Chapter

Severe Acute Respiratory Syndromes and Coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2)

Bradley Fevrier

Abstract

The current SARS-CoV-2 (coronavirus) outbreak has reached pandemic proportions with a large global imprint. In December 2019, COVID-19 was first reported in Wuhan, Hubei Province, China and has continued largely unabated. The SARS-CoV-2 (coronavirus) is much talked about currently; however, it is worth noting that there are several different coronaviruses known to man, with most of them being responsible for causing illness in animals. Seven (7) types of coronaviruses are identified as causing illnesses in humans. Of the seven human coronavirus infections, four involve mild upper respiratory tract complaints that produce slight symptoms of the common cold. Conversely, the other three human coronavirus infections present more severe consequences as recently demonstrated by the SARS-CoV-2. These deadly outbreaks of pneumonia can have consequences that are far-reaching and are global in nature. SARS-CoV was the first new viral pandemic of the 21st century. It had its beginnings in southern China during November 2002 having started mysteriously; It was contained in 2004 after having spread to five continents and thirty-three countries, infecting approximately 8000 people. MERS-CoV the virus that the causes Middle East respiratory syndrome (MERS) was first identified in 2012 in Saudi Arabia and Jordan and has since registered roughly 2,220 confirmed cases and 790 deaths.

Keywords: Coronavirus, SARS-CoV, CoVid-19, SARS-CoV-2, MERS-CoV, Pandemic

1. Introduction

Coronavirus (CoV) is one of the leading pathogens primarily targeting that the human respiratory system [1]. Earlier outbreaks of coronaviruses include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been formerly considered as a serious threat to public health [2]. The first iteration of coronavirus was identified in the mid-1960s and categorized into four separate subfamilies: α−/β−/γ−/δ-Coronavirus. Alpha and beta-coronaviruses predominantly causes infection in mammals, whereas gamma and delta-coronaviruses primarily infect birds [3]. A new contagious coronavirus is presently holding much of the worldwide population hostage. This virus,

SARS-CoV-2, which causes the COVID-19 disease, emerged in Hubei, China and has spread to most countries with ongoing devastating effects [4].

Since the era of the pneumonic plague, emergent respiratory infections have enthralled the scientific and Public communities' and more recently have manifested in popular films depicting airborne viral outbreaks [5]. This has led to deliberations pertaining to the possibility for respiratory spread of these infections [6]. Although numerous emerging agents can exhibit respiratory involvement, this chapter will focus on emerging pathogens that involve the respiratory system and focus on 3 agents that exhibit a range of characteristics of emerging diseases: SARS-CoV, MERS, and SARS-CoV-2.

2. SARS-CoV

2.1 Etiology, epidemiology, and clinical presentation

Severe acute respiratory virus (SARS) is a deadly pulmonary infection caused by the SARS coronavirus (SARS-CoV), first reported in Guangdong Province, China, in November 2002 [7]. The emergence of SARS-CoV signaled the first time the public, as well as numerous scientists, observed this cluster of viruses, and its potential to cause severe infections and death in humans [8]. By July 3, 2003, SARS global infections were 8439 cases of which 812 were fatal [9]. This prompted a full-bodied international response estimated at roughly 40 billion dollars which aided in containing the outbreak [10]. By the close 2004 there were no new reported cases [9, 10]. Genetic classification indicates that the introduction into the human population took place from civets or other mammals found in live-animal markets of China [9]. Furthermore, it is prevailingly considered that SARS-CoV originated in a colony of horseshoe bats in southern China, with civets acting as the intermediate amplifying and transmitting host to humans [11].

3. SARS-CoV infection in humans

SARS-CoV is an airborne virus transmissible between humans through small respiratory droplets, in a similar manner to influenza [6]. SARS-CoV can also be spread indirectly via surfaces that have been touched by someone who is infected with the virus, and by close interactions with infected individuals acting as so-called "super spreaders" [6]. The incubation period of SARS-CoV is generally 2–7 days, but infected persons may present symptoms as long as 10 days after infection [6]. Several epidemiological studies conducted during the outbreak identified numerous deaths occurring disproportionately among the elderly, and individuals who were immunosuppressed. At the onset of SARS-CoV illness, patients present with flu-like symptoms typically non-specific, with mild respiratory symptoms identified as most common in some cases, while other symptoms included rash, malaise, fever, and myalgia [12, 13]. Approximately 70% of the SARS-CoV patients experience shortness of breath and lingering or persistent fever, while clinical improvements were observed in 30% patients after the first week [14]. Intensive care treatments such mechanical ventilation was required by about 20 to 30% of SARS-CoV patients [14, 15]. Individuals 12 years of age and younger displayed limited severe disease manifestations [6, 13, 16]. Prognostic studies indicate greater risk of severe outcomes associated with increased age, high pulse, and lactate dehydrogenase (LDH) levels [7, 17, 18].

4. Pathological changes and clinical diagnosis in SARS-COV infection

Histopathologic data existing on SARS-CoV patients have been mostly determined from autopsy cases. Pathological lesions in certain organs of SARS-CoV victims, such as the lungs and intestines, have been extensively studied [1, 4]. The primary pathological change in SARS-CoV patients occurs in the lungs [4, 6]. Gross examination of the lungs revealed edematous, heavy lungs weighing up to 2100 g with several areas of extensive consolidation (**Figure 1**) [1, 4].

Histopathologic data for SARS-CoV of infected lungs characteristically displayed diffuse alveolar damage [DAD] [19, 20]. Through the initial period of the disease (7 to 10 days), SARS lungs exhibited the following characteristics of acute exudative DAD: 1) Widespread edema, 2) desquamation of alveolar epithelial cells, 3) formation of hyaline membrane, 4) collapse of alveoli, and 5) fibrous tissue in alveolar spaces (**Figure 2**) [6, 12, 19, 21, 22].

In SARS cases of lengthier disease duration, fibrous organization features of DAD were visible after approximately 10–14 days. These features included interstitial and airspace fibrosis and pneumocytic hyperplasia [12, 23, 24]. The more extensive the disease period, the more widespread the fibrous organization of the lung tissue [14, 25, 26]. Dense septal and alveolar fibrosis were exhibited in SARS cases with duration of more than 2 to 3 weeks [12, 19, 23, 24]. The overall histological data presentation of SARS lung infection is non-specific and dependent on symptom onset; Acute DAD is most frequently associated with early phase disease (<10 days) [6, 27]. Furthermore, there is limited documentation on the pathologic demonstration of SARS-CoV in living patients, since the bulk of patient tissue samples were taken from autopsy [1, 4, 6].

The predominant changes involving SARS-CoV cases have been visceral and involve severe pulmonary changes [1, 19]. Accurate and easily implementable diagnostics formed an essential part of SARS-CoV disease control, due to the non-specific nature of the infection and its rapid spread. Following the initial disease outbreak, many laboratories rapidly developed SARS-CoV reverse transcription polymerase chain reaction test (RT-PCR) analyzes, to detect viral RNA. These tests have numerous advantages over traditional RT-PCR tests [28].

Real-time RT-PCR assays use amplification primers and internal probes as a result, can be designed to be extremely precise for SARS-CoV RNA [6]. Real-time

Figure 1.
SARS gross morphology of the lung [19]. Images ©John Wiley and Sons Ltd. as cited.

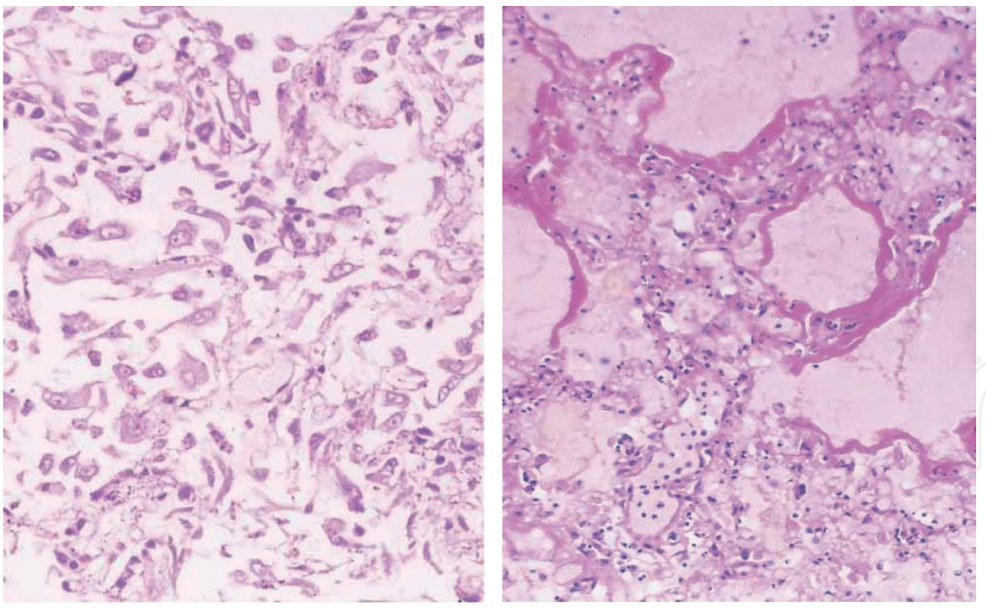

Figure 2.
(A) Alveoli filled with desquamated epithelial cells. (B) Formation of hyaline membrane (H&E, original magnification ×200).

RT-PCR analyzes can be extremely sensitive, with steady detection limits of between 1 and 10 SARS-CoV RNA copies per reaction [6, 29]. They can be completed quicker than traditional RT-PCR analyzes with reduced risk of contamination in the laboratory. Real-time RT-PCR assays often times give a very accurate estimate of the viral load present in a sample [29].

5. MERS-CoV

5.1 Etiology, epidemiology and clinical presentation

The Middle East respiratory syndrome coronavirus (MERS-CoV or MERS) was first identified in September 2012 in a fatal case of severe respiratory failure in a Saudi Arabian patient [30, 31]. Previous cases were retrospectively acknowledged from an outbreak of severe respiratory illness in Jordan in 2012 [32]. In contrast to the rapid spread and subsequent latency of SARS-CoV, MERS-CoV has moved continuously through the Arabian Peninsula and generated sporadic outbreaks in countries where infected persons have traveled [6]. As of January 2020, there have been 2519 laboratory-confirmed cases of MERS, and 866 associated deaths (case-fatality rate: 34.3%) reported globally [32].

A significant number of cases has been identified in Saudi Arabia and to a lesser extent the United Arab Emirates (UAE), Qatar and Jordan [33]. While the close relationship to numerous bat coronaviruses suggests a bat-related origin, overwhelming molecular and serological evidence points to the involvement of dromedary camels in the transmission of MERS-CoV to a human host [34]. While transmission from ancestral bats to camels cannot be excluded, and camels may have introduced the virus into human populations, the majority of reported MERS-CoV cases have ensued from human-to-human nosocomial transmission [6, 33].

A hospital outbreak was reported in Saudi Arabia with a cluster of six cases; Three of the cases were healthcare workers, two were patients (one of whom died) and one was a visitor. Another instance involved an ill patient admitted to a Korean

hospital which led to an outbreak of 186 infections including 36 fatal cases [35]. Person-to-person transmission has also been identified within households, where the highest risk of transmission involves patient respiratory secretions and individuals being within close proximity with each other. Individuals exhibiting signs and symptoms or other epidemiological characteristics suggestive of MERS should be promptly quarantined and tested for viral infection [32, 35].

6. MERS-CoV infection in humans

The clinical manifestation for MERS-CoV infection varies from asymptomatic/mild to severe disease. Generally, individuals with chronic comorbid conditions (diabetes, heart disease) and elderly patients are at increased risk for development of respiratory failure [35]. Although infection is commonly associated with respiratory disease, in some rare cases viral RNA has been discovered in blood, stool and urine signifying a systemic infection [33, 35].

Notwithstanding the increased mortality related to symptomatic cases, research studies have shown that roughly 25% of patients infected with MES-CoV are asymptomatic [36]. A seroepidemiological analysis of over 10,000 infected samples from Saudi Arabia revealed positive antibodies in approximately 0.15% of patients. Individuals with some level of camel-exposure had an increased likelihood of positive serology [33, 35]. Clinical symptoms are non-specific, and patients have reported an expansive range of diverse indicators including chest pain, fever, cough, myalgia, sore throat, shortness of breath, vomiting and diarrhea [32]. In more severe cases, mechanical ventilation is required for patients who are presented with acute hypoxic respiratory failure [15, 31]. Fatal outcome of MERS-CoV infection have been associated with underlying comorbidities such as hypertension, diabetes mellitus type II, obesity, and cardiac disease [37]. MERS-CoV infection has an incubation period that ranges from 2 to 14 days [30]. Signs and symptoms usually appear well before the patient reaches a detectable viremia i.e. the virus is present in the patients' bloodstream [30, 37]. Neurological sequelae, and gastrointestinal distress have also been documented in addition to these respiratory symptoms [37].

7. Pathological changes and clinical diagnosis in MERS-COV infection

The understanding of the pathological findings related to MERS-CoV infection have relied on a paucity of autopsy cases. Notwithstanding the limited number of autopsy cases, several studies have assessed the pathological features of MERS-CoV infection in human tissue. The pathogenesis of MERS-CoV infection in human tissue ex vivo revealed exudative diffuse alveolar damage (DAD) with hyaline membranes, interstitial pneumonia (which was primarily lymphocytic), pulmonary edema, multinucleate syncytial cells, and type II pneumocyte hyperplasia [38]. Researchers also observed bronchial submucosal gland necrosis in diseased lung tissue, where these bronchial lesions make up the pathologic origin for respiratory failure and radiologic anomalies of MERS-CoV infection [38]. Some of the cells in the lungs targeted by the MERS-CoV infection include: pneumocytes, multinucleated epithelial cells, and bronchial submucosal gland cells [39]. Microstructurally, viral particles were discovered in the pulmonary macrophages, pneumocytes, renal proximal tubular epithelial cells and macrophages infiltrating the skeletal muscles [38, 40]. Consistent with the microstructural results in the kidney, renal biopsies revealed acute tubulointerstitial nephritis and acute tubular sclerosis with proteinaceous cast formation [40].

Researchers discovered comparable replication of kinetics and cellular tropism in a study comparing the replication of camel-isolated MERS-CoV strains to human-isolated MERS-CoV strains. Non-ciliated bronchial epithelium and alveolar epithelial cells including type II pneumocytes were infected by all strains. It is important to note that no infection of the pulmonary macrophages was present [39]. Infection of several cell types including vascular endothelial cells, renal tubular cells, and podocytes was established in studies examining kidney explants [41]. Exploratory infection of small intestine tissue samples with MERS-CoV confirmed that infection was restricted to the surface enterocytes and formation of syncytial cells [6]. It has been observed that infected patients shed virus in their urine and stool, which is consistent with these findings.

RT-PCR has functioned as the main clinical laboratory diagnostic test throughout transmission events. Critical to the success of these tests is an understanding of the viral kinetics and tissue tropism discovered in MERS-CoV cases. Numerous studies have acknowledged that lower respiratory tract samples contain the highest viral loads, while upper respiratory swabs, whole blood or serum, feces, and urine may also contain significant viral load [35]. Samples from the upper respiratory tract, urine and blood may offer further diagnostic usefulness by delivering a convenient sample type, notwithstanding 10 to 100 times lower virus levels. Measurable viremia at the point of diagnosis has been linked with an increase in patient death due to the necessity for mechanical ventilation, despite blood only being positive in approximately one-half to one-third of cases [42]. The reduced viremia rate in MERS-CoV samples in comparison to SARS-CoV is significantly different, where RT-PCR on blood can be beneficial for preliminary diagnosis and is normally the primary positive site identified. Analyses of upper and lower respiratory samples as well as blood samples for MERS-CoV patients, has shown that it may benefit in maximizing the sensitivity while also stratifying risk [34]. Two RT-PCR testing approaches were approved for emergency use authorization by the FDA during the MERS-CoV outbreak: both targeted a region upstream of the envelope gene (principal target of the humoral immune response). Of these two tests, one additionally targets a specific region of the ORF1a gene, while the other targets two regions inside the nucleocapsid gene [6].

MERS-CoV serology tests share comparable kinetics to that of SARS-CoV infections. About 2–3 weeks following the onset of symptoms, a significant number of patients develop measurable levels of IgM and IgG antibodies. However, in many cases the detection of IgG has superior diagnostic value when compared to IgM [34]. Some researchers posit that if serologic testing is used to detect current infection, "a neutralization assay and 4-fold increase in titer after 14 days should be used to confirm a specific immune response" [6, 42]. Disease severity may affect antibody responses as numerous studies have established; PCR-positive patients exhibiting only mild disease symptoms often do not generate measurable quantities of antibodies, especially when monitored during the post-acute phase of disease [34].

8. SARS-CoV-2

8.1 Etiology, epidemiology, and clinical presentation

The coronavirus (SARS-CoV-2) (also known as the novel coronavirus) outbreak has reached pandemic proportions with a large global footprint [43, 44]. In late December 2019, SARS-CoV-2 was first reported in Wuhan, Hubei Province, China among clusters of patients with pneumonia of unknown etiology [43, 44]. In early

January 2020, the National Health Commission of People's Republic of China released information regarding the causative agent of an enigmatic pneumonia identified as a novel coronavirus (SARS-CoV-2). The novel coronavirus (SARS-CoV-2) was verified by several independent laboratories located in China [45, 46]. The World Health Organization (WHO) provisionally named the causative virus as 2019 novel coronavirus [2019-nCoV/SARS-CoV-2] [46]. Coronaviruses are known to cause respiratory, hepatic, and neurologic diseases and are generally spread among humans and animals [3]. The SARS-Cov-2 virus is illustrated by a spherical shape, and a characteristic "crown" appearance, and they belong to the family of coronaviruses of positive-stranded RNA viruses [47].

Genetically, SARS-CoV-2 has a closer resemblance to SARS-CoV than the Middle East respiratory syndrome coronavirus [MERS-CoV] [48]. Nevertheless, the span of the incubation period, clinical severity, and transmissibility of SARS-CoV-2 differs from SARS-CoV [49]. Public health and government efforts aimed at curbing the spread by implementing social practices through social distancing, mask wearing, isolating/quarantining and non-pharmacological and preventive treatments for psychophysical wellbeing, has been relatively successful in part, but SARS-CoV-2 has continued to increase globally [50, 51]. By the end of January 2021, SARS-CoV-2 accounted for more than two million deaths and more than 100 million confirmed cases of the disease [52]. Radiologically, SARS-CoV-2 has distinctive imaging features that constitute a visual identity. Besides, SARS-CoV-2 negatively impacts other organs in addition to the lungs. As a result of these developments, SARS-CoV-2 has grown exponentially with nearly 2000 articles being published per week [50].

9. SARS-CoV-2 infection in humans

SARS-CoV-2 infections are variable in nature, with some infections being asymptomatic with others causing minor to moderate illness with respiratory and flu-like symptoms, including sore throat, fever, chills, and cough [53]. Injury, inflammation and ensuing respiratory distress in SARS-CoV-2 patients occurs as a result of the SARS-CoV-2 spike protein binding to human angiotensin I-converting enzyme 2 (hACE2) predominantly targeting the virus to type II pneumocytes inside the lung [54, 55]. A substantial number (approximately 20%) of patients also develop severe infection and multi-organ failure which necessitates intensive care with mechanical ventilation or extracorporeal membrane oxygenation [50, 53]. In some cases, SARS-Cov-2 infection can be deadly, with a case fatality rate of ~5%. The incubation period of SARS-CoV-2 is generally 5–7 days, but the symptoms of infection may present itself well after that period [56]. The phase from the onset of symptoms to fatality usually varies from 7 to 40 days with a median of 14 days [57]. This phase is dependent on the patients' age, and the status of their immune system.

Similarities in the symptoms between SARS-CoV-2 and earlier beta-coronavirus such as fever, dry cough, and dyspnea are distinctive [50]. However, there are distinctive features presented by SARS-CoV-2 which involves affecting of the lower airway as evident by upper respiratory tract indicators like sneezing, rhinorrhoea, and sore throat [58]. Additionally, chest radiograph results taken upon admission, show an infiltrate in the upper lobe of the infected lungs, associated with increased difficulty breathing (dyspnea) resulting in low levels of oxygen in the blood (hypoxemia) [58]. Notably, while most SARS-CoV-2 patients exhibit gastrointestinal symptoms like diarrhea, very few MERS-CoV or SARS-CoV patients show similar gastrointestinal concerns. Thus, testing fecal and urine samples to exclude a potential alternative route of transmission among patients and healthcare workers [57].

10. Pathological changes and clinical diagnosis in SARS-COV-2 infection

Nasal droplets and saliva from infected patients function as the leading route of SARS-CoV-2 virus communicability [59]. According to Heydarloo et al., the virus accesses the alveolar-type 2 cells (AT2 cells) by attaching its viral spike (S1 and S2) proteins to the angiotensin-converting enzyme 2 (ACE2) receptor [60]. Researchers found that previous iterations of coronaviruses specifically SARS-CoV, replicated more aggressively in alveolar-type 2 cells than in alveolar type 1 cells in the lung [38]. This is significant since it has been reported that there is an 80% genetic similarity between the SARS-CoV and SARS-CoV-2 viruses [61]. SARS-CoV-2 has an extraordinary potential for binding with AT2 cells in the lungs as shown via molecular pathways [62].

The SARS-CoV-2 pandemic continues to affect much of the world and understanding its clinical diagnosis is important. Data on diagnostic testing for SARS-CoV-2 is still in its infancy, as such, understanding these tests and interpreting their results is imperative. The most frequently administered and dependable test for SARS-CoV-2 diagnosis thus far, has been the RT-PCR test completed using nasopharyngeal swabs. In some cases, alternative upper respiratory tract samples, comprising throat swabs and/or saliva have been used. Individual companies focus on a variety of RNA genes, with a significant number of tests affecting 1 or more of the envelope, RNA-dependent RNA polymerase (RdRp), and ORF1 genes [63].

In most SARS-CoV-2 patients with symptomatic infection, viral RNA in the nasopharyngeal swab becomes detectable as early as day 1 of symptoms and peaks within the first week of symptom onset. The cycle threshold (Ct) that is used to measure viral RNA, can be defined as "the number of replication cycles required to produce a fluorescent signal, with lower cycle threshold values representing higher viral RNA loads" [63]. A PCR positive is typically clinically reported as a Ct value of less than 40. By week three of infection, there is usually a decline in this positivity and subsequently becomes unnoticeable. In severely ill hospitalized SARS-CoV-2 patients, the cycle threshold values are lower than the cycle threshold values recorded in less severe cases. It is important to note, a "positive" PCR result reveals only the recognition of viral RNA and does not automatically suggest presence of viable virus [62]. It has been reported in a minority of positive test cases that viral RNA was detected by RT-PCR past week six. There have also been instances of a positive result being reported after consecutive negative PCR tests completed two days apart. Currently, it is unclear whether this is a testing error, reinfection, or recurrence.

SARSCoV-2 infection can also be identified indirectly by assessing the patients' immune response to infection. In patients who exhibit mild to moderate symptoms, serological diagnosis becomes extremely important past the first two weeks of illness onset. Serological diagnosis is an essential means of understanding the scope of SARSCoV-2 infection in the community and may assist in identifying individuals who are immune/protected from infection.

11. Conclusion

Wide-ranging efforts to decrease transmission of SARSCoV-2 infection are crucial to controlling the present epidemic. Lessons learned from the SARS-CoV and MERS-CoV outbreaks offer, valuable experiences and insights into how to fight the SARSCoV-2. Specific consideration aimed at decreasing spread must be applied in vulnerable populations specifically health care workers, and the elderly. Additionally, research into the pathogenesis of human coronavirus infection is crucial for finding suitable therapeutic objectives. Presently, no specific antiviral drug is available for SARS-CoV, MERS, and SARSCoV-2.

IntechOpen

Author details

Bradley Fevrier
Bowling Green State University, Bowling Green, Ohio, USA

*Address all correspondence to: fevrieb@bgsu.edu

References

[1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. 2020;109:102433.

[2] Weiss SR. Forty years with coronaviruses. 2020;217(5).

[3] Cristina S, Concetta R, Francesco R, Annalisa C. SARS-Cov-2 infection: Response of human immune system and possible implications for the rapid test and treatment. 2020;84:106519.

[4] Dimonaco NJ, Salavati M, Shih BB. Computational Analysis of SARS-CoV-2 and SARS-Like Coronavirus Diversity in Human, Bat and Pangolin Populations. 2021;13(1):49.

[5] Zhu Z, Lian X, Su X, Wu W, Marraro GA, Zeng Y. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. 2020;21(1).

[6] Bradley BT, Bryan A. Emerging respiratory infections: The infectious disease pathology of SARS, MERS, pandemic influenza, and Legionella. 2019;36(3):152-159. Available from: http://dx.doi.org/10.1053/j.semdp.2019.04.006

[7] Chan KH, Poon LL, Cheng V, Guan Y, Hung I, Kong J, et al. Detection of SARS coronavirus in patients with suspected SARS. 2004;10(2):294.

[8] Olsen SJ, Chang H-L, Cheung TY-Y, Tang AF-Y, Fisk TL, Ooi SP-L, et al. Transmission of the severe acute respiratory syndrome on aircraft. 2003;349(25):2416-2422.

[9] Yang Y, Xiao Z, Ye K, He X, Sun B, Qin Z, et al. SARS-CoV-2: characteristics and current advances in research. 2020;17(1):1-17.

[10] Kato V, Laure B. Neurological manifestations of COVID-19, SARS and MERS. 2020;1-10.

[11] Hu B, Zeng L-P, Yang X-L, Ge X-Y, Zhang W, Li B, et al. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. 2017;13(11):e1006698.

[12] Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, et al. Lung pathology of fatal severe acute respiratory syndrome. 2003;361(9371):1773-1778.

[13] Leung C, Kwan Y, Ko P, Chiu SS, Loung P, Fong N, et al. Severe acute respiratory syndrome among children. 2004;113(6):e535–e543.

[14] Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. 2007;170(4):1136-1147.

[15] Peiris J, Lai ST, Poon L, Guan Y, Yam L, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. 2003;361(9366):1319-1325.

[16] Goldsmith CS, Tatti KM, Ksiazek TG, Rollin PE, Comer JA, Lee WW, et al. Ultrastructural characterization of SARS coronavirus. 2004;10(2):320.

[17] Chan JC, Tsui EL, Wong VC, Group HASC. Prognostication in severe acute respiratory syndrome: A retrospective time-course analysis of 1312 laboratory-confirmed patients in Hong Kong. 2007;12(4):531-42.

[18] Donnelly CA, Ghani AC, Leung GM, Hedley AJ, Fraser C, Riley S, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. 2003;361(9371):1761-1766.

[19] Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. 2003;200(3):282-9.

[20] Tse GM, To KF, Chan PK, Lo A, Ng KC, Wu A, et al. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). 2004;57(3): 260-265.

[21] Cheung OY, Chan J, Ng CK, Koo CK. The spectrum of pathological changes in severe acute respiratory syndrome (SARS). 2004;45(2):119-124.

[22] Lang Z, Zhang L, Zhang S, Meng X, Li J, Song C, et al. A clinicopathological study of three cases of severe acute respiratory syndrome (SARS). 2003;35(6):526-531.

[23] Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. 2005;202(3):415-424.

[24] Sheahan TP, Baric RS. SARS coronavirus pathogenesis and therapeutic treatment design. Springer; 2010.

[25] Franks TJ, Chong PY, Chui P, Galvin JR, Lourens RM, Reid AH, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. 2003;34(8):743-8.

[26] Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. Pulmonary pathology of severe acute respiratory syndrome in Toronto. 2005;18(1):1-10.

[27] Shieh W-J, Blau DM, Denison AM, DeLeon-Carnes M, Adem P, Bhatnagar J, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. 2010;177(1):166-75.

[28] Grant PR, Garson JA, Tedder RS, Chan PK, Tam JS, Sung JJ. Detection of SARS coronavirus in plasma by real-time RT-PCR. 2003;349(25):2468-2469.

[29] Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, et al. van der WS, Escriou N, Manuguerra JC, Stohr K, Peiris JS, Osterhaus AD: Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. 2003;362:263-70.

[30] Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. 2012;367(19):1814-1820.

[31] Hilgenfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. 2013;100(1):286-95.

[32] Alyami MH, Alyami HS, Warraich A. Middle East Respiratory Syndrome (MERS) and novel coronavirus disease-2019 (COVID-19): From causes to preventions in Saudi Arabia. 2020;37.

[33] van Doremalen N, Munster VJ. Animal models of Middle East respiratory syndrome coronavirus infection. 2015;122:28-38. Available from: http://dx.doi.org/10.1016/j.antiviral.2015.07.005

[34] Mehyar N, Mashhour A, Islam I, Gul S, Adedeji AO, Askar AS, et al. Using in silico modelling and FRET-based assays in the discovery of novel FDA-approved drugs as inhibitors of MERS-CoV helicase. 2021;1-20.

[35] Halpin DM, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, et al. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee

Report on COVID-19 and Chronic Obstructive Pulmonary Disease. 2021;203(1):24-36.

[36] da Silva ML, Rocha RSB, Buheji M, Jahrami H, Cunha K da C. A systematic review of the prevalence of anxiety symptoms during coronavirus epidemics. 2021;26(1):115-125.

[37] Al-Abdallat MM, Payne DC, Alqasrawi S, Rha B, Tohme RA, Abedi GR, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. 2014;59(9):1225-1233.

[38] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. 2020;55:102763.

[39] Alsaad KO, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection–clinico pathological and ultrastructural study. 2018;72(3):516-24.

[40] Cha R, Yang SH, Moon KC, