaging. Most common cancer types were lymphoma (n = 61), lung (n = 54) and breast (n = 53) (Table 1). No statistically significant difference was noted between symptomatic and asymptomatic patients in terms of age, gender, proportion of patients who had surgical therapy and radiation therapy. A proportion of patients who received chemotherapy was higher in patients who were asymptomatic in the right shoulder compared to those symptomatic in the right shoulder (65% *vs* 48%, P = 0.012). No such difference was seen for the left shoulder.

In both shoulders, SUVmax and SUVmean were higher in symptomatic shoulders than asymptomatic shoulders (Left SUVmax 2.0 *vs* 1.6, SUVmean 1.6 *vs* 1.3, both $P < 0.002$; Right SUVmax 2.2 *vs* 1.8, SUVmean 1.8 *vs* 1.5, both $P < 0.01$), as shown in Table 2. Based on the multiple linear regression models, for lung cancer patients, bilateral RI SUVmax and SUVmean values were higher in symptomatic shoulders than asymptomatic shoulders after adjustment (Table 3). Examples of symptomatic shoulders with abnormal capsular FDG uptake are shown in Figures 1 and 2. For other cancer patients, symptomatic patients had higher left rotator interval SUVmax and SUVmean than asymptomatic patients after adjustment.

Table 1 The total number and types of cancers that were included in our patient population

Type of cancer	Total number
Lymphoma	61
Lung	54
Breast	53
Head and neck	12
Thyroid	10
Colon	9
Melanoma	9
Multiple myeloma	9
Endometrial	6
Pancreas	5
Bladder	5
Prostate	4
Kidney	3
Sarcoma	3
Esophageal	3
Other[1]	24

[1]"Other" cancers were cases in which the primary tumor type was not yet determined, but the patient already had metastatic disease, or cancer types which had only 2 or fewer patients including stomach, Castleman's disease, bone, cervical, ovarian, neurofibromatosis type 1 small bowel mass, brain, carcinoid, cholangiocarcinoma, small cell carcinoma, penile, anal, Merckel cell, cardiac, tracheal, and rectal cancers.

Table 2 Standard uptake value measurements of right and left shoulders in symptomatic and asymptomatic patients

Left shoulder	**Total (*n* = 200)**	**Asymptomatic (*n* = 143)**	**Symptomatic (*n* = 57)**	***P* value**
RI SUVmax	1.7 ± 0.9	1.6 ± 0.7	2.0 ± 1.1	< 0.001
RI SUVmean	1.4 ± 0.7	1.3 ± 0.6	1.6 ± 0.9	0.002
Deltoid SUVmax	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	0.068
Deltoid SUVmean	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.281
Normalized SUVmax	1.9 ± 1.3	1.9 ± 1.0	2.0 ± 1.5	0.125
Normalized SUVmean	1.8 ± 1.2	1.8 ± 1.1	1.9 ± 1.6	0.112
Right shoulder	**Total (*n* = 200)**	**Asymptomatic (*n* = 143)**	**Symptomatic (*n* = 57)**	***P* value**
RI SUVmax	1.9 ± 0.8	1.8 ± 0.8	2.2 ± 0.7	0.002
RI SUVmean	1.5 ± 0.7	1.5 ± 0.7	1.8 ± 0.8	0.012
Deltoid SUVmax	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.279
Deltoid SUVmean	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.3	0.160
Normalized SUVmax	2.2 ± 1.1	2.2 ± 1.1	2.3 ± 1.5	0.105
Normalized SUVmean	2.1 ± 1.0	2.2 ± 1.0	2.1 ± 1.1	0.392

P value was calculated using Wilcoxon rank sum test and median with Inter Quartile Ratio were reported. These results were unadjusted comparisons. RI: Rotator interval; SUV: Standard uptake value.

DISCUSSION

Adhesive capsulitis is a relatively common condition that can develop and perhaps, can predate, diagnosis of cancer in patients undergoing treatment[12], and can be

Table 3 Multiple linear regression analyses showing association between right or left shoulder standard uptake value measurements and symptom status after adjusting for covariates, stratified by cancer type

Cancer type	Left RI SUVmax		Right RI SUVmax	
	Value	95%CI	Value	95%CI
Breast	0.36	-0.37, 0.44	0.13	-0.51, 0.54
Lung	0.65	0.24, 1.07	0.56	0.14, 0.97
Lymphoma	0.28	-0.14, 0.70	0.08	-0.34, 0.51
Multiple	0.25	-0.21, 0.71	0.23	-0.01, 1.12
Other	0.57	0.23, 0.91	0.22	-0.21, 0.65
Cancer type	**Left RI SUVmean**		**Right RI SUVmean**	
	Value	**95%CI**	**Value**	**95%CI**
Breast	0.05	-0.30, 0.39	-0.03	-0.46, 0.41
Lung	0.50	0.14, 0.86	0.45	0.11, 0.80
Lymphoma	0.19	-0.17, 0.55	-0.06	-0.42, 0.29
Multiple	0.19	-0.21, 0.58	0.45	-0.02, 0.92
Other	0.44	0.14, 0.73	0.28	-0.08, 0.64

There was no statistically significant results for deltoid SUV measurements and normalized SUV measurements for right and left shoulders (results not shown). RI: Rotator interval; SUV: Standard uptake value.

incidentally identified on PET-CT imaging, or other imaging such as ultrasound and MRI[13]. In symptomatic patients, metabolic activities in the RI were higher than asymptomatic patients. The presence of adhesive capsulitis may explain shoulder pain or stiffness in cancer patients, which can be incidentally diagnosed on PET-CT. In general population, it has been shown that risk factors for adhesive capsulitis include age 40 years or older, female gender, immobility or reduced mobility of the shoulder (due to pathologies such as stroke, fracture, recovery from surgery, and rotator cuff injury), and underlying systemic diseases such as diabetes, thyroid disorders, and Parkinson's disease[14]. In our study sample, demographic characteristics, treatment regimen, and cancer type did not appear to be an independent risk factor.

Diagnostic utility of PET-CT for diagnosis of adhesive capsulitis of the shoulder has been infrequently documented in the literature, some are related to cancer patients[11,14,15] but others are not[10,16,17]. A retrospective analysis of patients with clinically diagnosed adhesive capsulitis showed increased FDG uptake in the RI or inferior glenohumeral joint capsule conferred a moderate increase in the likelihood of adhesive capsulitis[16]. In this study, of the 123 patients, 9 patients had clinical diagnosis of adhesive capsulitis, while 15 patients had FDG uptake in the RI or inferior joint capsule, with the sensitivity and specificity of PET for detection of capsulitis being 56% and 87%, respectively. PET-CT had a positive likelihood ratio for adhesive capsulitis was 6.3 (95%CI: 2.8-14.6)[16].

In a prospective study with 35 middle aged patients with unilateral idiopathic shoulder adhesive capsulitis, correlation between FDG PET-CT depicted metabolic pattern at the four ROIs (RI, anterior joint capsule, axillary recess, and posterior joint capsule) and clinical parameters (pain, functional scores, and passive range of motion) was evaluated[17]. Mean SUVmax values for the four ROIs of the affected shoulder were significantly higher than those of the unaffected shoulder. More specifically, the anterior-inferior capsular portion, including RI and axillary recess, was found to be the main pathologic site of idiopathic adhesive capsulitis and revealed significant correlations between the limited range of motion (both elevational and rotational) and increased FDG uptake in these locations[17].

While the above two studies did show PET-CT can be useful for imaging diagnosis of adhesive capsulitis, they were not directly related to cancer patients, which are actually the primary research interest in our study. A retrospective study including 230 breast cancer patients demonstrated FDG-PET is useful in evaluating adhesive capsulitis after breast cancer treatment[11]. Twenty two patients had clinically identified adhesive capsulitis and were categorized into 2 groups: With severely limited and mildly limited range of motion in the shoulder joint. SUVs of the shoulder

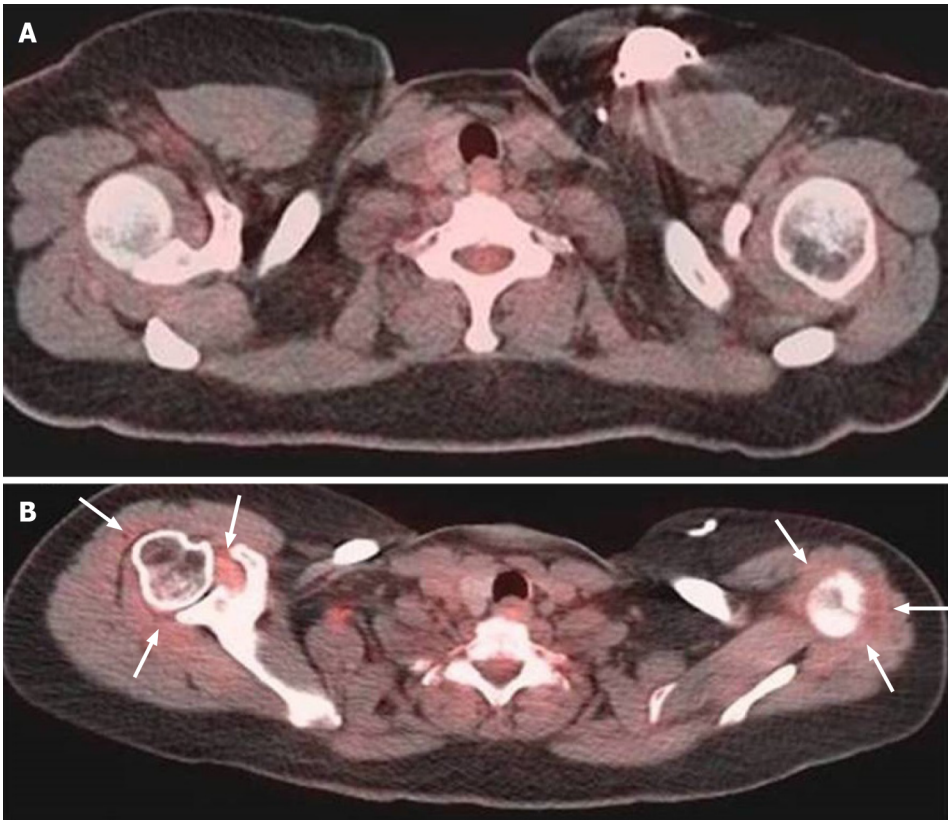


Figure 1 Fifty-two years old patient with lung cancer. A: Initial pre-therapy Positron emission tomography - computed tomography showed no significant capsular 18F-fluorodeoxyglucose (FDG) uptake; B: After the patient was treated with chemotherapy for his lung cancer, the patient developed bilateral shoulder pain with bilateral capsular FDG uptake.

joint capsule were significantly higher in patients with severely limited range of motion compared with those with mildly limited range of motion[11].

Although potentially useful for detection of adhesive capsulitis of the shoulder, interpretation of FDG PET-CT requires caution because a focus of increased metabolic activity can mimic a metastatic lesion in lung cancer patients due to non-specific nature of the positive PET finding and limited anatomical resolution of PET itself as well as potential misregistration of FDG avid focus onto CT images at the time of PET-CT fusion[15]. This is an important point to note, as our study showed the lung cancer was associated with higher SUVs in symptomatic shoulders bilaterally. It is thus important to confirm a suspicion for adhesive capsulitis (raised by PET-CT finding) by dedicated MRI of the shoulder, so as not to mistakenly diagnose a metastasis and potentially altering staging of the cancer and thus management plan.

Interestingly, one large scale study including prospectively collected 2572 incident cancers among 29098 adhesive capsulitis patients showed adhesive capsulitis might be an early predictor for a subsequent cancer[14]. Investigators followed these patients for development of cancer, and found 6-month cumulative incidence of any cancer was 0.70% (standardized incidence ratio [SIR] of 1.38, 95%CI: 1.19-1.58), and risk increases were highest for lung cancer (SIR: 2.19, 95%CI: 1.48-3.13). The findings of our study are in line with this study, in that lung cancer was the only cancer type that showed statistically significant association of higher SUV in symptomatic shoulders. It is unknown why such association was not demonstrated in other types of cancers, despite the fact that there were similar numbers of lymphoma and breast cancer patients in our study. All other types of cancers were likely too small in number to be able to show statistically meaningful association.

Although we attempted to correlate development of capsulitis and potential relationship with different therapy options, no statistically significant association of capsulitis with surgical therapy or radiation therapy was demonstrated. In the right shoulder, a higher proportion of asymptomatic patients received chemotherapy compared to symptomatic patients, but the same was not applicable to the left shoulder. This is likely an incidental finding, as the laterality of the capsulitis is unlikely to be affected by chemotherapy which is a systemic therapy and should not localize to one side of the shoulder.

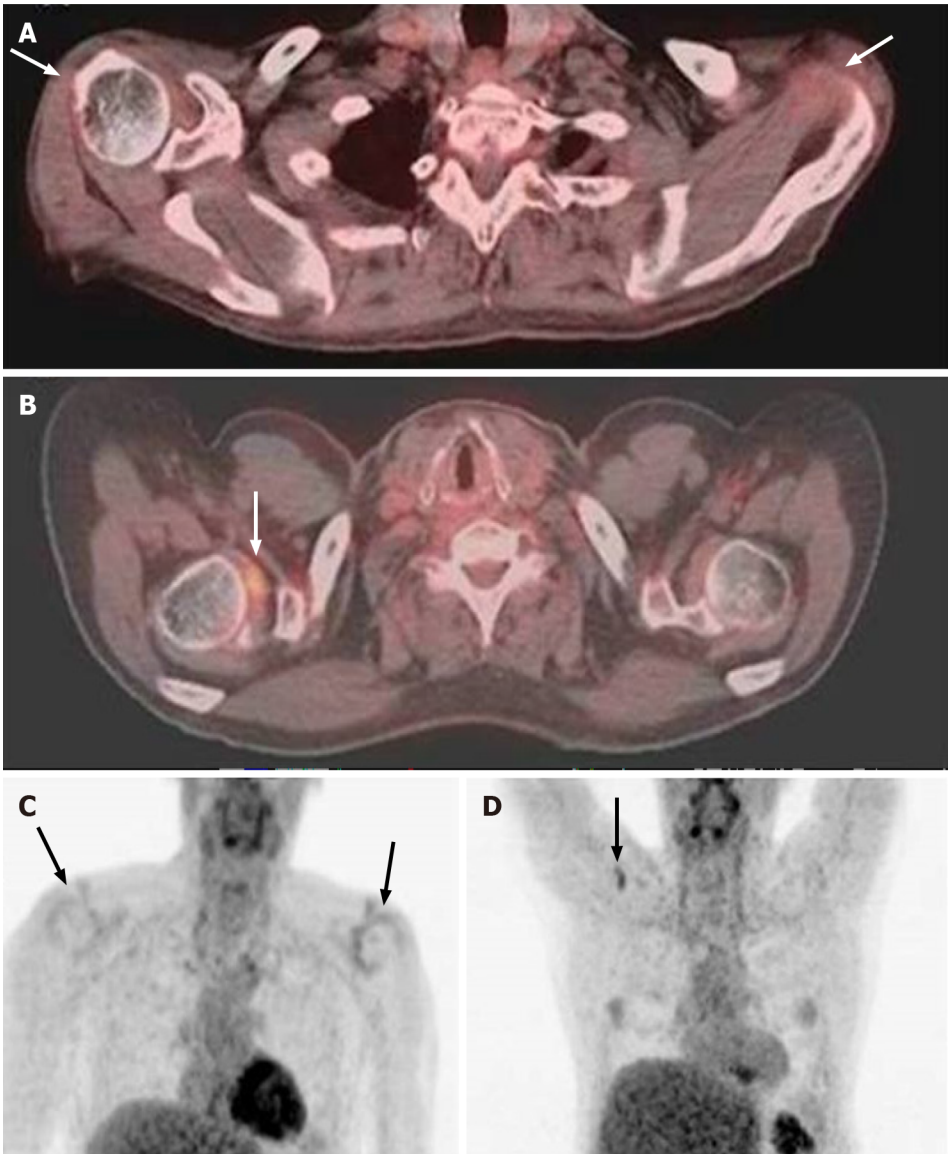


Figure 2 Fifty-six years old patient with lung cancer. Fused Positron emission tomography (PET) - computed tomography (A) and (C) maximum intensity projection (MIP) PET images demonstrate mild diffuse non-specific bilateral shoulder capsular FDG uptake at initial pre-therapy imaging (arrows, better seen on MIP images); B and D: After diagnosis of lung cancer and treatment, the patient developed right shoulder pain and more focal capsular uptake in the right shoulder capsule in the region of rotator interval (arrows).

