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

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

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of 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.

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

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

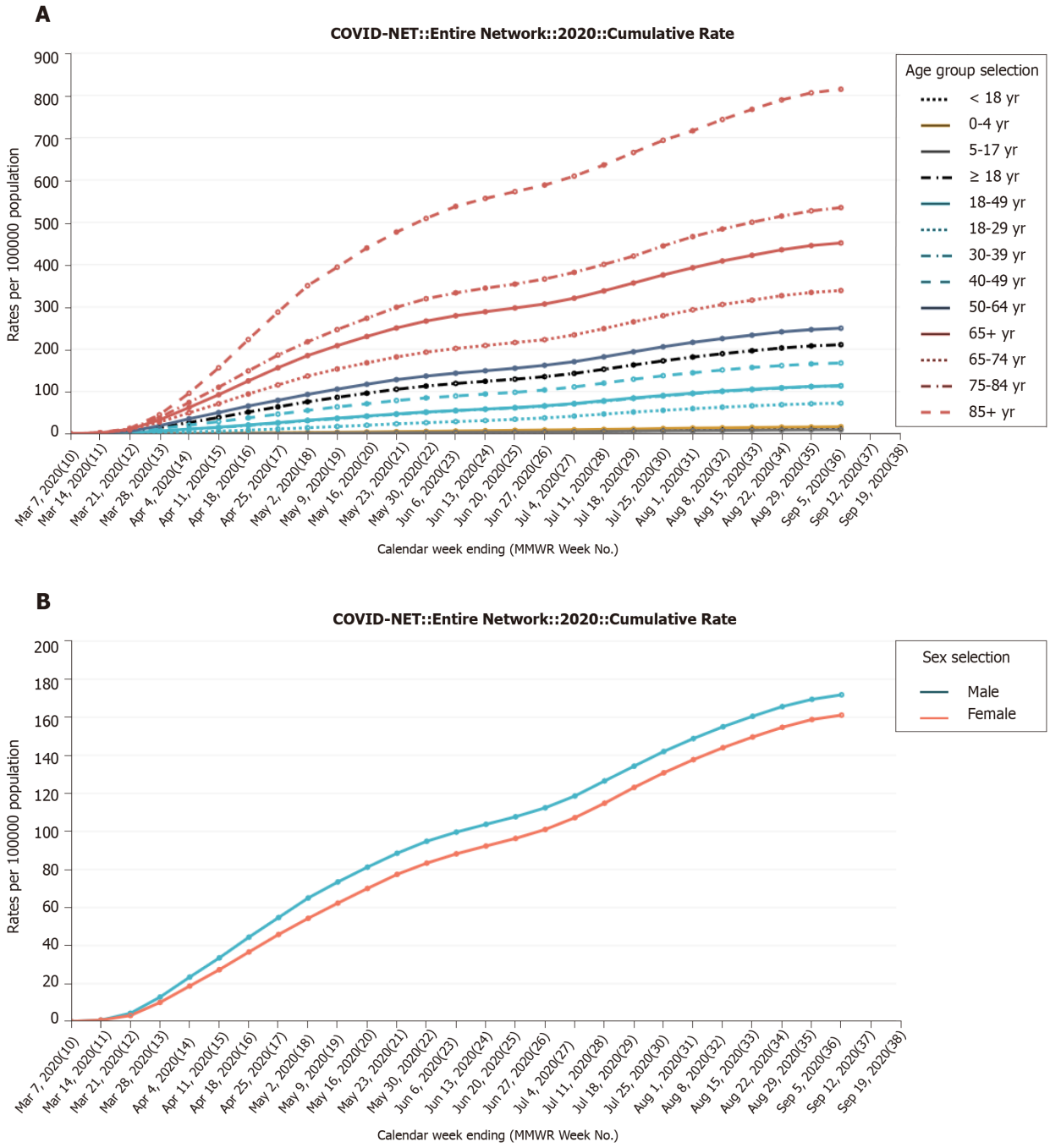

Figure 1 Cumulative rate of infection per 100000 population. A: In different age groups under the Coronavirus Disease-2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html); B: In gender-based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

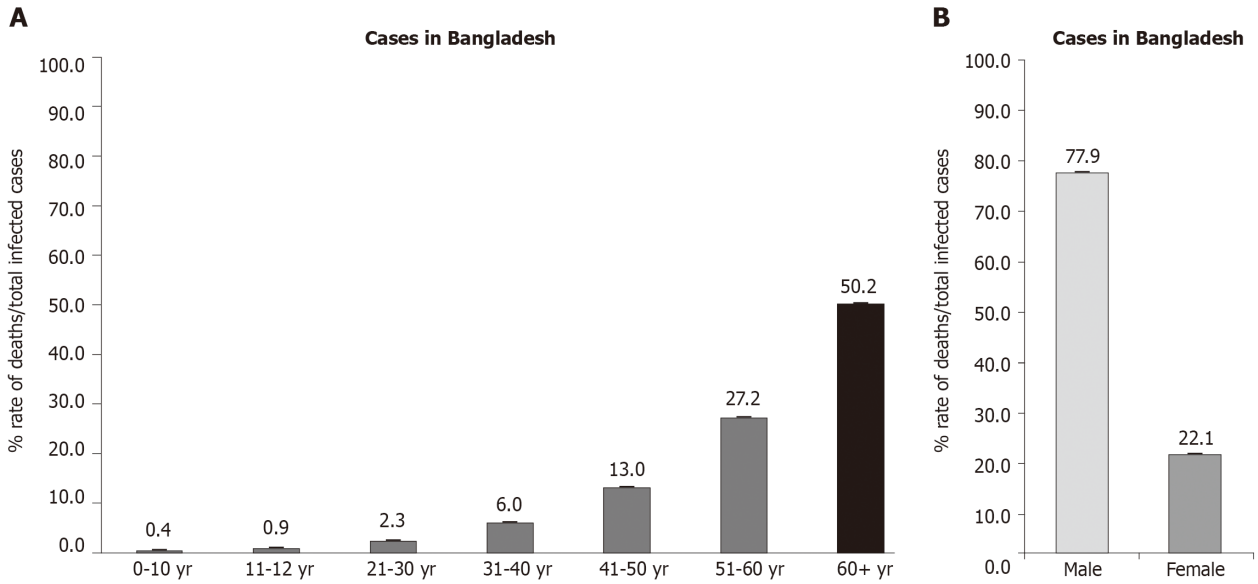

Figure 2 Percentage of rate of death per total infected cases. A: In different age groups in Bangladesh; B: In gender-based disparity in Bangladesh.

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

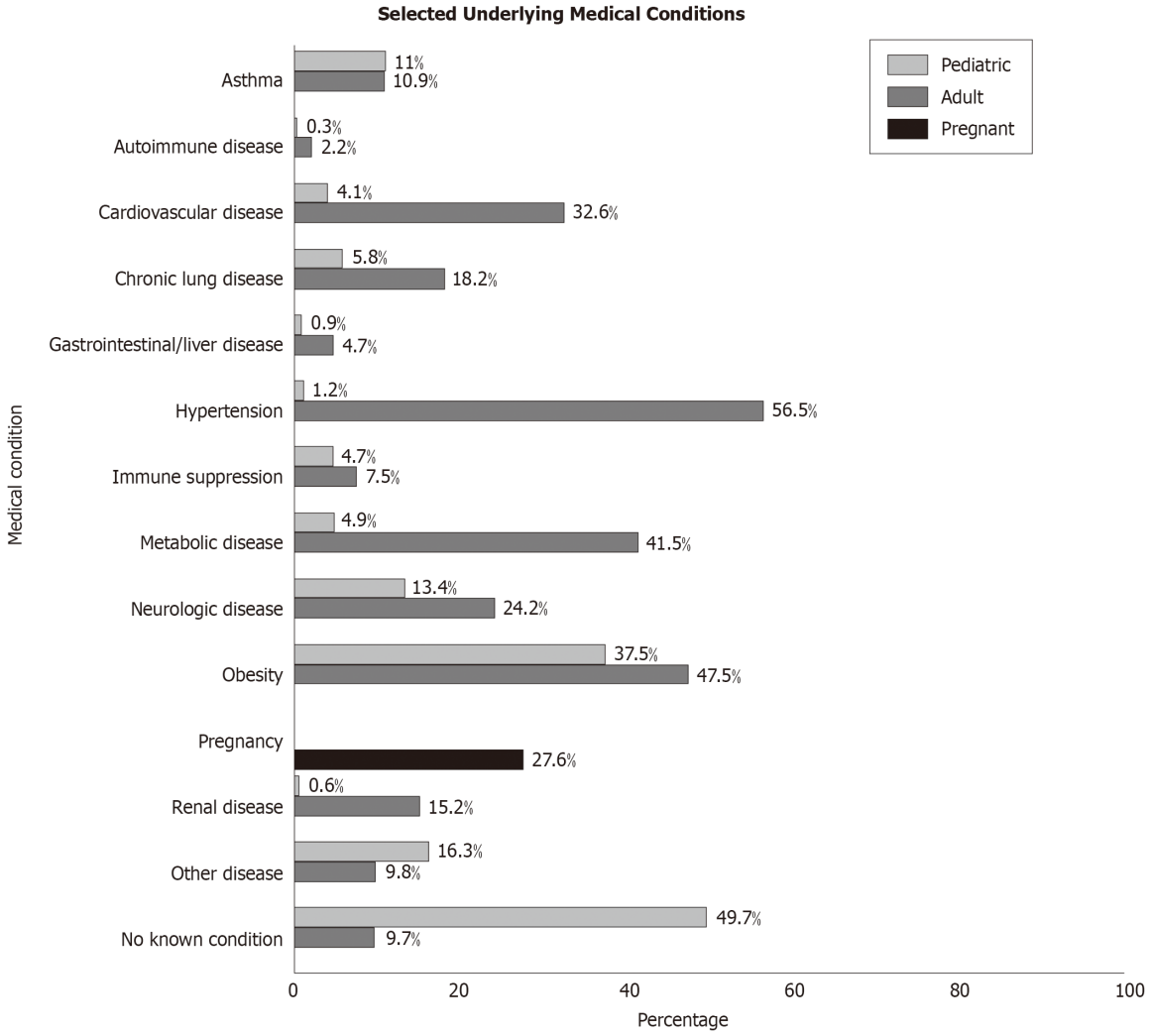

Figure 3 Percentage of selected underlying medical conditions under the coronavirus disease-2019-associated hospitalization surveillance network hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html).

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

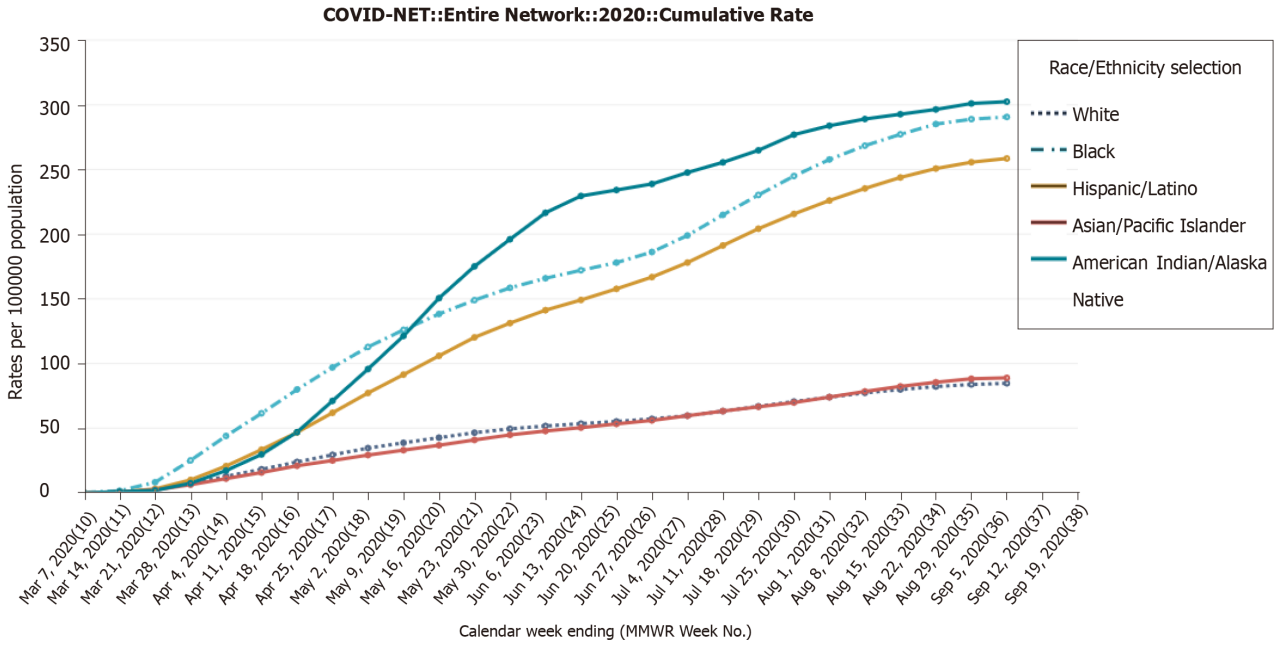

Figure 4 Cumulative rate of infection per 100000 population in baseline characteristics under the coronavirus disease-2019-associated hospitalization surveillance network hospitalization data (by September 5, 2020; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html).

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].

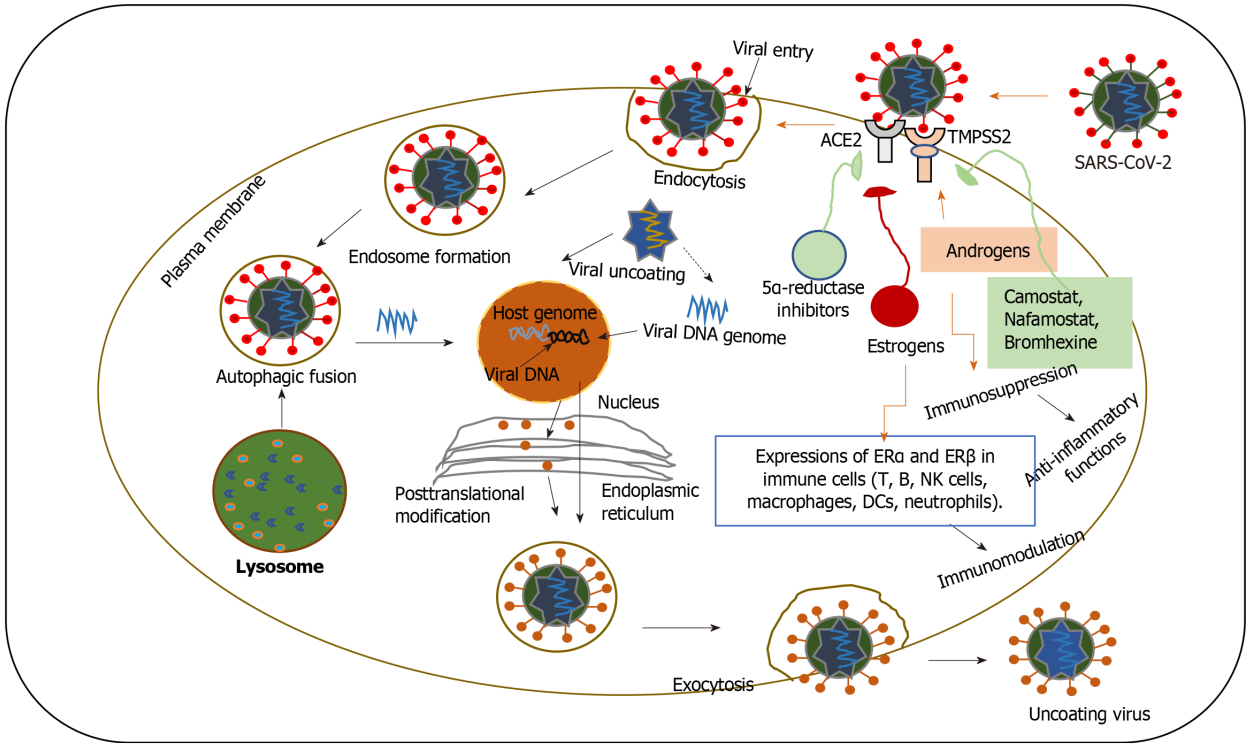

Figure 5 The role of sex hormones and hormone therapies in modulating severe acute respiratory syndrome coronavirus 2 entry in host cells and immune response. The replication cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) begins when the virion binds to the host cell receptor, 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.

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

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).

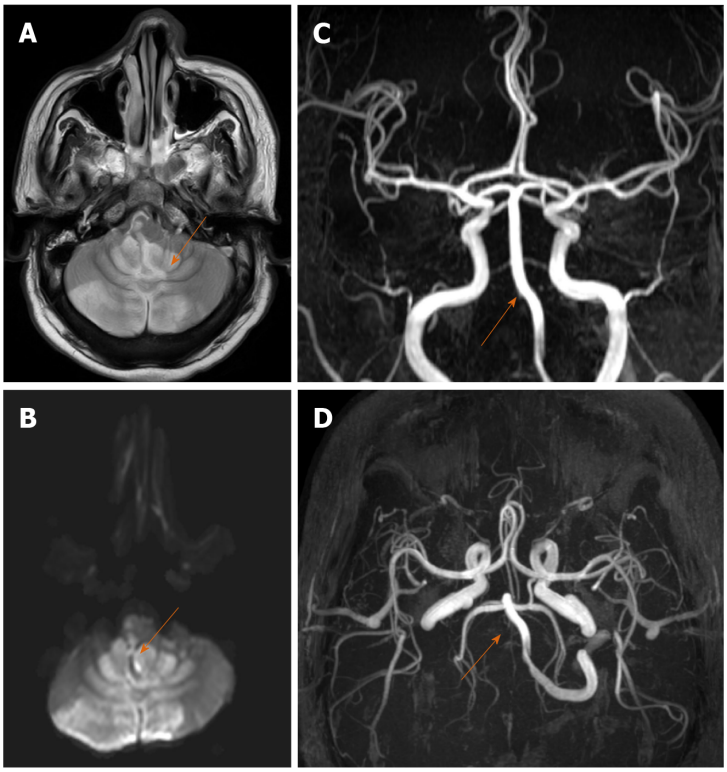

Figure 1 A 35-year-old male with posterior circulation stroke. A and B: Axial sections of magnetic resonance imaging brain (T2W, diffusion sequences) show areas of high signal in both cerebellar hemispheres, vermis and brainstem suggestive of acute infarcts; C and D: Magnetic resonance artery coronal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

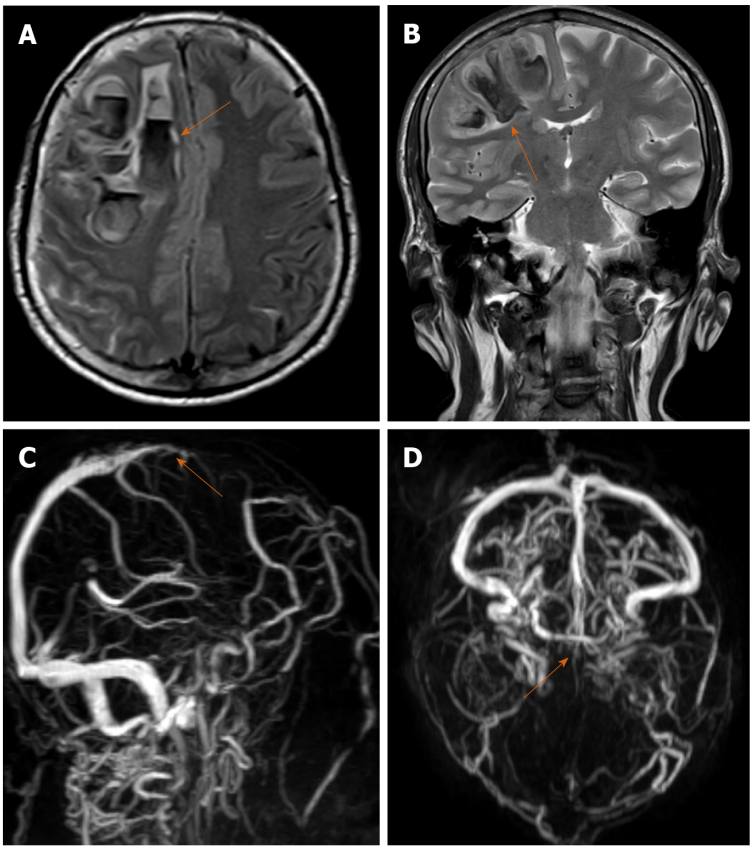

Figure 2 A 61-year-old male with Dural venous thrombosis. A and B: Axial and coronal sections of magnetic resonance imaging brain (T2WI sequence) show acute hemorrhage (arrow) in right frontal lobe with left sided midline shift; C and D: Magnetic resonance venography sagittal oblique and axial sections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

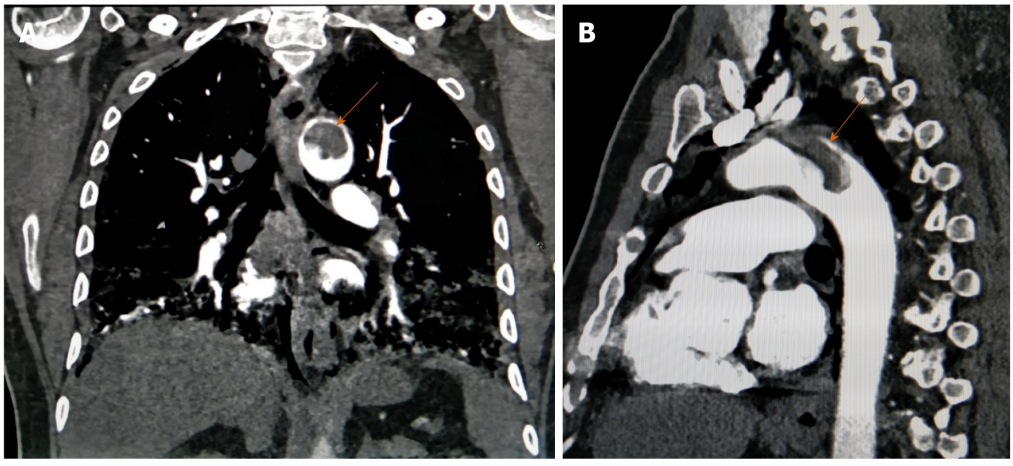

Figure 3 A 64-year-old male with aortic mural thrombosis. A and B: Coronal and sagittal sections of arterial phase of contrast-enhanced computed tomography thorax show pedunculated thrombus in aortic arch suggestive of aortic mural thrombus.

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

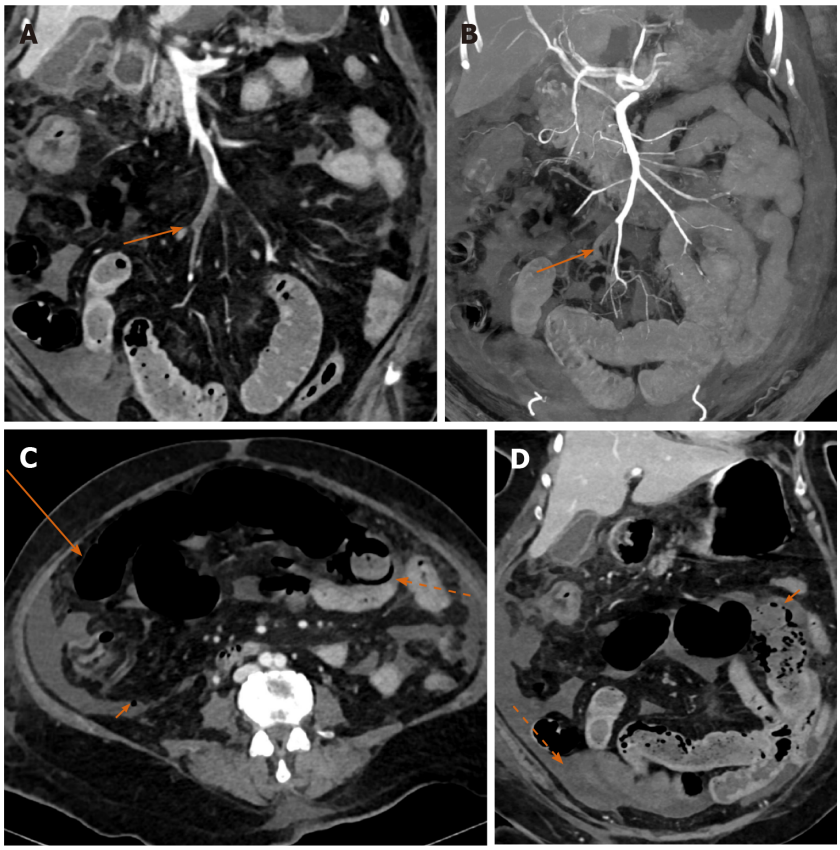

Figure 4 A 65-year-old female with acute mesenteric ischemia. A: Coronal reformatted image of contrast-enhanced computed tomography (CECT) abdomen shows filling defects (orange arrow) in ileal branches of superior mesenteric artery suggestive of thrombosis; B: Coronal reformatted image of CECT abdomen 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

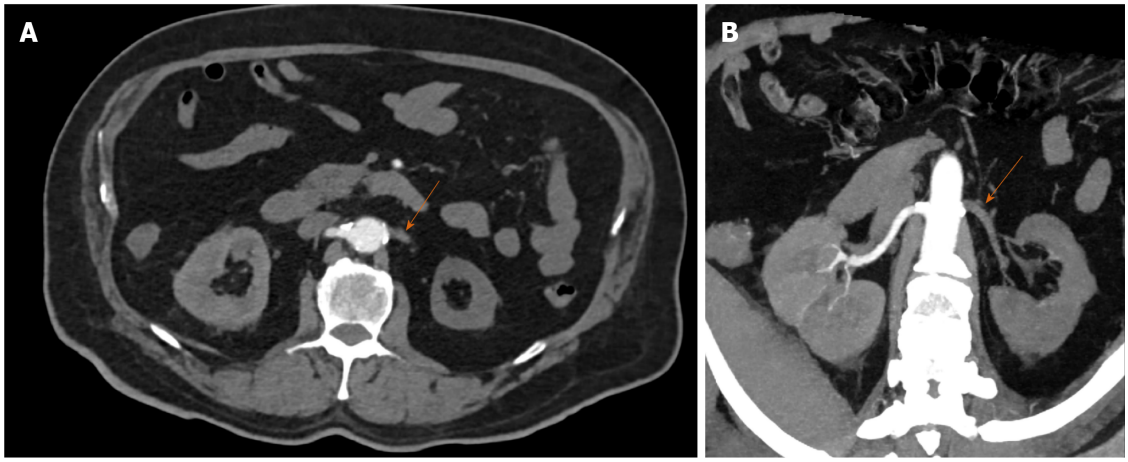

Figure 5 A 74-year-old male with renal artery thrombosis. A and B: Axial baseline and oblique coronal reformatted maximum intensity projection images of arterial phase contrast-enhanced computed tomography images showing hypodense filling defect involving left renal artery from ostium to hilum and its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

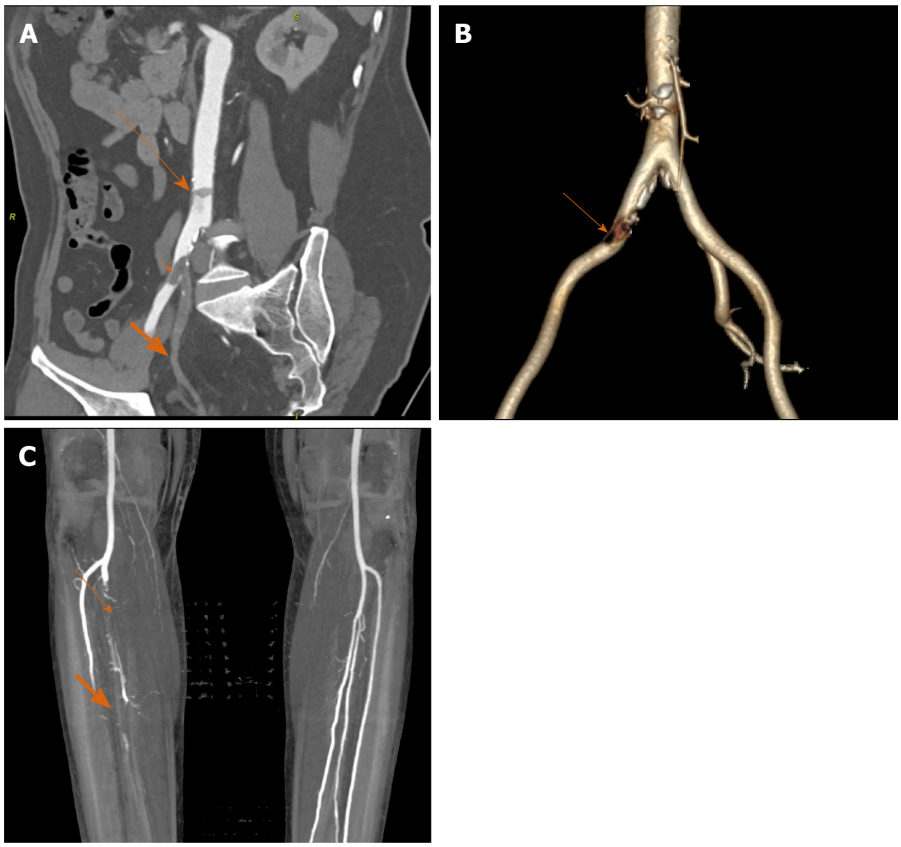

Figure 6 A 51-year-old male with peripheral arterial disease. A: Coronal oblique reformatted image of contrast-enhanced computed tomography abdomen shows mall mural thrombus in abdominal aorta (long arrow); and another partially occluding thrombus at right common iliac artery (short arrow) bifurcation 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

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

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

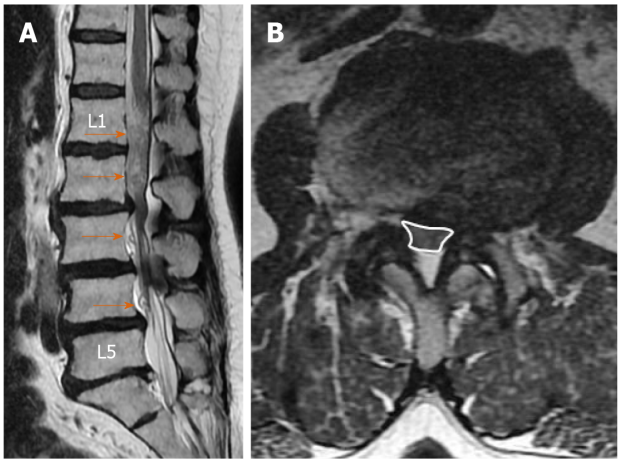

Figure 1 Seventy-one-year-old female patient with lumbar spondylosis. A: Redundant nerve roots (arrows) secondary to the stenosis at both the superior and inferior of the stenosis at the L2-L3 level, which are more prominent at the superior, are shown; B: On the axial T2-weighted image, the cross-sectional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

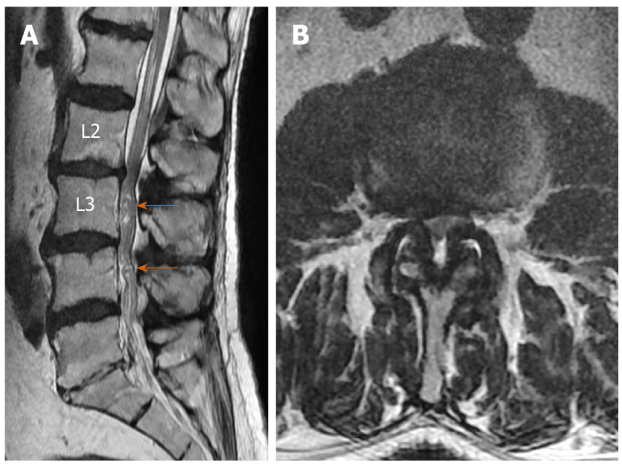

Figure 2 Seventy-one-year-old male patient with lumbar spondylosis. A: On the sagittal T2-weighted image, redundant nerve roots (arrows) secondary to the stenosis at L2-L3 level are shown at the inferior of stenosis level; B: On the axial T2-weighted image passing through L2-L3 intervertebral disc space 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).

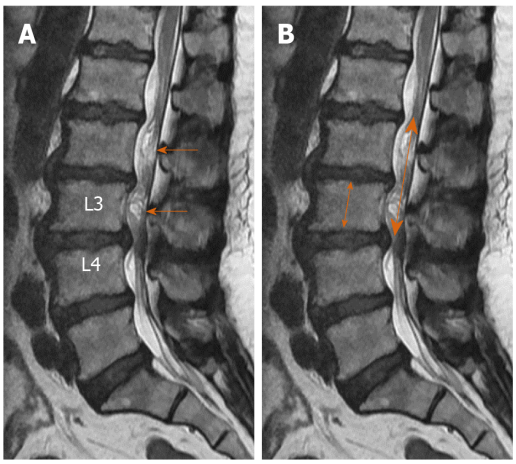

Figure 3 Forty-seven-year-old female patient with lumbar spondylosis. A: On the sagittal T2-weighted image, redundant nerve roots at the superior of the stenosis level secondary to the stenosis at the L3-L4 intervertebral disc space (arrows) are shown; B: Relative length was calculated by dividing the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

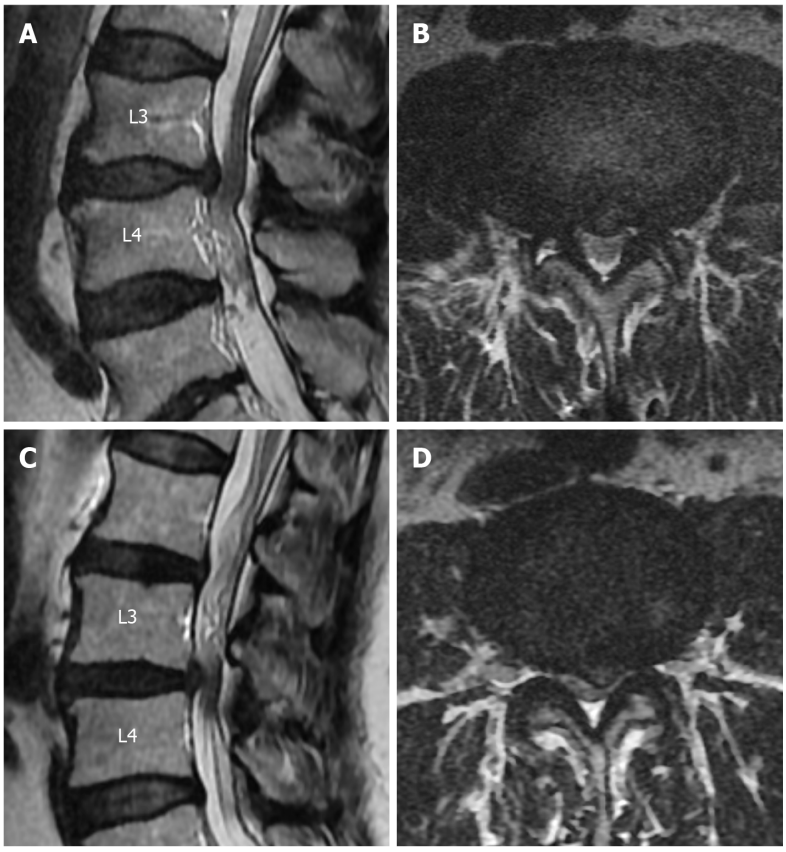

Figure 4 Soft and sharp margin types of disc herniation into the dural sac. A: On the sagittal T2-weighted image, soft margin disc herniation at the level of L3-L4 intervertebral disc space and redundant nerve roots at the inferior of the stenosis are shown; B: The axial T2-weighted images of soft margin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

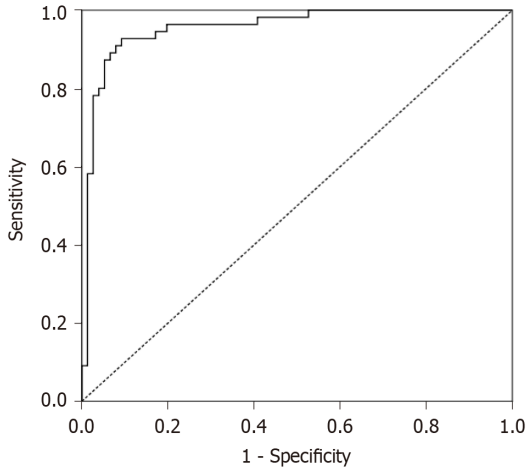

Figure 5 Receiver operating characteristic curve with a cut-off value of 55.22 mm² or less for the cross-sectional area of the dural sac.

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