Limitations of our study include a lack of clinical diagnosis of capsulitis based on clinical examination performed by non-radiologists, and our diagnosis of capsulitis is purely based on PET-CT finding and patient-reported symptoms. We do not know for sure if those patients with positive PET findings actually had clinical exam findings (such as pain and limited range of motion) consistent with adhesive capsulitis. Data collection was performed *via* internal electronic medical record review only. We did not have access to medical records of patients who were managed by physicians outside our institutional network. Lastly, there was no follow-up PET-CT data to assess for resolution of the adhesive capsulitis by imaging.

CONCLUSION

In conclusion, our study showed metabolic activities in RI were higher in symptomatic patients than asymptomatic patients. Although appearance and relationship of capsulitis with malignancy is not fully understood, adhesive capsulitis should be considered in cancer patients with shoulder pain or stiffness and positive FDG uptake in RI, as it may allow for therapy in earlier stages of disease to improve outcomes.

ARTICLE HIGHLIGHTS

Research background

Adhesive capsulitis of the shoulder is a relatively common condition that can develop and possibly predate diagnosis of cancer in patients undergoing treatment. The presence of adhesive capsulitis may explain the presence of shoulder pain or stiffness in cancer patients, which can be incidentally diagnosed on Positron emission tomography - computed tomography (PET-CT).

Research motivation

Since PET-CT imaging is routinely performed as a follow-up study in cancer patients after therapy, being aware of PET-CT findings to suggest shoulder adhesive capsulitis may help to alert clinicians for the diagnosis of unsuspected shoulder capsulitis and avoid potential misdiagnosis of cancer progression.

Research objectives

To: (1) Evaluate the frequency of shoulder capsulitis in cancer patients undergoing PET-CT; (2) Determine if there is correlation between cancer type/treatment regimen and frequency of adhesive capsulitis; (3) Evaluate if metabolic activities in the rotator interval are different between symptomatic and asymptomatic patients. We assessed if Standard Uptake Values (SUVs) are different between symptomatic and asymptomatic patients in both shoulders.

Research methods

In this prospective study, patients answered a questionnaire regarding shoulder pain/stiffness at the time of PET-CT study, between March 2015 and April 2019. Patterns of shoulder capsule 18F-fluorodeoxyglucose (FDG) uptake were noted. SUVmax and SUVmean values were measured at the rotator interval (RI) and deltoid muscle in bilateral shoulders. Wilcoxon rank sum tests were used to compare unadjusted marginal differences for age, SUV measurements between symptomatic and asymptomatic patients. Multiple linear regression models were used to examine the relationship between right or left shoulder SUV measurements and symptom status, after adjusting for covariates.

Research results

200 right shoulders and 200 Left shoulders were included in our study. No significant difference was noted between symptomatic and asymptomatic patients in terms of age, gender, proportion of patients who had surgical therapy and radiation therapy. In both shoulders, SUVmax and SUVmean were higher in symptomatic shoulders than asymptomatic shoulders (Left SUVmax 2.0 *vs* 1.6, SUVmean 1.6 *vs* 1.3, both $P < 0.002$; Right SUVmax 2.2 *vs* 1.8, SUVmean 1.8 *vs* 1.5, both $P < 0.01$). For lung cancer patients, bilateral RI SUVmax and SUVmean values were higher in symptomatic shoulders than asymptomatic shoulders.

Research conclusions

In symptomatic patients metabolic activities in the RI were higher than asymptomatic patients. Adhesive capsulitis should be considered in cancer patients with shoulder pain or stiffness and positive FDG uptake in the RI, as it may allow for therapy in earlier stages of disease to improve outcomes.

Research perspectives

Future studies may endeavor to perform radiomics research (texture analysis) on the PET-CT images.

REFERENCES

1 **Manske RC**, Prohaska D. Diagnosis and management of adhesive capsulitis. *Curr Rev Musculoskelet Med* 2008; **1**: 180-189 [PMID: 19468904 DOI: 10.1007/s12178-008-9031-6]

2 **Neviaser AS**, Hannafin JA. Adhesive capsulitis: a review of current treatment. *Am J Sports Med* 2010; **38**: 2346-2356 [PMID: 20110457 DOI: 10.1177/0363546509348048]

3 **Brue S**, Valentin A, Forssblad M, Werner S, Mikkelsen C, Cerulli G. Idiopathic adhesive capsulitis of the shoulder: a review. *Knee Surg Sports Traumatol Arthrosc* 2007; **15**: 1048-1054 [PMID: 17333122 DOI: 10.1007/s00167-007-0291-2]

4 **Hand GC**, Athanasou NA, Matthews T, Carr AJ. The pathology of frozen shoulder. *J Bone Joint Surg Br* 2007; **89**: 928-932 [PMID: 17673588 DOI: 10.1302/0301-620X.89B7.19097]

5 **Emig EW**, Schweitzer ME, Karasick D, Lubowitz J. Adhesive capsulitis of the shoulder: MR diagnosis. *AJR Am J Roentgenol* 1995; **164**: 1457-1459 [PMID: 7754892 DOI: 10.2214/ajr.164.6.7754892]

6 **Carrillon Y**, Noel E, Fantino O, Perrin-Fayolle O, Tran-Minh VA. Magnetic resonance imaging findings in idiopathic adhesive capsulitis of the shoulder. *Rev Rhum Engl Ed* 1999; **66**: 201-206 [PMID: 10339775]

7 **Yoon JP**, Chung SW, Lee BJ, Kim HS, Yi JH, Lee HJ, Jeong WJ, Moon SG, Oh KS, Yoon ST. Correlations of magnetic resonance imaging findings with clinical symptom severity and prognosis of frozen shoulder. *Knee Surg Sports Traumatol Arthrosc* 2017; **25**: 3242-3250 [PMID: 26611904 DOI: 10.1007/s00167-015-3887-y]

8 **Wandler E**, Kramer EL, Sherman O, Babb J, Scarola J, Rafii M. Diffuse FDG shoulder uptake on PET is associated with clinical findings of osteoarthritis. *AJR Am J Roentgenol* 2005; **185**: 797-803 [PMID: 16120937 DOI: 10.2214/ajr.185.3.01850797]

9 **Glaudemans AW**, de Vries EF, Galli F, Dierckx RA, Slart RH, Signore A. The use of (18)F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. *Clin Dev Immunol* 2013; **2013**: 623036 [PMID: 24027590 DOI: 10.1155/2013/623036]

10 **Kim du H**, Sung DH, Ga HY, Choi JY. Metabolic patterns of the shoulder joint on (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in adhesive capsulitis. *Ann Nucl Med* 2014; **28**: 136-144 [PMID: 24317879 DOI: 10.1007/s12149-013-0794-5]

11 **Park JH**, Lee YK, Kim DH, Kim SJ, Lee JH, Jeon TJ, Ryu YH, Lee JD. Usefulness of 18F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography in Monitoring Adhesive Capsulitis After Breast Cancer Treatment. *J Comput Assist Tomogr* 2015; **39**: 349-355 [PMID: 25700225 DOI: 10.1097/RCT.0000000000000222]

12 **Yang S**, Park DH, Ahn SH, Kim J, Lee JW, Han JY, Kim DK, Jeon JY, Choi KH, Kim W. Prevalence and risk factors of adhesive capsulitis of the shoulder after breast cancer treatment. *Support Care Cancer* 2017; **25**: 1317-1322 [PMID: 27942856 DOI: 10.1007/s00520-016-3532-4]

13 **Kim JH**, Kim SH, Kim HR, Lee SH, Yoon SY, Yang JH, Yoo YB, Park KS, Nam SE, Hong S, Min HK. Ultrasonographic evaluation of chronic shoulder pain after breast cancer surgery: single center, cross-sectional study. *Sci Rep* 2020; **10**: 16792 [PMID: 33033299 DOI: 10.1038/s41598-020-73769-8]

14 **Pedersen AB**, Horváth-Puhó E, Ehrenstein V, Rørth M, Sørensen HT. Frozen shoulder and risk of cancer: a population-based cohort study. *Br J Cancer* 2017; **117**: 144-147 [PMID: 28524156 DOI: 10.1038/bjc.2017.146]

15 **Salem U**, Zhang L, Jorgensen JL, Kumar R, Amini B. Adhesive capsulitis mimicking metastasis on 18F-FDG-PET/CT. *Clin Nucl Med* 2015; **40**: e145-e147 [PMID: 24999685 DOI: 10.1097/RLU.0000000000000524]

16 **Sridharan R**, Engle MP, Garg N, Wei W, Amini B. Focal uptake at the rotator interval or inferior capsule of shoulder on ^{18}F-FDG PET/CT is associated with adhesive capsulitis. *Skeletal Radiol* 2017; **46**: 533-538 [PMID: 28161721 DOI: 10.1007/s00256-017-2587-8]

17 **Won KS**, Kim DH, Sung DH, Song BI, Kim HW, Song KS, Lee SW, Cho CH. Clinical correlation of metabolic parameters on ^{18}F-FDG PET/CT in idiopathic frozen shoulder. *Ann Nucl Med* 2017; **31**: 211-217 [PMID: 28168397 DOI: 10.1007/s12149-016-1147-y]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 November 28; 13(11): 354-370

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 11 November 28, 2021

REVIEW

World Journal of Radiology

Monthly Volume 13 Number 11 November 28, 2021

Contents

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
November 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 November 28; 13(11): 354-370

DOI: 10.4329/wjr.v13.i11.354

ISSN 1949-8470 (online)

REVIEW

Impact of COVID-19 pandemic on radiology education, training, and practice: A narrative review

Md Anwarul Azim Majumder, Uma Gaur, Keerti Singh, Latha Kandamaran, Subir Gupta, Mainul Haque, Sayeeda Rahman, Bidyadhar Sa, Mizanur Rahman, Fidel Rampersad

ORCID number: Md Anwarul Azim Majumder 0000-0003-3398-8695; Uma Gaur 0000-0002-8017-6035; Keerti Singh 0000-0001-7532-1229; Latha Kandamaran 0000-0001-7207-1228; Subir Gupta 0000-0002-0512-6652; Mainul Haque 0000-0002-6124-7993; Sayeeda Rahman 0000-0002-7005-8801; Bidyadhar Sa 0000-0001-8702-7641; Mizanur Rahman 0000-0002-3827-4678; Fidel Rampersad 0000-0003-4354-9274.

Author contributions: Majumder MAA conducted an extensive literature review and outlined a plan for the review; all the authors contributed to the first draft of this manuscript, and review of the draft and final version of this manuscript.

Conflict-of-interest statement: No conflict of interest for this work.

Country/Territory of origin: Barbados

Specialty type: Radiology, nuclear medicine and medical imaging

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Md Anwarul Azim Majumder, Uma Gaur, Keerti Singh, Latha Kandamaran, Subir Gupta, Faculty of Medical Sciences, The University of the West Indies, Cave Hill Campus, Cave Hill BB23034, Barbados

Mainul Haque, Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sugai Besi, Kuala Lumpur 57000, Malaysia

Sayeeda Rahman, School of Medicine, American University of Integrative Sciences (AUIS), Bridgetown BB11318, Barbados

Bidyadhar Sa, Fidel Rampersad, Faculty of Medical Sciences, The University of the West Indies, St Augustine Campus, St Augustine 33178, Trinidad and Tobago

Mizanur Rahman, Principal's Office, International Medical College, Dhaka 1207, Bangladesh

Corresponding author: Md Anwarul Azim Majumder, MBBS, PhD, Director of Medical Education, Faculty of Medical Sciences, The University of the West Indies, Cave Hill Campus, Cave Hill Road, Cave Hill BB23034, Barbados. azim.majumder@cavehill.uwi.edu

Abstract

Radiology education and training is of paramount clinical importance given the prominence of medical imaging utilization in effective clinical practice. The incorporation of basic radiology in the medical curriculum has continued to evolve, focusing on teaching image interpretation skills, the appropriate ordering of radiological investigations, judicious use of ionizing radiation, and providing exposure to interventional radiology. Advancements in radiology have been driven by the digital revolution, which has, in turn, had a positive impact on radiology education and training. Upon the advent of the corona virus disease 2019 (COVID-19) pandemic, many training institutions and hospitals adhered to directives which advised rescheduling of non-urgent outpatient appointments. This inevitably impacted the workflow of the radiology department, which resulted in the reduction of clinical in-person case reviews and consultations, as well as in-person teaching sessions. Several medical schools and research centers completely suspended face-to-face academic activity. This led to challenges for medical teachers to complete the radiology syllabus while ensuring that teaching activities continued safely and effectively. As a result, online teaching platforms have virtually replaced didactic face-to-face lectures. Radiology educators also

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Received: May 30, 2021
Peer-review started: May 30, 2021
First decision: July 31, 2021
Revised: August 26, 2021
Accepted: October 25, 2021
Article in press: October 27, 2021
Published online: November 28, 2021

P-Reviewer: Shrestha DB
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

sought other strategies to incorporate interactive teaching sessions while adopting the e-learning approach, as they were cognizant of the limitations that this may have on students' clinical expertise. Migration to online methods to review live cases, journal clubs, simulation-based training, clinical interaction, and radiology examination protocolling are a few examples of successfully addressing the limitations in reduced clinical exposure. In this review paper, we discuss (1) The impact of the COVID-19 pandemic on radiology education, training, and practice; (2) Challenges and strategies involved in delivering online radiology education for undergraduates and postgraduates during the COVID-19 pandemic; and (3) Difference between the implementation of radiology education during the COVID-19 pandemic and pre-COVID-19 era.

Key Words: Radiology; Education; Training; Practice; COVID-19 pandemic; Impact

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The COVID-19 pandemic has had a tremendous impact on radiology education. Even before the pandemic, educators often encountered many difficulties in delivering the radiology curriculum. During the pandemic, there was an almost complete transition of radiology education to a blended online platform. Many hiccups in implementing online teaching were reported, such as suitable hardware/software, reliable internet connection, innovative and interactive teaching methods and contents, and meaningful participation and interaction of the students. However, despite many challenges and restrictions, the current pandemic revealed opportunities for radiology educators and students to apply the technological acumen and wisdom they gained by teaching and learning remotely.

Citation: Majumder MAA, Gaur U, Singh K, Kandamaran L, Gupta S, Haque M, Rahman S, Sa B, Rahman M, Rampersad F. Impact of COVID-19 pandemic on radiology education, training, and practice: A narrative review. *World J Radiol* 2021; 13(11): 354-370
URL: https://www.wjgnet.com/1949-8470/full/v13/i11/354.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i11.354

INTRODUCTION

Recent surveys have explicitly stated the necessity of radiology education for undergraduate medical students[1,2]. Radiology education and training, over the last decade, has undergone a significant transformation from purely didactic lectures toward early clinical exposure and team-based learning, with an emphasis on hands-on workshops and case-based teaching[3]. Over the last decade, much before the corona virus disease 2019 (COVID-19) pandemic, e-learning has become a highly effective and valuable asset in the field of radiology education, just like many other areas of medical education[2,4]. In recent years, the majority of the medical teaching institutions throughout Europe were reportedly using e-learning extensively in radiology teaching and training[5]. Face-to-face learning, combined with online education, was found to be very successful in enhancing students' knowledge in basic radiology, clinical radiology skill application, and long-term retention of knowledge and basic skills in radiology[6].

The COVID-19 pandemic has resulted in an unprecedented worldwide disruption in medical education training and patient care[7-11]. Several medical schools and research centers suspended face-to-face academic activity and scientific research activities to maximize social distancing and minimize the spread of infection COVID-19 among staff and others[12-14]. Similarly, there has been a disruption in the activity of academic programs and research activities in radiology, with both short-term and long-term implications[1,15,16]. This disruption affected radiology practice and teaching of both undergraduate medical students and postgraduate trainees/fellows. It has now become important for medical teachers to deliver their lectures safely while ensuring the effectiveness and integrity of the process. Electronic or online teaching platforms have completely or almost completely replaced didactic lectures and all the

forms of face-to-face teaching. These online activities are structured to promote knowledge and skills defined in the curriculum while facilitating an individualized learning experience[17].

In the preclinical years, medical students have traditionally learned radiology through didactic lectures, case-based learnings, integrated anatomy laboratories, and clinical skill sessions, an example of which is hands-on ultrasound sessions. This fosters the student's ability to select the most appropriate imaging modality for the relevant clinical situation. Evidence-based selection of imaging tests, best suited for individual clinical scenarios, is a fundamental value in providing greater value to patient care[18]. The COVID-19 pandemic has posed significant challenges in utilizing these established formats of radiology education[19].

However, despite many challenges and restrictions, the current pandemic revealed opportunities for radiology educators to apply and expand the technological acumen and wisdom they gained by delivering content remotely[20]. In this review paper, we have discussed (1) The impact of the COVID-19 pandemic on radiology education, training and practice; (2) Challenges and strategies involved in delivering online radiology education for undergraduate and postgraduate students during the COVID-19 pandemic; and (3) Difference between the implementation of radiology education during the COVID-19 pandemic and pre-COVID-19 era.

LITERATURE SEARCH

We performed literature searches with PubMed, Scopus, and Google Scholar using specific keywords, *e.g.*, "Radiology," "Education," "Training," "practice," "COVID-19 pandemic," and "Impact." Original studies, reviews, editorials, commentaries, perspectives, short or unique communications, and policy papers on radiology education, training and practice were reviewed. Information from websites of different professional associations and national/international organizations was searched to retrieve relevant information.

RADIOLOGY TEACHING/TRAINING IN UNDER- AND POST-GRADUATE EDUCATION

Although the necessity of teaching radiology among undergraduate medical students has been continuously emphasized[1,5,21-23], medical students often receive inadequate teaching-learning input, and are, therefore, inadequately trained in basic radiology[22,24,25]. The usage and interpretation of medical images are very ubiquitous in clinical practice; therefore, basic radiology must be incorporated in the medical curriculum for interpretation of common abnormalities, such as those found in radiographs of the chest, abdomen, and limbs, as well as basic computed tomography (CT) scans of the head and abdomen. This exposure will allow medical students to become competent in basic medical image interpretation, and in recognizing the critical situations when expert radiological opinion should be sought [5,6]. Currently, the selection of the right imaging technique has become very challenging for the general practitioners, due to numerous medical imaging options which are becoming increasingly complex. Multiple studies reported that even in certain centers within the United States of America, radiology teaching among undergraduate medical students, including clinical clerkships, remains very "inadequate"[26-28]. Furthermore, British undergraduate medical students mentioned several limitations in their radiology teaching-learning program[22,29]. The aforesaid facts highlight the significance of radiology teaching in undergraduate medical education as an imperative building block. The central focus should be on teaching image interpretation skills and appropriate ordering of medical investigations, which should relate to prospective clinical practice. For radiology postgraduate programs (including residencies and fellowships), exposure and rotations through the various radiology subspecialties are mandatory, facilitating a wide exposure of the various imaging modalities, techniques, and clinical scenarios. Participation in multidisciplinary team meetings (MDTs) also facilitates a greater level of discourse with other specialists, such as surgeons, physicians, and pathologists.

Radiology instructional strategies should incorporate interactive teaching sessions and target all levels of medical education, at the undergraduate and postgraduate level as well as in the delivery of continuing medical education[28]. The current practice of

an e-learning approach has limitations in providing adequate clinical experience to the students and there has thus been an urgent call for more effective, modern teaching-learning methods to better train students in radiology[22,30]. Most teaching centers have a standardized core radiology curriculum that extensively covers general radiology experience supplemented by the subspeciality curricula, ensuring the equal status of radiologists in a multidisciplinary team. Further, with a growing number of cliniciansacquiring interpretative skills in radiological imaging and diagnosis, radiologists are needed to prove mastery of their skills and knowledge to justify their inclusion in the team[31].

Pre-COVID-19 status of radiology education

Radiology teaching has undergone significant and continuous advancements during the pre-COVID-19 era. Fast-paced, expeditious technology-oriented innovations were introduced in clinical practice, which has transformed the specialty. This is highlighted by the change in the many radiology certification examinations from written and oral modes to computer-based testing. Although most universities have already embraced the new learning methods, some still find it difficult to administer these changes in the curriculum[32]. Radiology teaching in most of the European education centers was assembled and delivered as a part of the formal curriculum, mainly by the "classical approach" as an independent discipline, "modular approach" integrated with the clinical teaching modules, or by the "hybrid approach"–a combination of classical and the modular components. A growing need for more radiology education has been highlighted by the medical students, as radiology is frequently underrepresented in the medical curriculum and is usually taught by non-radiologists[26,33-35]. A study in the United States in Medical and Osteopathic schools reported that only 25% of United States medical schools required radiology clinical rotations, although students valued having radiology as a regular part of the medical school curriculum[36]. Medical students pursuing their clinical years have reported that radiology was being poorly taught, and highlighted a need for detailed teaching on topics such as radiation safety, magnetic resonance imaging (MRI) safety, and standardized requesting algorithms, such as the American College of Radiology appropriateness criteria (AC). The need to embrace the Alliance of Medical Student Educators in Radiology (ACR-AMSER) curriculum was recognized[28,35]. A United Kingdom study by Singh *et al*[36] established the core curriculum in the vital area of radiation protection (RP), thus formally establishing what medical students should be expected to know[36]. With the arrival and adoption of the latest imaging techniques and the growing demand for image-guided minimally invasive surgical procedures, interventional radiology (IR) has shown steady growth as a core element in medical and surgical therapeutics. However, a lacuna of teaching principles of IR, methods and techniques in the medical undergraduate curriculum was recognized[37]. Radiology has seen a digital revolution in the past decade having a notable impact on the education and training of radiologists. This includes the advent of handheld mini computer devices, virtual, online knowledge and skill assessments, enhancement of radiological procedural training with the use of simulations or virtual patients, high-quality videoconferencing tools, and the worldwide alliance of radiological resources *via* international databases [38]. Computer-assisted education or e-learning in radiology has become an important source of medical education especially for developing competencies in such areas as clinical X-ray interpretation. A study in Australia and New Zealand showed e-learning in combination with traditional learning can be more effective on radiological interpretation skills[39]. In 2014, following a detailed survey by the combined American College of Radiologists and the ACR-AMSER, recommendations and actionable interventions were proposed to allow measurable improvements to fulfill expectations surrounding medical imaging education[33]. Action plans were charted to meet the growing demands of radiology education and changes were adopted in the medical school curriculum by many teaching centers[33].

Radiology education: Issues and challenges

As radiology is not introduced as a separate discipline in the undergraduate curriculum, radiology tends to be marginalized in the examinations, a substantial reason for students to omit radiological anatomy and radiology topics[1,21,33]. Radiology educators often encounter challenges such as allocating adequate teaching time, education budgetary constraints, framing educational needs, professional development for facilitating radiology teaching-learning sessions, and difficulties in developing instruments to assess teaching quality. Radiology teaching-learning sessions in most institutions are frequently conducted by non-subject experts, although it is recognized that radiologists teach diagnostic imaging better than any other

specialty. Therefore, it was suggested as pertinent and timely for the development of a core curriculum and that radiologists should start playing a more active role in undergraduate medical education[21]. Severe competition due to encroachment of other clinical specialists in the field, lack of proper recognition, lack of recognized clinical training, inefficient management of the relationship of IR with diagnostic radiology and complexities of IR along with an obligation to the best clinical care for patients, cost escalation, workforce issues, and time constraints were seen as major threats and challenges of teaching IR techniques[40,41]. Cohen *et al*[42] reported that radiology faculty spent 72% of their time in clinical activities and only 19% on radiology education-related activities, revealing suboptimal time spent on educational activities. Faculty members usually spend more time teaching rather than asking questions to the students, which doesn't develop the cognitive and critical thinking skills, demanding a need for more "safe space" for students to learn by making mistakes[42]. There is a need for more apprenticeship training time for more active and stimulating interactions and more professional development time to facilitate radiology teaching-learning sessions. Another study among medical students revealed that a gap exists between theoretical input and clinical practice, inadequate exposure to specialized procedures (such as IR cases), and time allocated teaching-learning sessions[37]. Although IR is the most expanding field in radiology due to increased patient demand, regardless of the many accomplishments, public awareness of IR is however extremely limited[40,42].

Impact of technological innovation

As indicated before, the old style of medical education was enhanced by incorporating e-learning strategies[2]. A significant evolution from when teaching resources were limited to films developed in dark rooms and stored as archives or film museums[43]. Over the past several decades, the practice of radiology has undergone remarkable changes, accompanying the digital revolution and advances in imaging technology [22]. The digital modalities and extensive networking technology prompted the development of Digital Imaging and Communications in Medicine (DICOM) in 1993 [44]. In addition, wireless technologies, including smartphones and tablets were adopted by the radiologist for instant transmission or exchange of radiological images. We are moving into virtual machines, operated by one server as a host optimizing the processing power of that single device instead of multi-single servers. Artificial intelligence (AI) is capable of learning without explicit instruction and has emerging radiology applications[45]. Radiology informatics system and picture archiving and communication system (PACS), included several advanced technologies taught to radiologists. Many simple and advanced software options are now widely available on our desktops and portable devices. An example of such widely used technology is computer-assisted diagnosis[46]. Other emerging tools include online search tools and point of service tools, integrated into the radiology reporting process. A dictation/transcription vendor has incorporated a semi-automatic search wizard. Another highly advanced tool currently in development involves "watching" the radiology dictation in real-time and employing natural language processing to identify key trigger words, search the internet resources in the background, and display relevant information on another window. Healthcare data exchange of radiology images using "cloud services" is fundamental to maintaining the integrity of the patient's longitudinal medical record and for communication amongst conditions on the managing team[47]. Similar advancements including digital and model-based simulations allow the undergraduate and postgraduate students to have a greater practical experience with simple and advanced IR techniques. Across the board, these technological advancements which assist in better radiology workflow, also ultimately contribute to a more streamlined radiology teaching process, as these advanced softwares are usually integrated into didactic and hands-on sessions.

E-learning in radiology teaching and training

Research revealed that the continuous development of computer-related information technology, multimedia, online publishing, and increased Internet availability offer cherished opportunities for medical instruction strategy and continuing medical education, explicitly for radiology[48]. Additionally, the disposition of digital imaging networks, the PACS, teleradiology, and Internet services stalwartly advocates that e-learning will contribute an essential basis of education in radiology, principally among young medical graduates and students, as they are more contented in utilizing the Internet and computers[48]. Furthermore, medical students recognize the need to embrace computer-supported collaborative learning educational programs to embark on radiology training in order to be qualified and competent medical doctors[1]. It has

been reported that the choice of the teaching-learning approach has a superior impact on learning consequences, which is an important learning point for competent medical educators[49]. There are quite a few areas in teaching-learning sessions of radiology in theoretical and practical clinical teaching sessions where mobile electronic devices (MEDs) could pose an advantage for both pupils and teachers. In particular, these gadgets increase the possibility of improving efficiency in data acquisition and clinical interpretation and are therefore highly prized as an information delivery instrument [50,51]. Another study reported that implementation of an e-learning strategy regarding RP education is achievable and practicable, which resulted in a better-quality acquaintance among medical students regarding RP[52]. This study concluded that coalescing e-learning with traditional instructional strategy resulted in a definite improvement in acquiring radiology competence. Additionally, utilizing MEDs is a cost-effective educational instrument that has augmented practicing competencies, improved access to study resources, facilitate increased interactivity in educational meetings, and promotes interactions with the use of audience response software. As such, a preconfigured tablet effusively holds the technology transference into movable computing and characterizes a new effective approach in radiology education[53].

E-learning is a growing phenomenon in education that supports students learning in flexible environments, self-paced or instructor-led learning and that can include media in the form of text, images, animation, video, and audio[54,55]. E-learning can help address some of the challenges in healthcare education by allowing on-demand access, control of standardized content, quality assurance, and learning analytics. E-learning and blended learning have been particularly exploited in radiology because the field is rich in digital images and is thus suited for online access and viewing. Various e-learning methods used are Web-based software/platforms[56], interactive modules with multiple-choice questions (MCQs), self-assessment tests/quizzes/matching questions[57], interactive animations with videos[58], and online word documents/notes[59]. E-mails can also be used containing MCQ questions, and an additional follow-up email including the correct answers can also be an effective strategy[60]. Radiology teaching is being revolutionized by emerging tools such as Audience Response Systems, Web-based video tools, and interactive educational games. These tools are uniquely suited to radiology given the intense imaging nature of radiology education[2]. Virtual training methods have been well perceived by the student as there is better engagement, increased attendance and increased imaging confidence in trainees, and a significantly higher overall number of students performing radiology rotations[61]. E-learning can be considered more than suitable for "knowledge" including procedural performance knowledge but has limited utilization in actual patient care.

RADIOLOGY EDUCATION, TRAINING AND PRACTICE: IMPACT OF COVID-19 PANDEMIC

Radiology education, training and service underwent a significant transformation during the COVID-19 pandemic, primarily as a result of a temporarily reduced radiology workload and social distancing guidelines (Table 1)[62-74]. The alterations in case volume and teaching schedule resulted in significant changes to undergraduate and postgraduate trainee education[66]. Many teaching and research activities were limited, with some training programs even being suspended. Many certification examinations were canceled, with consequent effects on the mental health of both students and teachers alike. There was a complete transformation of the previously primarily didactic experience to embracing internet-based educational activities involving online content and virtual interactions, thus providing a blended learning environment[19]. These strategies, however, were not easily incorporated, as there were many challenges in their implementation. Innovative solutions were required, considering the psychological impact on the trainee and teacher. Institutions involved in radiology education require considerable investment and retooling to incorporate appropriate digital technologies to simulate a clinical type learning environment[75]. To survive and meet these challenges, we must continue to embrace varying strategies to maintain undergraduate and postgraduate radiology education in a safe environment, particularly with COVID-19 surging around us.

Radiology education: Impact of the COVID-19 pandemic

Radiology departments worldwide instituted policies and procedures designed to continue efficient operation, facilitating COVID-19 patients, all the while attending to

Table 1 Impact of COVID-19 on radiology education, training, and service

Ref.	Country	Institute	Study population, *n* (%)	Time of the study	Survey tools	Findings
Alamer and Alharbi[62], 2021	Saudi Arabia	Department of Radiology, College of Medicine, Qassim University	Medical student (*n* = 145)	2019-2020 Academic session	On-line questionnaire	The sudden transition to completely distance learning was well received Synchronous learning was the preferred mode of delivery Student attendance in the synchronous sessions was high Synchronous interaction was found to be as effective as on-campus face-to-face learning The use of recorded sessions proved to be a source for knowledge gain and a solution for technical difficulties
Durfee *et al* [63], 2020	United States	Department of Radiology, Brigham and Women's Hospital, Harvard Medical School	Medical student (*n* = 111)	April 2020	Online final exam. On-line questionnaire	Virtual radiology clerkship was a successful educational experience Final exam scores were similar to the in-person clerkship Students expressed their satisfaction with small group homerooms learning activities Lack of personal connections between faculty and students
McRoy *et al* [64], 2020	United States	Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine	Radiology residents (*n* = 16)	March 15-May 15, 2020	Novel cloud-based Distance Learning Workstation	The model improved residents' confidence and knowledge to take the independent call.
Veerasuri *et al*[65], 2020	United Kingdom	A regional United Kingdom radiology school	All specialty trainees	May 5-May 19, 2020	On-line questionnaire	Overall radiology workload had decreased in response to COVID-19 Decreased subspecialty experience Complete lack of subspecialty training Decrease well-being compared to before the pandemic
Odedra *et al* [66], 2020	Canada	Canadian Association of Radiologists	Resident members of the Canadian Association of Radiologists (*n* = 96)	May 1-May 15, 2020	On-line questionnaire	COVID-19 pandemic has had a significant impact on radiology residency programs Experienced an overall higher disruption in daytime schedules and case volumes Teaching rounds were moderately affected Virtual interviews for fellowship have been proposed Internal and external assessments were heavily affected Impact on the psychological well-being of the trainees
Rainford *et al*[67], 2021	12 countries	Selected Radiography training institutions (*n* = 14)	Student radiographer, including final year students (*n* = 592)	Mid-June-Mid-July 2020	On-line questionnaire	Highlighted challenges related to clinical placements *e.g.*, accommodation, travel, childcare. finance
Shanahan and Akudjedu [68], 2021	Australia	Members of the Australian Society of Medical Imaging and Radiation Therapy	Radiographers and radiation therapists (*n* = 218)	June 24-July 15, 2020	On-line questionnaire	Changes in work hours and workload were experienced due to COVID-19 PPE was in short supply Increased personal stress and anxiety

						at work In addition, their work caused increased stress to their family, partners, or friends
Hoegger *et al*[69], 2021	North America	86 institutions	Radiology chief residents (*n* = 140)	March 20-May 15, 2020	On-line questionnaire	59% of residents reported increased stress 93% of programs had fewer residents on service
Robbins *et al* [70], 2020	United States	Members of Association of Program Directors in Radiology	Program directors, Associate program directors, department chairs, Education vice-chair, and Faculty (*n* = 108)	April 16–May 14, 2020	On-line questionnaire	Educational mission–moderate/marked negative impact (70.1%) Resident morale–moderate/marked negative impact (44.8%) Adequate resident access to mental health resources during the acute phase of the pandemic (88.8%) The morale of program directors–mild or marked decreased (61%)
Foley *et al* [71], 2020	Ireland	All six Irish healthcare regions	Radiographers (*n* = 370 first survey, and 266 second survey)	March 2020 (first survey). Late May 2020 (second survey)	On-line questionnaire	Almost 50% of the radiographers were exposed to COVID-19-positive patients without appropriate PPE Anxiety levels reduced substantially 6 weeks into the crisis period 40% of the radiographers reported burnout symptoms 30% reported considering changing jobs or retiring since the pandemic
Alhasan *et al* [72], 2021	Saudi Arabia	National survey	Radiology residents (*n* = 109)	Academic year 2019-2020	On-line questionnaire	Most residents reported a negative impact of the pandemic on their educational and clinical activities, and personal well-being
Coppola *et al*[73], 2021	Italy	National survey	Members of the Italian Society of Medical and Interventional Radiology (*n* = 2150)	2020	On-line questionnaire	Working and personal life of the respondents was impacted by the pandemic
Patel *et al* [74], 2021	Canada	National survey	Interventional radiologists (*n* = 142)	May 5-28, 2020	On-line questionnaire	Pandemic had a profound impact on IR services, particularly for elective cases Considerable percentage of trainees would have a delay in starting their careers

PPE: Personal protective equipment.

all other emergent/non-emergent patients[76]. Additionally, to protect both patients and healthcare workers from COVID-19 exposure, many healthcare departments temporarily postponed all non-emergency imaging examinations and interventions [77]. To minimize person-to-person virus transmission among radiology staff, many social distancing strategies were implemented, reporting stations were spaced apart, shift systems were developed, and radiology staff were staggered and were advised to work remotely by using online platforms[78]. Traditional in-person meetings were canceled, and the normal face-to-face training and interactions were minimized or eliminated. This led to a tremendous impact on undergraduate and postgraduate exposure to radiology training, as there was less interaction with colleagues and seniors in the radiology department, a vital component of training[79]. The number of hours of exposure to practical radiology was significantly decreased, and some radiology residents were even temporarily redeployed to other clinical disciplines. Similarly, many medical schools even suspended all clinical rotations of medical students, even to the radiology department. Didactic sessions for medical students became virtual and clinical teaching had been suspended or limited. Traditional case-based learning had been hampered and medical students can no longer shadow radiologists and radiology residents as they once did[19].

The COVID-19 pandemic even led to many extraordinary challenges in continuing to offer Radiology Residency and Fellowship programs, some being temporarily suspended[77]. One United States study regarding the educational impact of COVID-19 revealed that 70.1% and 2.8% reported moderate/marked negative impact and cessation of educational activities, respectively[70]. In Canada, COVID-19 has intensely altered the radiology resident training program. Virtual learning replaced face-to-face teaching-learning sessions. Consequently, it resulted in canceling rotations and clerkships, which resulted in case volumes affecting practical learning and staff-resident interaction[80]. Another Canadian study identified that the COVID-19 pandemic heavily affected four teaching-learning domains of radiology. Those were daylight hours' case volumes, daytime timetables, internal and external evaluations, and vacation/travel[66]. One more study reported that there has been a total halt in mammography after the inception of the COVID-19 pandemic and thereby affecting the radiology training program regarding breast cancer assessment. This study also demonstrated that mental stress and burnout have significantly increased among radiologists[81]. Overall breast cancer mammographic screening reduced nationally by 22.2% in Taiwan, more so in hospitals (37.2%) than in community settings (12.9%)[82]. Another United States study reported that the total mean weekly volume of imaging cases in 2020 post-COVID-19 was statistically significantly reduced compared with 2019[83]. The highest reduction was observed at week-16 of 2020 for all types of procedures, such as mammography (94%), nuclear medicine (85%), MRI (74%), ultrasound (64%), interventional (56%), CT (46%), and X-ray (22%). Additionally, "economic recessions generally tend to result in decreased health care expenditures, radiology groups have never experienced an economic shock that is simultaneously exacerbated by the need to restrict the availability of imaging" that occurred during this COVID-19 pandemic[84].

Following the World Health Organization directives for the COVID-19 pandemic, the workflow of the radiology department was restructured with minimal physical presence at work, preventing in-person case reviews and teaching sessions, in order to maintain physical distancing and safety precautions[79]. All non-urgent diagnostic and IR procedures were shifted to outpatient settings, elective surgeries were rescheduled, and only cancer-related appointments and therapies were categorized as urgent or semi-urgent and were followed. Traditional trainee-faculty member workstation teaching was sidestepped putting the year 1 and 2 residents at a disadvantage, although teleconferencing and remote readout screen sharing sessions were put in place as an alternate replacement, feelings of low motivation, abandonment and demoralization were more likely[85]. Important didactic teaching conferences offering lectures, case reviews, and discussions were either canceled or replaced by recorded conferences[86]. The majority of the radiology society meetings and interviews for fellowships and jobs were canceled which reduced networking and collaborative opportunities for trainees. Research activities were interrupted due to laboratory closures and mandates served by the institutional review boards[79]. Delay and rescheduling of the Diagnostic Radiology Core Exam by the American Board of Radiology has delayed graduation and certification, thereby impacting the commencement of radiology residencies and fellowships[87]. A significant decrease in the overall caseload in diagnostic imaging and IR procedures may impede the ability of residents to fulfill the graduation requirements. Consequently, this poses challenges for postgraduates in the Early Specialization in IR programme and increases the predicament of senior residents in meeting training requirements of the Mammography Quality Standards Act or Nuclear Regulatory Commission[88]. Many radiation oncology centers observed a decline in patients undergoing treatment due to patients' fear of getting infected with COVID-19 while traveling for radiotherapy. There is anticipated concern regarding these patients presenting with more advanced stages of disease in the future[89].

Innovative approaches to education and training

The reality of the COVID-19 pandemic requires the traditional undergraduate radiology curriculum to almost complete transition to online materials and interactive virtual teaching sessions, providing an effective blended learning environment, with a combination of didactic lectures, virtual case-based learning, and exposure to virtual clinical discussions[19].

Practical and innovative solutions are needed to compensate for the reduced variety and volume of patients presenting for routine radiological imaging during the pandemic. The development of a local repository of navigable interesting cases for radiology residents to access may compensate for the suboptimal clinical workload. Appropriate cases can be anonymized and collated for cloud-based teaching activities,

including viva practice or long case reporting[90]. To facilitate this, specially purposed integrative software (*e.g.* "Pacsbin"-Orion Medical Technologies) can allow for seamless transfer of hospital cases into the bank of interesting cases, which can then be reviewed by residents at their leisure or as part of sessional teaching activities[64]. Additionally, case collections may also be reviewed as part of group activity by maximizing video conferencing tools such as "Zoom" (Zoom Video Communications), since social distancing protocols prohibit such face-to-face interactions in the Radiology Department. This has been shown to suitably replicate teaching and learning activities at the Radiology reporting station[64].

Virtual learning environments using digital solutions and innovative approaches have proven to be helpful in radiology teaching during the COVID-19 pandemic. They impart knowledge and skills to medical students and trainees in reviewing radiological anatomy *via* online intelligent tutorial systems that provide a personalized, active, and interactive e-learning experience[32]. Learning anatomy from radiology studies has a myriad of pedagogical advances, as it displays "living anatomy". Apart from depicting normal anatomy and pathology, radiology images when transferred and incorporated in virtual/augmented reality and 3-D printing potentiates anatomy teaching by making it a most authentic learning experience[19]. Customized applications/modules/tools provide many benefits of self-directed learning and are widely used *e.g.* student response systems, learning management systems (LMS) and customized LMS, RP modules (improved radiation protection knowledge), radiological ordering module (improved quality of radiological examination orders), CaseTrain software (significantly increased knowledge level); case-based e-learning tool VetsDataWeb (increased identification and accurate diagnosis of key radiological structures)[2]. Simulated mannequins with PACS simulator and Sectional-Anatomy™ software were used as effective online alternatives to face-to-face teaching[91]. Practicing physicians concordantly declared radiology teaching as a priority for medical students[92]. Virtual dissection tools used on near-life-size touchscreens, using "cut and dissect" commands on volumetric CT data help understanding and clinically correlate anatomical visuospatial relationships. 3D cinematic rendered images in absence of virtual dissection software have also been successfully used[93]. Videoconferencing platforms are also useful in the demonstration of radiological anatomy, Srinivasan *et al*[94] 2020. used "Zoom" which includes a screen annotation tool to teach anatomy to Singaporean medical students during COVID-19 and 89% of students were satisfied with this mode of content delivery[94]. De Ponti *et al*[95] surveyed online training sessions using Body Interact™, with 21 patient-based simulated clinical case scenarios for undergraduate medical students, while O'Connor *et al*[96] used a 3D virtual simulation tool in combination with radiology images of a virtual patient in the VR suite using HTC vive Pro™ headsets and hand controllers. These studies reported that simulated clinical scenarios can be incorporated in curricula as useful learning resources, as they avoided training interruption and met student expectations, with only a minority experiencing online access challenges to the virtual platform[95,96].

Radiological examination protocolling, clinical interaction (with radiographers, radiologists, clinicians, and trainees) and MDTs can be made more effective using existing technologies and online platforms for trainees in remote locations. Recorded/live cases, online lectures providing live and on-demand screening, virtual journal clubs, digital repositories for educational cases, simulation-based training as assessments with wider adoption on online tools can also be utilized[79]. Appropriate cases can be anonymized and collated for cloud-based teaching activities, "simulated" or phone-based daily readout (SDR) can be used for viva practice or long case reporting[90,97]. "Pacsbin" can be used by residents at all levels of training, and it is also useful for peer-to-peer resident learning or as part of sessional teaching activities [64]. Additionally, suitably replicable teaching and learning activities such as reviewing case collections at the radiology reporting station as part of group activity can be maximized by video conferencing tools[64] Institutional libraries *via* WebEx supports a series of organized specialist presentations providing information about useful technology tools, applications and resources and services available for faculty, staff and students to facilitate more efficient working from home. Additionally, support is provided through Library portals, Interlibrary Loan Internet-accessible database requests and publication services[77].

Special strategies and tools should be utilized to maximize meaningful participation in a flipped learning environment, develop critical thinking and complex reasoning skills, effective time management and communication strategies, as well as the incorporation of more interactive tools such as audience response systems and other advanced practical based software (Alvin, 2020)[79]. Practical and innovative solutions

are needed to compensate for the reduced variety and volume of patients presenting for routine radiological imaging during the pandemic.

Technological and academic challenges

The upheaval of the COVID-19 pandemic, following economic turmoil and its far-flung social unrest caused tumultuous shifts in the way radiologists work and teach, even affecting their work life harmony. It should be noted that remote sessions for Radiology teaching may lead to difficulties for some participants, especially when there are hardware and software issues, poor internet connectivity, and suboptimal interactions/content[90]. The set-up cost for these remote viewing systems can also be prohibitive. Additionally, there may be logistical and legal hurdles in the sharing of sensitive patient data *via* online teaching platforms. Private practices, hospitals and educational institutions facing significant monetary constraints may resort to possible salary cuts, redeployment, furloughs, shift to part-time employment and remote works. Academic institutions face new challenges of modified resident schedules, transformation to virtual platforms for evaluating imaging studies, and teaching and assessing trainees due to remote readouts[89]. Newly appointed junior trainees may be more significantly affected by technical challenges of remote image interpretation and readouts, busier rotations, limited in-person communication, unfamiliarity with team, exams and workflow, and the advent of the second wave in most countries may further worsen all factors to two fold.

With reduced numbers of diagnostic imaging and interventions, radiology residents may face the dilemma of meeting the training requirements, such as those mandated by the Mammography Quality Standards Act or the Nuclear Regulatory Commission [98]. Significant reductions in hands-on training sessions for fellows in IR could have a negative impact. Although live virtual conferences and recorded lectures have replaced face-to-face senior supervision, feedback and pedagogy, unfortunately, gauging the effectiveness of studying diagnostic and IR by virtual mode still remains vague, especially without any substantial supporting evidence on validity of remote and simulated learning[2,99].

Review of the COVID-19 impact on academic output in medicine has recognized a gender gap in women's first authorships which reduced to 23%, last authorships to 16% and there was a 16% drop in the general representation of women *per* author group in COVID-19 publications compared to publications in same journals last year [100]. This is a clear indication that women's productivity has been exceedingly affected than of men. This gender disparity is a possible result of increased demands at home and family responsibilities, which may limit academic and research output. In the future, the anticipated increase in workload due to rescheduling, backlog lists and procedures after COVID-19 may further widen the gender gap[100]. Studies reviewing the impact of COVID-19 show women work 20 more hours/week than men. With the major responsibility of childcare and domestic work, cancellations of child-care facilities and schools may affect women in radiology and radiation oncology more than men[101].

The reality of social distancing and working remotely have been recognized as potential stressors that have the potential to cause a negative psychological impact on the trainee, as they struggle to cope with an altered work and teaching environment and postponement of assessments/examinations while dealing with the realities of the pandemic[102]. Dedicated online psychological support for both the trainee and trainer is needed, in order to cope with these challenges to radiology education, so that solutions can be found to shared concerns[103]. Human relations and interactions must be maintained so that the feeling of remoteness does not become overwhelming.

Future directions

Technological advances in the field of radiology training must rise to the challenge and be able to foster the remote or "off-site" radiology interpretive skills of the radiology residents, while promoting self-motivated study[104]. Radiology Educators should also continue to increasingly integrate the use of recorded cases, enhance online lectures, digital repositories of educational cases, virtual journal clubs, and also acquire simulator-based training equipment. Teaching institutions should invest in appropriate technology and incorporate the utilization of the dynamic capabilities of an actual Radiology viewing platform, which facilitates a better learning experience for the Radiology Resident, mimicking a real-life scenario[75]. This is preferred to viewing static cases in film libraries, textbooks, and online databases, and will be a suitable substitute for the workstation learning experience. During the challenging time of the COVID-19 pandemic, it is paramount to utilize these strategies to maintain undergraduate and postgraduate radiology education in a safe but effective

environment.

Educational institutions should adopt e-learning, acquire new tools for teaching and digital transformation. Flipped classroom is a preferred model in medical education with small group interactions and instant feedback during in-class sessions. Integration of problem-solving scenarios and team-based learning in undergraduate curricula with appropriate use of imaging studies: simulating diagnostic reasoning, in a community-based design can improve imaging decisions and provide high-value care. Simulator-training models using Virtual Reality can be applied to ultrasonography and IR for trainees and working teams to enhance knowledge, experience, and learning skills by deliberate practice without compromising patient safety. Proper documentation of dynamic modifications in the radiology department's daily practices and learning experiences is crucial for handling current circumstances and in preparation for the second wave.

CONCLUSION

The COVID-19 pandemic has had a tremendous impact on undergraduate and postgraduate radiology education. Implementation of social distancing strategies resulted in infrastructural and human resource changes to the radiology department, resulting in a decreased physical presence/interaction and consequent limitation in face-to-face consultations and teaching exposure. Even before the COVID-19 pandemic, radiology educators often encountered many difficulties in delivering the radiology curriculum to undergraduate and postgraduate trainees, including limited teaching times, radiology education budgetary constraints and limited support in assessing/developing professional quality teaching.

During the pandemic, there was an almost complete transition of radiology education to a blended online platform, with the incorporation of didactic lectures, online interactive sessions and online participation in MDTs and other radiology department-related activities. There were many hiccups in the implementation of online teaching activities, such as challenges with respect to the procurement of hardware/software and a reliable Internet connection. Finding suitable innovative and interactive radiology teaching content proved to be another major challenge. Encouraging meaningful participation and interaction, while simulating the clinical environment was also particularly difficult, but not insurmountable. Technological advances in radiology education and training must continue to rise to address the challenges and meet the educational requirements needed to aid in the development of the undergraduate and postgraduate radiology trainees. This is particularly important in the face of the trials COVID-19 has provided.

REFERENCES

1 **Emin EI**, Ruhomauly Z, Theodoulou I, Hanrahan JG, Staikoglou N, Nicolaides M, Thulasidasan N, Papalois A, Sideris M. Are interventional radiology and allied specialities neglected in undergraduate medical education? *Ann Med Surg (Lond)* 2019; **40**: 22-30 [PMID: 30962927 DOI: 10.1016/j.amsu.2019.03.004]

2 **Zafar S**, Safdar S, Zafar AN. Evaluation of use of e-Learning in undergraduate radiology education: a review. *Eur J Radiol* 2014; **83**: 2277-2287 [PMID: 25242658 DOI: 10.1016/j.ejrad.2014.08.017]

3 **Skochelak SE**, Stack SJ. Creating the Medical Schools of the Future. *Acad Med* 2017; **92**: 16-19 [PMID: 27008357 DOI: 10.1097/ACM.0000000000001160]

4 **Guliato D**, Bôaventura RS, Maia MA, Rangayyan RM, Simedo MS, Macedo TA. INDIAM--an e-learning system for the interpretation of mammograms. *J Digit Imaging* 2009; **22**: 405-420 [PMID: 18425550 DOI: 10.1007/s10278-008-9111-6]

5 **Al Qahtani F**, Abdelaziz A. Integrating radiology vertically into an undergraduate medical education curriculum: a triphasic integration approach. *Adv Med Educ Pract* 2014; **5**: 185-189 [PMID: 24959094 DOI: 10.2147/AMEP.S58858]

6 **Tshibwabwa E**, Mallin R, Fraser M, Tshibwabwa M, Sanii R, Rice J, Cannon J. An Integrated Interactive-Spaced Education Radiology Curriculum for Preclinical Students. *J Clin Imaging Sci* 2017; **7**: 22 [PMID: 28584689 DOI: 10.4103/jcis.JCIS_1_17]

7 **Gaur U**, Majumder MAA, Sa B, Sarkar S, Williams A, Singh K. Challenges and Opportunities of Preclinical Medical Education: COVID-19 Crisis and Beyond. *SN Compr Clin Med* 2020; 1-6 [PMID: 32984766 DOI: 10.1007/s42399-020-00528-1]

8 **Singh K**, Gaur U, Hall K, Mascoll K, Cohall D, Majumder MAA. Teaching anatomy and dissection in an era of social distancing and remote learning. *Adv Hum Biol* 2020; **10**: 90-94 [DOI: 10.4103/aihb.aihb_87_20]

9 **Majumder MAA**. COVID-19 pandemic: Medical education is clinging on a knife's edge! *Adv Hum Biol* 2020; **10**: 83 [DOI: 10.4103/aihb.aihb_88_20]

10 **Rose S**. Medical Student Education in the Time of COVID-19. *JAMA* 2020; **323**: 2131-2132 [PMID: 32232420 DOI: 10.1001/jama.2020.5227]

11 **Dedeilia A**, Sotiropoulos MG, Hanrahan JG, Janga D, Dedeilias P, Sideris M. Medical and Surgical Education Challenges and Innovations in the COVID-19 Era: A Systematic Review. *In Vivo* 2020; **34**: 1603-1611 [PMID: 32503818 DOI: 10.21873/invivo.11950]

12 **Vagal A**, Reeder SB, Sodickson DK, Goh V, Bhujwalla ZM, Krupinski EA. The Impact of the COVID-19 Pandemic on the Radiology Research Enterprise: Radiology Scientific Expert Panel. *Radiology* 2020; **296**: E134-E140 [PMID: 32293224 DOI: 10.1148/radiol.2020201393]

13 **Alsoufi A**, Alsuyihili A, Msherghi A, Elhadi A, Atiyah H, Ashini A, Ashwieb A, Ghula M, Ben Hasan H, Abudabuos S, Alameen H, Abokhdhir T, Anaiba M, Nagib T, Shuwayyah A, Benothman R, Arrefae G, Alkhwayildi A, Alhadi A, Zaid A, Elhadi M. Impact of the COVID-19 pandemic on medical education: Medical students' knowledge, attitudes, and practices regarding electronic learning. *PLoS One* 2020; **15**: e0242905 [PMID: 33237962 DOI: 10.1371/journal.pone.0242905]

14 **Gao H**, Hu R, Yin L, Yuan X, Tang H, Luo L, Chen M, Huang D, Wang Y, Yu A, Jiang Z. Knowledge, attitudes and practices of the Chinese public with respect to coronavirus disease (COVID-19): an online cross-sectional survey. *BMC Public Health* 2020; **20**: 1816 [PMID: 33256707 DOI: 10.1186/s12889-020-09961-2]

15 **Mohammad S**, Osman A, Abd-Elhameed A, Ahmed KA, Mohamed MA. The battle against Covid-19: the experience of an Egyptian radiology department in a university setting. *Egypt J Radiol Nucl Med* 2020; **51**: 216 [DOI: 10.1186/s43055-020-00335-7]

16 **England E**, Jordan S, Kanfi A, Patel MD. Radiology residency program management post-pandemic-peak: looking down the curve and around the bend. *Clin Imaging* 2021; **69**: 243-245 [PMID: 32979790 DOI: 10.1016/j.clinimag.2020.09.007]

17 **Rowell MR**, Johnson PT, Fishman EK. Radiology education in 2005: world wide web practice patterns, perceptions, and preferences of radiologists. *Radiographics* 2007; **27**: 563-571 [PMID: 17374870 DOI: 10.1148/rg.272065049]

18 **Praschinger A**, Stieger S, Kainberger F. Diagnostic grand rounds in undergraduate medical education. *Med Educ* 2007; **41**: 1107-1108 [PMID: 17973777 DOI: 10.1111/j.1365-2923.2007.02888.x]

19 **Darras KE**, Spouge RJ, de Bruin ABH, Sedlic A, Hague C, Forster BB. Undergraduate Radiology Education During the COVID-19 Pandemic: A Review of Teaching and Learning Strategies [Formula: see text]. *Can Assoc Radiol J* 2021; **72**: 194-200 [PMID: 32749165 DOI: 10.1177/0846537120944821]

20 **Nicholas JL**, Bass EL, Otero HJ. Can lessons from the COVID-19 pandemic help define a strategy for global pediatric radiology education? *Pediatr Radiol* 2020; **50**: 1641-1644 [PMID: 32889584 DOI: 10.1007/s00247-020-04822-x]

21 **Mirsadraee S**, Mankad K, McCoubrie P, Roberts T, Kessel D. Radiology curriculum for undergraduate medical studies--a consensus survey. *Clin Radiol* 2012; **67**: 1155-1161 [PMID: 22705185 DOI: 10.1016/j.crad.2012.03.017]

22 **Alexander AG**, Deas D, Lyons PE. An Internet-Based Radiology Course in Medical School: Comparison of Academic Performance of Students on Campus Versus Those With Absenteeism Due to Residency Interviews. *JMIR Med Educ* 2018; **4**: e14 [PMID: 29776902 DOI: 10.2196/mededu.8747]

23 **Chew C**, Cannon P, O'Dwyer PJ. Radiology for medical students (1925-2018): an overview. *BJR Open* 2020; **2**: 20190050 [PMID: 33178968 DOI: 10.1259/bjro.20190050]

24 **Friloux L**. The vital role of radiology in the medical school curriculum. *AJR Am J Roentgenol* 2003; **181**: 1428 [DOI: 10.2214/ajr.181.5.1811428]

25 **Dmytriw AA**, Mok PS, Gorelik N, Kavanaugh J, Brown P. Radiology in the Undergraduate Medical Curriculum: Too Little, Too Late? *Med Sci Educ* 2015; **25**: 223-227 [PMID: 28286696 DOI: 10.1007/s40670-015-0130-x]

26 **Holt NF**. Medical students need more radiology education. *Acad Med* 2001; **76**: 1 [PMID: 11154184 DOI: 10.1097/00001888-200101000-00001]

27 **Barzansky B**, Jonas HS, Etzel SI. Educational programs in US medical schools, 1998-1999. *JAMA* 1999; **282**: 840-846 [PMID: 10478690 DOI: 10.1001/jama.282.9.840]

28 **Rumack CM**. American diagnostic radiology residency and fellowship programmes. *Ann Acad Med Singap* 2011; **40**: 126-131 [PMID: 21603730]

29 **Naeger DM**, Webb EM, Zimmerman L, Elicker BM. Strategies for incorporating radiology into early medical school curricula. *J Am Coll Radiol* 2014; **11**: 74-79 [PMID: 24161457 DOI: 10.1016/j.jacr.2013.07.013]

30 **Lindsell D**. Changes in postgraduate medical education and training in clinical radiology. *Biomed Imaging Interv J* 2008; **4**: e19 [PMID: 21614310 DOI: 10.2349/biij.4.1.e19]

31 **Nanapragasam A**, Mashar M. Postgraduate radiology education: what has Covid-19 changed? *BJR Open* 2021; **3**: 20200064 [PMID: 34381944 DOI: 10.1259/bjro.20200064]

32 **Chew C**, O'Dwyer PJ, Sandilands E. Radiology for medical students: Do we teach enough? *Br J Radiol* 2021; **94**: 20201308 [PMID: 33560874 DOI: 10.1259/bjr.20201308]

33 **Morrissey B**, Heilbrun ME. Teaching Critical Thinking in Graduate Medical Education: Lessons Learned in Diagnostic Radiology. *J Med Educ Curric Dev* 2017; **4**: 2382120517696498 [PMID:

29349332 DOI: 10.1177/2382120517696498]
34 **Commander CW**, Pabon-Ramos WM, Isaacson AJ, Yu H, Burke CT, Dixon RG. Assessing medical students' knowledge of IR at two American medical schools. *J Vasc Interv Radiol* 2014; **25**: 1801-1806, 1807.e1 [PMID: 25066590 DOI: 10.1016/j.jvir.2014.06.008]
35 **Ghatan CE**, Kuo WT, Hofmann LV, Kothary N. Making the case for early medical student education in interventional radiology: a survey of 2nd-year students in a single U.S. institution. *J Vasc Interv Radiol* 2010; **21**: 549-553 [PMID: 20189831 DOI: 10.1016/j.jvir.2009.12.397]
36 **Singh RK**, McCoubrie P, Burney K, Miles JA. Teaching medical students about radiation protection--what do they need to know? *Clin Radiol* 2008; 12: 1344-1349 [DOI: 10.1016/j.crad.2008.06.010]
37 **Agrawal D**, Renfrew MA, Singhal S, Bhansali Y. Awareness and knowledge of interventional radiology among medical students at an Indian institution. *CVIR Endovasc* 2019; **2**: 45 [PMID: 32026159 DOI: 10.1186/s42155-019-0093-x]
38 **Scarsbrook AF**, Graham RN, Perriss RW. Radiology education: a glimpse into the future. *Clin Radiol* 2006; **61**: 640-648 [PMID: 16843746 DOI: 10.1016/j.crad.2006.04.005]
39 **Salajegheh A**, Jahangiri A, Dolan-Evans E, Pakneshan S. A combination of traditional learning and e-learning can be more effective on radiological interpretation skills in medical students: a pre- and post-intervention study. *BMC Med Educ* 2016; **16**: 46 [PMID: 26842495 DOI: 10.1186/s12909-016-0569-5]
40 **Hamady M**, McCafferty I. The rocky road to recognizing interventional radiology as a full clinical speciality. *CVIR Endovasc* 2021; **4**: 7 [PMID: 33409817 DOI: 10.1186/s42155-020-00202-6]
41 **Bulman JC**, Moussa M, Lewis TK, Berkowitz S, Sarwar A, Faintuch S, Ahmed M. Transitioning the IR Clinic to Telehealth: A Single-Center Experience during the COVID-19 Pandemic. *J Vasc Interv Radiol* 2020; **31**: 1315-1319.e4 [PMID: 32620320 DOI: 10.1016/j.jvir.2020.05.008]
42 **Cohen MD**, Gunderman RB, Frank MS, Williamson KB. Re: commentary on "Challenges facing radiology educators". *J Am Coll Radiol* 2005; **11** [DOI: 10.1016/j.jacr.2005.09.004]
43 **Choudhary A**, Tong L, Zhu Y, Wang MD. Advancing Medical Imaging Informatics by Deep Learning-Based Domain Adaptation. *Yearb Med Inform* 2020; **29**: 129-138 [PMID: 32823306 DOI: 10.1055/s-0040-1702009]
44 **Pianykh O**. Digital imaging and communications in medicine (DICOM): a practical introduction and survival guide. *Springer* 2012 [DOI: 10.1007/978-3-642-10850-1_1]
45 **Duong MT**, Rauschecker AM, Rudie JD, Chen PH, Cook TS, Bryan RN, Mohan S. Artificial intelligence for precision education in radiology. *Br J Radiol* 2019; **92**: 20190389 [PMID: 31322909 DOI: 10.1259/bjr.20190389]
46 **Dromain C**, Boyer B, Ferré R, Canale S, Delaloge S, Balleyguier C. Computed-aided diagnosis (CAD) in the detection of breast cancer. *Eur J Radiol* 2013; **82**: 417-423 [PMID: 22939365 DOI: 10.1016/j.ejrad.2012.03.005]
47 **Flanders AE**. Medical image and data sharing: are we there yet? *Radiographics* 2009; **29**: 1247-1251 [PMID: 19755594 DOI: 10.1148/rg.295095151]
48 **Xiberta P**, Boada I. A new e-learning platform for radiology education (RadEd). *Comput Methods Programs Biomed* 2016; **126**: 63-75 [PMID: 26774237 DOI: 10.1016/j.cmpb.2015.12.022]
49 **Min Q**, Wang X, Huang B, Xu L. Web-Based Technology for Remote Viewing of Radiological Images: App Validation. *J Med Internet Res* 2020; **22**: e16224 [PMID: 32975520 DOI: 10.2196/16224]
50 **Applegate JS**. The role of mobile electronic devices in radiographer education. *Radiol Technol* 2010; **82**: 124-131 [PMID: 21048063]
51 **Bedi HS**, Yucel EK. "I Just bought my residents iPads… now what? *AJR Am J Roentgenol* 2013; **201**: 704-709 [PMID: 24059358 DOI: 10.2214/AJR.13.10674]
52 **Marshall NL**, Spooner M, Galvin PL, Ti JP, McElvaney NG, Lee MJ. Informatics in radiology: evaluation of an e-learning platform for teaching medical students competency in ordering radiologic examinations. *Radiographics* 2011; **31**: 1463-1474 [PMID: 21775674 DOI: 10.1148/rg.315105081]
53 **Gupta S**, Johnson EM, Peacock JG, Jiang L, McBee MP, Sneider MB, Krupinski EA. Radiology, Mobile Devices, and Internet of Things (IoT). *J Digit Imaging* 2020; **33**: 735-746 [PMID: 31898039 DOI: 10.1007/s10278-019-00311-2]
54 **Botelho MG**, Agrawal KR, Bornstein MM. An systematic review of e-learning outcomes in undergraduate dental radiology curricula-levels of learning and implications for researchers and curriculum planners. *Dentomaxillofac Radiol* 2019; **48**: 20180027 [PMID: 30028185 DOI: 10.1259/dmfr.20180027]
55 **Donnelly P**, Kirk P, Benson J. How to succeed at e-learning. 12th ed. New York: John Wiley & Sons, 2012
56 **Cruz AD**, Costa JJ, SM A. Distance learning in dental radiology: Immediate impact of the implementation. *Braz Den Sci* 2014; **17**: 90 [DOI: 10.14295/bds.2014.v17i4.930]
57 **Busanello FH**, da Silveira PF, Liedke GS, Arús NA, Vizzotto MB, Silveira HE, Silveira HL. Evaluation of a digital learning object (DLO) to support the learning process in radiographic dental diagnosis. *Eur J Dent Educ* 2015; **19**: 222-228 [PMID: 25393811 DOI: 10.1111/eje.12125]
58 **Al-Rawi WT**, Jacobs R, Hassan BA, Sanderink G, Scarfe WC. Evaluation of web-based instruction for anatomical interpretation in maxillofacial cone beam computed tomography. *Dentomaxillofac Radiol* 2007; **36**: 459-464 [PMID: 18033941 DOI: 10.1259/dmfr/25560514]
59 **Kavadella A**, Tsiklakis K, Vougiouklakis G, Lionarakis A. Evaluation of a blended learning course

for teaching oral radiology to undergraduate dental students. *Eur J Dent Educ* 2012; **16**: e88-e95 [PMID: 22251359 DOI: 10.1111/j.1600-0579.2011.00680.x]

60 **Girard N**. Evidence appraisal of Wang R, Shi N, Bai J, Zheng Y, Zhau Y. Implementation and evaluation of an interprofessional simulation-based education program for undergraduate nursing students in operating room nursing education: a randomized controlled trial. BMC Med Educ. 2015;15:115. Published online July 9, 2015. *AORN J* 2016; **103**: 448-454 [PMID: 27455541 DOI: 10.1016/j.aorn.2016.02.009]

61 **Adams CC**, Shih R, Peterson PG, Lee MH, Heltzel DA, Lattin GE. The Impact of a Virtual Radiology Medical Student Rotation: Maintaining Engagement During COVID-19 Mitigation. *Mil Med* 2020 [DOI: 10.1093/milmed/usaa293]

62 **Alamer A**, Alharbi F. Synchronous distance teaching of radiology clerkship promotes medical students' learning and engagement. *Insights Imaging* 2021; **12**: 41 [PMID: 33765254 DOI: 10.1186/s13244-021-00984-w]

63 **Durfee SM**, Goldenson RP, Gill RR, Rincon SP, Flower E, Avery LL. Medical Student Education Roadblock Due to COVID-19: Virtual Radiology Core Clerkship to the Rescue. *Acad Radiol* 2020; **27**: 1461-1466 [PMID: 32747181 DOI: 10.1016/j.acra.2020.07.020]

64 **McRoy C**, Patel L, Gaddam DS, Rothenberg S, Herring A, Hamm J, Chelala L, Weinstein J, Smith E, Awan O. Radiology Education in the Time of COVID-19: A Novel Distance Learning Workstation Experience for Residents. *Acad Radiol* 2020; **27**: 1467-1474 [PMID: 32800692 DOI: 10.1016/j.acra.2020.08.001]

65 **Veerasuri S**, Vekeria M, Davies SE, Graham R, Rodrigues JCL. Impact of COVID-19 on UK radiology training: a questionnaire study. *Clin Radiol* 2020; **75**: 877.e7-877.e14 [PMID: 32847684 DOI: 10.1016/j.crad.2020.07.022]

66 **Odedra D**, Chahal BS, Patlas MN. Impact of COVID-19 on Canadian Radiology Residency Training Programs. *Can Assoc Radiol J* 2020; **71**: 482-489 [PMID: 32522010 DOI: 10.1177/0846537120933215]

67 **Rainford LA**, Zanardo M, Buissink C, Decoster R, Hennessy W, Knapp K, Kraus B, Lanca L, Lewis S, Mahlaola TB, McEntee M, O'Leary D, Precht H, Starc T, McNulty JP. The impact of COVID-19 upon student radiographers and clinical training. *Radiography (Lond)* 2021; **27**: 464-474 [PMID: 33223416 DOI: 10.1016/j.radi.2020.10.015]

68 **Shanahan MC**, Akudjedu TN. Australian radiographers' and radiation therapists' experiences during the COVID-19 pandemic. *J Med Radiat Sci* 2021; **68**: 111-120 [PMID: 33590670 DOI: 10.1002/jmrs.462]

69 **Hoegger MJ**, Shetty AS, Denner DR, Gould JE, Wahl RL, Raptis CA, Ballard DH. A Snapshot of Radiology Training During the Early COVID-19 Pandemic. *Curr Probl Diagn Radiol* 2021; **50**: 607-613 [PMID: 32690337 DOI: 10.1067/j.cpradiol.2020.06.012]

70 **Robbins JB**, England E, Patel MD, DeBenedectis CM, Sarkany DS, Heitkamp DE, Milburn JM, Kalia V, Ali K, Gaviola GC, Ho CP, Jay AK, Ong S, Jordan SG. COVID-19 Impact on Well-Being and Education in Radiology Residencies: A Survey of the Association of Program Directors in Radiology. *Acad Radiol* 2020; **27**: 1162-1172 [PMID: 32571648 DOI: 10.1016/j.acra.2020.06.002]

71 **Foley SJ**, O'Loughlin A, Creedon J. Early experiences of radiographers in Ireland during the COVID-19 crisis. *Insights Imaging* 2020; **11**: 104 [PMID: 32986225 DOI: 10.1186/s13244-020-00910-6]

72 **Alhasan AS**, Alahmadi SM, Altayeb YA, Daqqaq TS. Impact of COVID-19 Pandemic on Training and Well-Being in Radiology Residency: A National Survey of Diagnostic Radiology Trainees in Saudi Arabia. *Acad Radiol* 2021; **28**: 1002-1009 [DOI: 10.1016/j.acra.2021.03.019]

73 **Coppola F**, Faggioni L, Neri E, Grassi R, Miele V. Impact of the COVID-19 outbreak on the profession and psychological wellbeing of radiologists: a nationwide online survey. *Insights Imaging* 2021; **12**: 23 [PMID: 33595747 DOI: 10.1186/s13244-021-00962-2]

74 **Patel NR**, El-Karim GA, Mujoomdar A, Mafeld S, Jaberi A, Kachura JR, Tan KT, Oreopoulos GD. Overall Impact of the COVID-19 Pandemic on Interventional Radiology Services: A Canadian Perspective. *Can Assoc Radiol J* 2021; **72**: 564-570 [PMID: 32864995 DOI: 10.1177/0846537120951960]

75 **Rizvi T**, Borges NJ. "Virtual Radiology Workstation": Improving Medical Students' Radiology Rotation. *Med Sci Educ* 2020; **30**: 117-121 [PMID: 34457649 DOI: 10.1007/s40670-020-00920-5]

76 **CDC**. How to Protect Yourself & Others. CDC. [cited 21 October 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

77 **Virarkar M**, Jensen C, Javadi S, Saleh M, Bhosale PR. Radiology Education Amid COVID-19 Pandemic and Possible Solutions. *J Comput Assist Tomogr* 2020; **44**: 472-478 [PMID: 32649427 DOI: 10.1097/RCT.0000000000001061]

78 **Mossa-Basha M**, Meltzer CC, Kim DC, Tuite MJ, Kolli KP, Tan BS. Radiology Department Preparedness for COVID-19: *Radiology* Scientific Expert Review Panel. *Radiology* 2020; **296**: E106-E112 [PMID: 32175814 DOI: 10.1148/radiol.2020200988]

79 **Alvin MD**, George E, Deng F, Warhadpande S, Lee SI. The Impact of COVID-19 on Radiology Trainees. *Radiology* 2020; **296**: 246-248 [PMID: 32216719 DOI: 10.1148/radiol.2020201222]

80 **Warnica W**, Moody A, Probyn L, Bartlett E, Singh N, Pakkal M. Lessons Learned from the Effects of COVID-19 on the Training and Education Workflow of Radiology Residents-A Time for Reflection: Perspectives of Residency Program Directors and Residents in Canada. *Can Assoc Radiol J* 2020; 846537120963649 [DOI: 10.1177/0846537120963649]

81 **Freer PE**. The Impact of the COVID-19 Pandemic on Breast Imaging. *Radiol Clin North Am* 2021; **59**: 1-11 [PMID: 33222992 DOI: 10.1016/j.rcl.2020.09.008]

82 **Tsai HY**, Chang YL, Shen CT, Chung WS, Tsai HJ, Chen FM. Effects of the COVID-19 pandemic on breast cancer screening in Taiwan. *Breast* 2020; **54**: 52-55 [PMID: 32919172 DOI: 10.1016/j.breast.2020.08.014]

83 **Naidich JJ**, Boltyenkov A, Wang JJ, Chusid J, Hughes D, Sanelli PC. Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Imaging Case Volumes. *J Am Coll Radiol* 2020; **17**: 865-872 [PMID: 32425710 DOI: 10.1016/j.jacr.2020.05.004]

84 **Sreedharan S**, Mian M, McArdle DJT, Rhodes A. The impact of the COVID-19 pandemic on diagnostic imaging services in Australia. *J Med Imaging Radiat Oncol* 2021 [PMID: 34288493 DOI: 10.1111/1754-9485.13291]

85 **Alhasan M**, Al-Horani Q. Students' perspective on the online delivery of radiography & medical imaging program during COVID-19 pandemic. *J Med Imaging Radiat Sci* 2021 [PMID: 34483086 DOI: 10.1016/j.jmir.2021.07.009]

86 **Currie G**, Hewis J, Nelson T, Chandler A, Nabasenja C, Spuur K, Barry K, Frame N, Kilgour A. COVID-19 impact on undergraduate teaching: Medical radiation science teaching team experience. *J Med Imaging Radiat Sci* 2020; **51**: 518-527 [PMID: 32981889 DOI: 10.1016/j.jmir.2020.09.002]

87 **Radiology ABo**. ABR statement on COVID-19 Impact on ACGME Residency Training. American Board on Radiology. [cited 21 October 2021]. Available from: https://www.theabr.org/announcements/coronavirus-updates#residents

88 **Iezzi R**, Valente I, Cina A, Posa A, Contegiacomo A, Alexandre A, D'Argento F, Lozupone E, Barone M, Giubbolini F, Milonia L, Romi A, Scrofani AR, Pedicelli A, Manfredi R, Colosimo C. Longitudinal study of interventional radiology activity in a large metropolitan Italian tertiary care hospital: how the COVID-19 pandemic emergency has changed our activity. *Eur Radiol* 2020; **30**: 6940-6949 [PMID: 32607633 DOI: 10.1007/s00330-020-07041-y]

89 **Esfahani SA**, Lee A, Hu JY, Kelly M, Magudia K, Everett C, Szabunio M, Ackerman S, Spalluto LB. Challenges faced by women in radiology during the pandemic - A summary of the AAWR Women's Caucus at the ACR 2020 annual meeting. *Clin Imaging* 2020; **68**: 291-294 [DOI: 10.1016/j.clinimag.2020.08.016]

90 **Belfi LM**, Dean KE, Bartolotta RJ, Shih G, Min RJ. Medical student education in the time of COVID-19: A virtual solution to the introductory radiology elective. *Clin Imaging* 2021; **75**: 67-74 [PMID: 33497880 DOI: 10.1016/j.clinimag.2021.01.013]

91 **Aziz J**, Madhusudan V, Joanna T. A journey on an unknown path: the unexpected experience of online simulation-based teaching to medical imaging students under COVID-19 Lockdown. presented at: the simulation-based education in MRS/radiography: a response to Covid19, Online; June, 2020; Liverpool. [cited 21 October 2021]. Available from: https://hdl.handle.net/10652/4960

92 **Orsbon CP**, Kaiser RS, Ross CF. Physician opinions about an anatomy core curriculum: a case for medical imaging and vertical integration. *Anat Sci Educ* 2014; **7**: 251-261 [PMID: 24022941 DOI: 10.1002/ase.1401]

93 **Darras KE**, Spouge R, Hatala R, Nicolaou S, Hu J, Worthington A, Krebs C, Forster BB. Integrated virtual and cadaveric dissection laboratories enhance first year medical students' anatomy experience: a pilot study. *BMC Med Educ* 2019; **19**: 366 [PMID: 31590672 DOI: 10.1186/s12909-019-1806-5]

94 **Srinivasan DK**. Medical Students' Perceptions and an Anatomy Teacher's Personal Experience Using an e-Learning Platform for Tutorials During the Covid-19 Crisis. *Anat Sci Educ* 2020; **13**: 318-319 [DOI: 10.1002/ase.1970]

95 **De Ponti R**, Marazzato J, Maresca AM, Rovera F, Carcano G, Ferrario MM. Pre-graduation medical training including virtual reality during COVID-19 pandemic: a report on students' perception. *BMC Med Educ* 2020; **20**: 332 [PMID: 32977781 DOI: 10.1186/s12909-020-02245-8]

96 **O'Connor M**, Stowe J, Potocnik J, Giannotti N, Murphy S, Rainford L. 3D virtual reality simulation in radiography education: The students' experience. *Radiography (Lond)* 2021; **27**: 208-214 [PMID: 32800641 DOI: 10.1016/j.radi.2020.07.017]

97 **Sutherland DEK**. It's a small world after all: A Canadian resident's perspective on COVID-19. *J Nucl Cardiol* 2020; **27**: 2283-2286 [PMID: 32596790 DOI: 10.1007/s12350-020-02222-0]

98 **American College of Radiology**. Mammography Quality Standards Act. American College of Radiology. [cited 21 October 2021]. Available from: https://www.acr.org/Advocacy-and-Economics/Legislative-Issues/MQSA

99 **Zhong J**, Datta A, Gordon T, Adams S, Guo T, Abdelaziz M, Barbour F, Palkhi E, Adusumilli P, Oomerjee M, Lake E, Walker P. The Impact of COVID-19 on Interventional Radiology Services in the UK. *Cardiovasc Intervent Radiol* 2021; **44**: 134-140 [PMID: 33145699 DOI: 10.1007/s00270-020-02692-2]

100 **Andersen JP**, Nielsen MW, Simone NL, Lewiss RE, Jagsi R. COVID-19 medical papers have fewer women first authors than expected. *Elife* 2020; **9** [PMID: 32538780 DOI: 10.7554/eLife.58807]

101 **Tertilt TAMDJO-RM**. "The Impact of COVID-19 on Gender Equality". CRC TR 224 Discussion Paper Series crctr224_2020_163. University of Bonn and University of Mannheim, Germany, 2020

102 **Barral M**, Dohan A, Marcelin C, Carteret T, Zurlinden O, Pialat JB, Kastler A, Cornelis FH. COVID-19 pandemic: A stress test for interventional radiology. *Diagn Interv Imaging* 2020; **101**: 333-334 [PMID: 32359930 DOI: 10.1016/j.diii.2020.04.008]

103 **Ricciardi G**, Biondi R, Tamagnini G. Go back to the basics: Cardiac surgery residents at the time of

COVID-19. *J Card Surg* 2020; **35**: 1400-1402 [PMID: 32500923 DOI: 10.1111/jocs.14680]

104 **Singh CS**, Sethuraman KR, Ehzumalai G, Adkoli BV. Effectiveness of problem-solving exercises in radiology education for undergraduates. *Natl Med J India* 2019; **32**: 103-106 [PMID: 31939409 DOI: 10.4103/0970-258X.275353]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2021 December 28; 13(12): 371-379

Published by Baishideng Publishing Group Inc

World Journal of Radiology

Contents

Monthly Volume 13 Number 12 December 28, 2021

ORIGINAL ARTICLE

Retrospective Study

World Journal of Radiology

Monthly Volume 13 Number 12 December 28, 2021

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Radiology*, Lee K Rousslang, MD, Resident Physician, Department of Radiology, Tripler Army Medical Center, Honolulu, HI 96859, United States. lee.k.rousslang.civ@mail.mil

AIMS AND SCOPE

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

WJR mainly publishes articles reporting research results and findings obtained in the field of radiology and covering a wide range of topics including state of the art information on cardiopulmonary imaging, gastrointestinal imaging, genitourinary imaging, musculoskeletal imaging, neuroradiology/head and neck imaging, nuclear medicine and molecular imaging, pediatric imaging, vascular and interventional radiology, and women's imaging.

INDEXING/ABSTRACTING

The *WJR* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJR* as 0.51.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Venkatesh Mani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
December 28, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Radiology

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

World J Radiol 2021 December 28; 13(12): 371-379

DOI: 10.4329/wjr.v13.i12.371

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Retrospective Study

Prevalence of hypercoagulable states in stented thrombotic iliac vein compression syndrome with comparison of re-intervention and anticoagulation regimens

Peyton Cramer, Cheryl Mensah, Maria DeSancho, Anuj Malhotra, Ronald Winokur, Andrew Kesselman

ORCID number: Peyton Cramer 0000-0003-1048-3555; Cheryl Mensah 0000-0001-5305-8618; Maria DeSancho 0000-0001-9239-5131; Anuj Malhotra 0000-0002-8464-2857; Ronald Winokur 0000-0002-7366-7530; Andrew Kesselman 0000-0002-5286-7912.

Author contributions: Cramer P and Kesselman A designed the research study and performed the research; Cramer P, Mensah C, Desancho M, Malhotra A, Winokur R, and Kesselman A analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Weill Cornell Medicine Institutional Review Board, No. 20-03021729.

Informed consent statement: Informed consent was waived for this study by the institutional review board.

Conflict-of-interest statement: There is no conflict-of-interest.

Data sharing statement: No additional data available.

Peyton Cramer, Anuj Malhotra, Andrew Kesselman, Department of Radiology, Division of Interventional Radiology, New York Presbyterian Hospital/Weill Cornell Medicine, New York, NY 10065, United States

Cheryl Mensah, Maria DeSancho, Department of Medicine, Division of Hematology-Oncology, New York Presbyterian Hospital/Weill Cornell Medicine, New York, NY 10065, United States

Ronald Winokur, Department of Radiology, Division of Interventional Radiology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania 19107, United States

Corresponding author: Peyton Cramer, MD, Doctor, Department of Radiology, Division of Interventional Radiology, New York Presbyterian Hospital/Weill Cornell Medicine, No. 501 Payson Pavilion 25 E. 68th St., New York, NY 10065, United States. pmc9010@nyp.org

Abstract

BACKGROUND

Endovascular therapy is playing an increasing role in the treatment of iliofemoral venous disease. Iliac stent patency is multifactorial, and current management is based on best clinical practices, varying by institution.

AIM

To evaluate how thrombophilia influences management and outcomes of patients who undergo venous stenting for thrombotic iliac vein compression syndromes.

METHODS

A retrospective observational analysis was performed on 65 patients with thrombotic iliac vein compression syndrome that underwent common iliac vein (CIV) stenting between December 2013 and December 2019 at a large academic center. Search criteria included CIV stenting and iliac vein compression. Non-thrombotic lesions and iliocaval thrombosis and/or occlusions were excluded. A total of 65 patients were selected for final analysis. Demographic information, procedural data points, and post-procedural management and outcomes were collected. Statistical analyses included Fisher's exact and Chi-square tests to compare discrete variables and the Wilcoxon rank-sum test to compare continuous variables between thrombophilia positive and negative patients.

Country/Territory of origin: United States

Specialty type: Radiology, nuclear medicine and medical imaging

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

Peer-review model: Single blind

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Received: February 10, 2021
Peer-review started: February 10, 2021
First decision: October 17, 2021
Revised: November 25, 2021
Accepted: December 9, 2021
Article in press: December 9, 2021
Published online: December 28, 2021

P-Reviewer: Nayak S
S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

RESULTS
65 patients underwent successful balloon angioplasty and CIV stenting. Of these patients, 33 (50.8%) underwent thrombophilia testing, with 16 (48.5%) testing positive. Stent patency on ultrasound did not significantly differ between thrombophilia positive and negative patients at 1 mo (92.3% *vs* 81.3%, $P = 0.6$), 6 mo (83.3% *vs* 80%, $P > 0.9$), or 12 mo (77.8% *vs* 76.9%, $P = 0.8$). Immediately after stent placement, thrombophilia patients were more likely to be placed on dual therapy (aspirin and anticoagulation) or triple therapy (aspirin, clopidogrel, and anticoagulation) (50% *vs* 41.2%, $P > 0.9$), and remain on dual therapy at 6 mo (25% *vs* 12.5%, $P = 0.5$) and 12 mo (25% *vs* 6.7%, $P = 0.6$). There was no significant difference in re-intervention rates (25% *vs* 35.3%, $P = 0.7$) or number of re-interventions (average 2.3 *vs* 1.3 per patient, $P = 0.4$) between thrombophilia positive and negative patients.

CONCLUSION
Half of patients with stented thrombotic iliac vein compression syndrome and thrombophilia testing were positive. The presence of thrombophilia did not significantly impact stent patency or re-intervention rates.

Key Words: Thrombophilia; Iliac vein compression syndrome; Iliac vein stent; May Thurner; Anticoagulation; Endovascular

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Endovascular therapy is playing an increasing role in the treatment of iliofemoral venous disease. Iliac stent patency is multifactorial, and current management is based on best clinical practices. Despite an underlying anatomic venous abnormality, half of our patient cohort with stented thrombotic iliac vein compression syndrome tested positive for thrombophilia. The presence of thrombophilia did not demonstrate a statistically significant difference in stent patency rates or re-intervention rates.

Citation: Cramer P, Mensah C, DeSancho M, Malhotra A, Winokur R, Kesselman A. Prevalence of hypercoagulable states in stented thrombotic iliac vein compression syndrome with comparison of re-intervention and anticoagulation regimens. *World J Radiol* 2021; 13(12): 371-379
URL: https://www.wjgnet.com/1949-8470/full/v13/i12/371.htm
DOI: https://dx.doi.org/10.4329/wjr.v13.i12.371

INTRODUCTION

Iliofemoral vein thrombosis accounts for approximately 25% of all deep vein thrombosis and is associated with an increased risk of embolic and post-thrombotic complications[1]. Anticoagulation is the standard of care for the treatment of symptomatic acute deep vein thrombosis. However, despite appropriate anticoagulant therapy, the post-thrombotic syndrome (PTS) remains a frequent complication seen in 30% to 50% of patients diagnosed with iliofemoral deep vein thrombosis. The clinical manifestations of PTS include pain, swelling, heaviness, fatigue, itching, or cramping of the affected leg[1-3]. To reduce the burden of post-thrombotic symptoms, endovascular approaches with thrombolysis, thrombectomy, balloon angioplasty and stenting are being increasingly utilized in centers with expertise in these procedures[4-7]. The current C-TRACT trial is further investigating the role of endovascular intervention for chronic iliac vein obstruction. Guidelines for therapeutic anticoagulation after iliocaval stent placement remain variable by institution, however long-term anticoagulation is often recommended in patients with underlying thrombophilia[8].

Thrombophilia is an inherited or acquired condition that predisposes a person to develop a thrombotic event. Thrombophilia screening should only be done if the discovery of the thrombophilia will require extending the duration of the anticoagulation treatment. Conversely, if a thrombotic event occurred in the presence of a major

transient risk factor, thrombophilia screening should not be performed. Whether or not the presence of an underlying thrombophilia increases the risk of recurrent thrombosis, particularly in-stent thrombosis in patients that have undergone venous interventional procedures, remains unknown[9]. Therefore, we sought out to identify the prevalence of thrombophilias in patients with thrombotic iliac vein compression syndrome who underwent venous stenting. We also compared if the presence of thrombophilia influenced post-procedure antithrombotic regimens, stent patency and re-intervention rates.

MATERIALS AND METHODS

The institutional review board approved this study with waiver of informed consent. We performed a retrospective review of electronic medical records at a large academic medical center from December 2013 to December 2019. Search criteria included common iliac vein (CIV) stenting and iliac vein compression. Non-thrombotic lesions and iliocaval thrombosis and/or occlusions were excluded. A total of 65 patients were selected for final analysis.

Medical records were reviewed for demographic information, procedural data points, and post-procedural management and outcomes. Procedural data points included pre-intervention venous patency, stent location, stent type and diameter, and any additional endovascular procedures performed at that time. Post-procedural outcomes included subjective clinical symptom improvement, medication regimen and duration, stent patency on imaging, and re-intervention requirement. Types of antithrombotic therapy included antiplatelet, anticoagulation, single antiplatelet and anticoagulation (dual therapy), or dual antiplatelet agents and anticoagulation (triple therapy). Hematology consultations with or without thrombophilia evaluations were also reviewed. Statistical analyses included Fisher's exact and Chi-square tests to compare discrete variables and the Wilcoxon rank-sum test to compare continuous variables between thrombophilia positive and negative patients.

RESULTS

Baseline demographics are summarized in Table 1. Our patient population included 38 (58.5%) males and 27 (41.5%) females. Clinical symptoms included lower extremity swelling (n = 57, 87.7%), pain (n = 44, 67.7%), venous stasis ulceration (n = 7, 10.8%), varicose veins (n = 3, 4.6%), and pelvic pain (n = 2, 3.1%). Venous thromboembolism histories were reviewed for high risk features suspicious for thrombophilia; 24 (36.9%) experienced their first venous thrombosis (VTE) at a young age (less than 40 years old), 12 (18.5%) had a strong family history of thrombosis, and 16 (24.6%) were unprovoked.

A total of 33 (50.8%) underwent thrombophilia testing, with 16 (48.5%) testing positive. There were ten patients with Factor V Leiden heterozygous mutations (G1691A), four with antiphospholipid antibodies (three lupus anticoagulant, one anticardiolipin antibody), one prothrombin gene mutation G20210A, one antithrombin deficiency, and one protein S deficiency. Only one patient had two concomitant thrombophilias, comprising Factor V Leiden and lupus anticoagulant.

Procedure Details

Procedure details are summarized in Table 2. All 65 subjects included in this study underwent venography, balloon angioplasty, and CIV stenting. The majority of interventions were left-sided (n = 50, 76.9%) with stenting extending into the external iliac vein (n = 54, 83.1%) and common femoral vein (n = 45, 69.2%).

Procedure Outcomes

Technical success, defined by CIV stent placement and clearance of thrombus burden, was achieved in 65 (100%) patients. Clinical success, defined by patient reported symptom improvement, was achieved in 14 (87.5%) thrombophilia positive, 12 (70.6%)

Table 1 Baseline demographics

Variable	Summary (*n* = 65)
Median age in years (interquartile range)	54 (41-63)
Median BMI in kg/m^2 (interquartile range)	28 (25.1-32.7)
Gender	
Male	38 (58.5%)
Female	27 (41.5%)
Clinical symptoms	
Lower extremity swelling	57 (87.7%)
Lower extremity pain	44 (67.7%)
Venous stasis ulceration	7 (10.8%)
Varicose veins	3 (4.6%)
Pelvic pain	2 (3.1%)
Symptomatic side	
Left	49 (75.4%)
Right	14 (21.5%)
Bilateral	2 (3.1%)
Thrombophilia risk factor	
Young age (< 40 yr)	24 (35.9%)
Family history	12 (18.5%)
Unprovoked	16 (24.6%)
VTE provoking factor	
Prolonged immobilization	15 (23.1%)
Malignancy	13 (20.0%)
Recent surgery	5 (7.7%)
Trauma	5 (7.7%)
Pregnancy	7 (14.6%)
Hormonal supplement	4 (6.2%)
None	16 (24.6%)

BMI: Body mass index; VTE: Venous thrombosis.

thrombophilia negative, and 21 (65.6%) untested. Median follow-up duration was 14 mo.

Antithrombotic regimens were reviewed at post-procedure day 1 (n = 65), 6 mo (n = 61), and 12 mo (n = 57). The day after stent placement, 2 (3.1%) patients were on single antiplatelet, 34 (52.3%) patients were on anticoagulation, 17 (26.2%) patients were on dual therapy, 11 (16.9%) patients were on triple therapy, and 1 (1.5%) patient was off antithrombotic medication. At 6 mo, 3 (4.9%) patients were on single antiplatelet, 34 (55.7%) patients were on anticoagulation, 17 (27.9%) patients were on dual therapy, 0 (0%) patients were on triple therapy, and 7 (11.5%) patients were off antithrombotic medication. At 12 mo, 11 (19.3%) patients were on single antiplatelet, 26 (45.6%) were on anticoagulation, 9 (15.8%) patients were on dual therapy, 0 (0%) patients were on triple therapy, and 11 (19.3%) patients were off antithrombotic medication.

Post-stenting antithrombotic regimens are broken down by thrombophilia testing in Figures 1 and 2. Immediately after stent placement, thrombophilia patients were more likely to be placed on dual or triple therapy (50% *vs* 41.2%, $P > 0.9$) and remain on dual therapy at 6 mo (25% *vs* 12.5%, $P = 0.5$) and 12 mo (25% *vs* 6.7%, $P = 0.6$) compared to thrombophilia negative patients. Stent patency on ultrasound did not significantly differ between thrombophilia positive and negative patients at 1 mo (92.3% *vs* 81.3%, P

Table 2 Procedure details

Variable	Summary (*n* = 65)
Pre-procedure CIV patency	
Stenosis	47 (72.3%)
Occlusion	16 (24.6%)
In-stent thrombosis	2 (3.1%)
Stent location	
Left CIV	50 (76.9%)
Right CIV	11 (16.9%)
Bilateral CIV	4 (6.2%)
Stent type	
Wallstent	51 (78.5%)
Venovo	9 (13.8%)
Smart	2 (3.1%)
Vici	3 (4.6%)
CIV stent balloon dilation diameter (mm)	
12	1 (1.5%)
14	14 (21.5%)
16	28 (43.1%)
18	19 (29.2%)
20	3 (4.6%)
Additional stented segments	
External iliac vein	54 (83.1%)
Common femoral vein	45 (69.2%)
Simultaneous endovascular interventions	
Thrombolysis	25 (38.5%)
Thrombectomy	17 (26.2%)
CIV filter retrieval	3 (4.6%)

CIV: Common iliac vein.

= 0.6), 6 mo (83.3% *vs* 80%, $P > 0.9$), or 12 mo (77.8% *vs* 76.9%, $P = 0.8$).

Stent thrombosis occurred in 2 (12.5%) thrombophilia positive and 4 (23.5%) thrombophilia negative patients. The median time to stent thrombosis was longer in thrombophilia patients (1.1 mo *vs* 0.5 mo). At the time of stent thrombosis, 3 (50%) patients were on anticoagulation, 1 (16.7%) patient was on dual therapy, and 2 (33.3%) patients were off antithrombotic medication. Following thrombosis, all patients were transitioned to anticoagulation alone ($n = 3$) or dual therapy ($n = 3$). Anticoagulation therapies included full-dose direct oral anticoagulants, half-dose direct oral anticoagulants, and enoxaparin. There was no significant difference in re-intervention rates (25% *vs* 35.3%, $P = 0.7$) or number of re-interventions (average 2.3 *vs* 1.3 per patient, $P = 0.4$) between thrombophilia positive and negative patients, as seen in Table 3.

Bleeding complications from antithrombotic medications were seen in 14 (21.5%) patients, including ecchymoses, hematuria, rectal bleeding, epistaxis, and menorrhagia. None of these events required medication cessation or intervention. Of the patients that experienced bleeding complications, 7 (50.0%) were on anticoagulation, 4 (28.6%) were on dual therapy, and 3 (21.4%) were on triple therapy.

Table 3 Complications by thrombophilia testing

Thrombophilia work-up (*n* = 33)	Positive (*n* = 16)	Negative (*n* = 17)
Clinical success		
Stent patency	14 (87.5%)	12 (70.6%)
1 mo	12 of 13 (92.3%)	13 of 16 (81.3%)
6 mo	10 of 12 (83.3%)	12 of 15 (80%)
12 mo	7 of 9 (77.8%)	10 of 13 (76.9%)
Stent thrombosis	2 (12.5%)	4 (23.5%)
Anticoagulated during stent thrombosis	1 of 2 (50%)	2 of 4 (50%)
Re-intervention rates	4 (25%)	6 (35.3%)
Number of re-interventions		
1	50%	67%
2	0%	33%
3	25%	0%
4	25%	0%

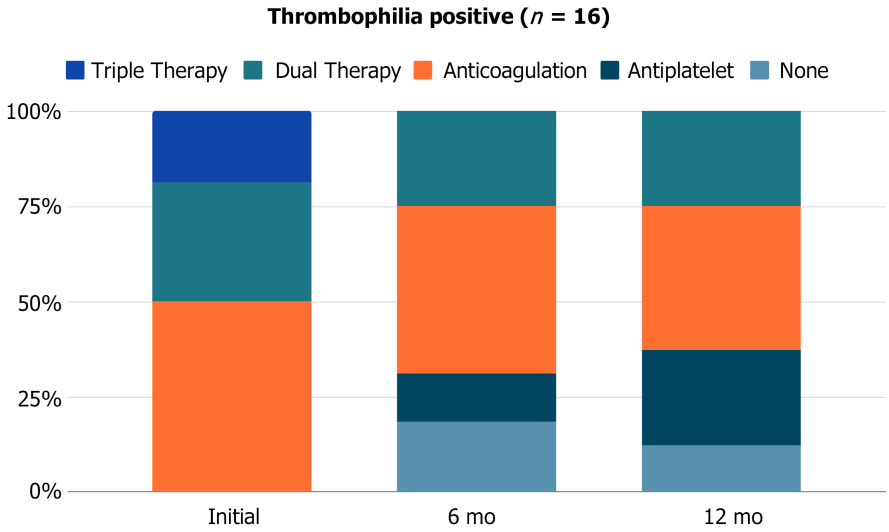


Figure 1 Post-stenting antithrombotic regimens in thrombophilia positive patients at day 1 (*n* = 16), 6 mo (*n* = 16), and 12 mo (*n* = 16).

DISCUSSION

Endovascular therapy is playing an increasing role in the treatment of iliofemoral venous disease. Iliac stent patency is multifactorial, and current management is based on best clinical practices, varying by institution[11].

Diagnostic thrombophilia testing is recommended in patients with idiopathic or recurrent VTE, first VTE at a young age (< 40 years), VTE in the setting of a strong family history or VTE in atypical locations. There is no single laboratory test available to identify all thrombophilias and results can be affected by a variety of clinical conditions and drugs. Based on this premise, thrombophilia testing should only be performed by a coagulation specialist who knows when to do the screening, provide accurate interpretation of the results and educate the patient[9]. Our cohort demonstrated that despite having an anatomic consideration for increased thrombosis risk, 48.5% of patients who undergo venous stenting for thrombotic iliac vein compression syndrome had an underlying thrombophilia when testing was performed. This result is higher than the 32% rate of positive thrombophilia identified in 4494 patients with symptomatic VTE in the RIETE registry[12] and similar to other studies ranging from 55% to 61%[13,14]. Therefore, the decision for thrombophilia testing should be discussed by a multidisciplinary team and considered only when it

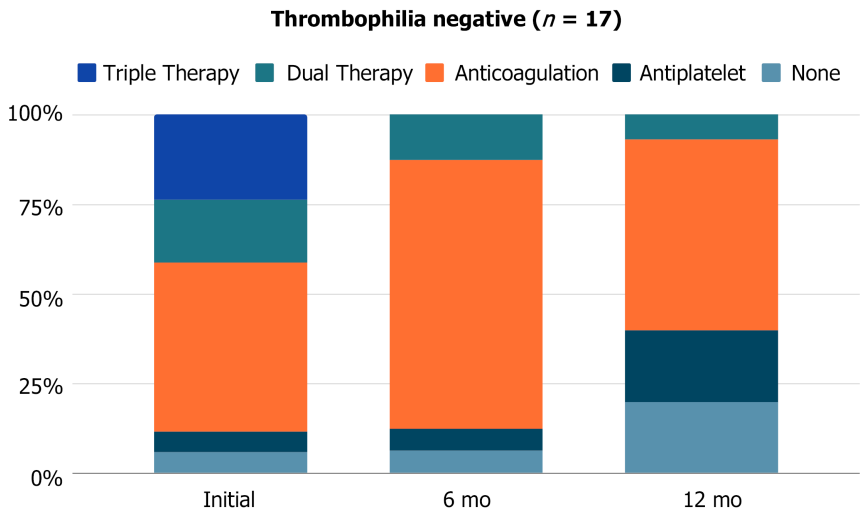


Figure 2 Post-stenting antithrombotic regimens in thrombophilia negative patients at day 1 (*n* = 17), 6 mo (*n* = 16), and 12 mo (*n* = 15).

will impact post-procedural medical management.

The extent of influence of inherited thrombophilia on the risk of VTE recurrence remains controversial[10]. In our cohort, stent patency and re-intervention rates were not significantly different between thrombophilia positive and negative patients. In all patients with thrombotic iliac vein compression syndrome, antithrombotic compliance and close imaging follow-up are necessary to optimize stent patency and prevent or delay re-intervention. The median time to stent thrombosis was less than one month, emphasizing the importance of the immediate post-procedural period. Immediately after stent placement, thrombophilia patients were more likely to be placed on dual or triple therapy and remain on dual therapy at 6 mo and 12 mo, although this finding was not statistically significant given the smaller sample size. Following thrombosis, all patients were transitioned to long-term anticoagulation or dual therapy, including full-dose or half-dose direct oral anticoagulants.

There is controversy around whether venous stent patency is best maintained by combined antiplatelet and anticoagulation therapy *vs* anticoagulation alone[15]. Antiplatelet agents did not appear to significantly increase the bleeding risk in our study, with almost half of thrombophilia patients remaining on long term antiplatelet medications and more than half on anticoagulation. The long-term management following venous stenting in thrombotic iliac vein compression syndrome is complex and patient specific. Because there was no significant difference in stent patency or re-intervention rates amongst thrombophilia positive and negative patients, the need for thrombophilia testing should be individualized and only considered when it will impact post-procedural medical management.

This study has several limitations. First it is a single center retrospective design; second, there is provider bias in choosing antithrombotic regimens based on their presumed risk of thrombosis; and third, venous stent type and extent varied, introducing confounders. Moreover, given our small sample size, our study was underpowered to obtain statistical significance for subgroups and antithrombotic regimens. Future studies focusing on anticoagulation related to venous stenting in larger cohorts would be helpful. Larger prospective randomized control trials are needed.

CONCLUSION

Despite an underlying anatomic venous abnormality, in our cohort of patients that underwent thrombophilia testing in the setting of stented common iliac thrombosis, half tested positive for thrombophilia. The presence of thrombophilia did not demonstrate a statistically significant difference in stent patency rates or re-intervention rates. The need for thrombophilia workup should be individualized and discussed by multidisciplinary teams and considered only when it will impact post-procedural medical management.

ARTICLE HIGHLIGHTS

Research perspectives

The long-term management following venous stenting in thrombotic iliac vein compression syndrome is complex and patient specific. Because there was no significant difference in stent patency or re-intervention rates amongst thrombophilia positive and negative patients, the need for thrombophilia testing should be individualized and only considered when it will impact post-procedural medical management. Future studies focusing on anticoagulation related to venous stenting in larger cohorts would be helpful.

Research conclusions

Half of patients with stented thrombotic iliac vein compression syndrome and thrombophilia testing were positive. The presence of thrombophilia did not demonstrate a significant difference in stent patency or re-intervention rates.

Research results

65 patients underwent successful balloon angioplasty and common iliac vein (CIV) stenting. Stent patency on ultrasound did not significantly differ between thrombophilia positive and negative patients at 1 mo (92.3% *vs* 81.3%, $P = 0.6$), 6 mo (83.3% *vs* 80%, $P > 0.9$), or 12 mo (77.8% *vs* 76.9%, $P = 0.8$). Immediately after stent placement, thrombophilia patients were more likely to be placed on dual therapy (aspirin and anticoagulation) or triple therapy (aspirin, clopidogrel, and anticoagulation) (50% *vs* 41.2%, $P > 0.9$), and remain on dual therapy at 6 mo (25% *vs* 12.5%, $P = 0.5$) and 12 mo (25% *vs* 6.7%, $P = 0.6$). There was no significant difference in re-intervention rates (25% *vs* 35.3%, $P = 0.7$) or number of re-interventions (average 2.3 *vs* 1.3 per patient, $P = 0.4$) between thrombophilia positive and negative patients.

Research methods

A retrospective observational analysis was performed on 65 patients with thrombotic iliac vein compression syndrome that underwent CIV stenting at a large academic center. Non-thrombotic lesions and iliocaval thrombosis and/or occlusions were excluded. Demographic information, procedural data points, and post-procedural management were compared between thrombophilia positive and negative patients.

Research objectives

To evaluate the prevalence and compare how thrombophilia influences management and outcomes of patients who undergo venous stenting for thrombotic iliac vein compression syndromes.

Research motivation

Guidelines for therapeutic anticoagulation after iliocaval stent placement remain variable by institution, however long-term anticoagulation is often recommended in patients with underlying thrombophilia. Whether or not the presence of an underlying thrombophilia increases the risk of recurrent thrombosis, particularly in-stent thrombosis in patients that have undergone venous interventional procedures, remains unknown.

Research background

Iliofemoral vein thrombosis accounts for approximately 25% of all deep vein thrombosis and is associated with an increased risk of embolic and post-thrombotic complications. Anticoagulation is the standard of care for the treatment of symptomatic acute deep vein thrombosis. However, despite appropriate anticoagulant therapy, the post-thrombotic syndrome remains a frequent complication seen in 30% to 50% of patients diagnosed with iliofemoral deep vein thrombosis. To reduce the burden of post-thrombotic symptoms, endovascular therapy is playing an increasing role in the treatment of iliofemoral venous disease.

ACKNOWLEDGEMENTS

We would like to thank Charlene Thomas for her support with our statistical analysis.

REFERENCES

1 **Nyamekye I**, Merker L. Management of proximal deep vein thrombosis. *Phlebology* 2012; **27**: 61-72 [PMID: 22457306 DOI: 10.1258/phleb.2012.012s37]

2 **Kahn SR**, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, Gupta DK, Prandoni P, Vedantham S, Walsh ME, Weitz JI; American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2014; **130**: 1636-1661 [PMID: 25246013 DOI: 10.1161/CIR.0000000000000130]

3 **Vedantham S**, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ, Magnuson E, Razavi MK, Comerota AJ, Gornik HL, Murphy TP, Lewis L, Duncan JR, Nieters P, Derfler MC, Filion M, Gu CS, Kee S, Schneider J, Saad N, Blinder M, Moll S, Sacks D, Lin J, Rundback J, Garcia M, Razdan R, VanderWoude E, Marques V, Kearon C; ATTRACT Trial Investigators. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. *N Engl J Med* 2017; **377**: 2240-2252 [PMID: 29211671 DOI: 10.1056/NEJMoa1615066]

4 **Kahn SR**, Julian JA, Kearon C, Gu CS, Cohen DJ, Magnuson EA, Comerota AJ, Goldhaber SZ, Jaff MR, Razavi MK, Kindzelski AL, Schneider JR, Kim P, Chaer R, Sista AK, McLafferty RB, Kaufman JA, Wible BC, Blinder M, Vedantham S; ATTRACT Trial Investigators. Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord* 2020; **8**: 8-23 [PMID: 31843251 DOI: 10.1016/j.jvsv.2019.03.023]

5 **Kuetting D**, Luetkens J, Wolter K, Faron A, Kania A, Thomas D. Catheter-directed thrombectomy for highly symptomatic patients with iliofemoral deep venous thrombosis not responsive to conservative treatment. *Cardiovasc Intervent Radiol* 2020; **43**: 556-564 [DOI: 10.1007/s00270-020-02415-7]

6 **Mabud TS**, Cohn DM, Arendt VA, Jeon GS, An X, Fu J, Souffrant AD, Sailer AM, Shah R, Wang D, Sze DY, Kuo WT, Rubin DL, Hofmann LV. Lower Extremity Venous Stent Placement: A Large Retrospective Single-Center Analysis. *J Vasc Interv Radiol* 2020; **31**: 251-259 [PMID: 31542273 DOI: 10.1016/j.jvir.2019.06.011]

7 **Razavi MK**, Jaff MR, Miller LE. Safety and Effectiveness of Stent Placement for Iliofemoral Venous Outflow Obstruction: Systematic Review and Meta-Analysis. *Circ Cardiovasc Interv* 2015; **8**: e002772 [PMID: 26438686 DOI: 10.1161/CIRCINTERVENTIONS.115.002772]

8 **Mahnken AH**, Thomson K, de Haan M, O'Sullivan GJ. CIRSE standards of practice guidelines on iliocaval stenting. *Cardiovasc Intervent Radiol* 2014; **37**: 889-897 [PMID: 24633533 DOI: 10.1007/s00270-014-0875-4]

9 **Nakashima MO**, Rogers HJ. Hypercoagulable states: an algorithmic approach to laboratory testing and update on monitoring of direct oral anticoagulants. *Blood Res* 2014; **49**: 85-94 [PMID: 25025009 DOI: 10.5045/br.2014.49.2.85]

10 **Rybstein MD**, DeSancho MT. Hypercoagulable States and Thrombophilias: Risks Relating to Recurrent Venous Thromboembolism. *Semin Intervent Radiol* 2018; **35**: 99-104 [PMID: 29872244 DOI: 10.1055/s-0038-1642037]

11 **Attaran RR**, Ozdemir D, Lin IH, Mena-Hurtado C, Lansky A. Evaluation of anticoagulant and antiplatelet therapy after iliocaval stenting: Factors associated with stent occlusion. *J Vasc Surg Venous Lymphat Disord* 2019; **7**: 527-534 [PMID: 31203859 DOI: 10.1016/j.jvsv.2019.01.058]

12 **Roldan V**, Lecumberri R, Muñoz-Torrero JF, Vicente V, Rocha E, Brenner B, Monreal M; RIETE Investigators. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. *Thromb Res* 2009; **124**: 174-177 [PMID: 19101711 DOI: 10.1016/j.thromres.2008.11.003]

13 **Caprini JA**, Goldshteyn S, Glase CJ, Hathaway K. Thrombophilia testing in patients with venous thrombosis. *Eur J Vasc Endovasc Surg* 2005; **30**: 550-555 [PMID: 16055356 DOI: 10.1016/j.evs.2005.05.034]

14 **Signorelli S**, Fiore V, Puccia G, Mastrosimone G, Anzaldi M. Thrombophilia in patients with lower limb deep vein thrombosis (LVDT) results of a monocentric survey on 103 consecutive outpatients. *Clin Appl Thromb Hemost* 2014; **20**: 589-593 [DOI: 10.1177/1076029612474716]

15 **Endo M**, Jahangiri Y, Horikawa M, Kaufman JA, Schenning RC, Kolbeck KJ, Barton RE, Ohuchi Y, Liang KW, Farsad K. Antiplatelet Therapy is Associated with Stent Patency After Iliocaval Venous Stenting. *Cardiovasc Intervent Radiol* 2018; **41**: 1691-1698 [PMID: 30120531 DOI: 10.1007/s00270-018-2062-5]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.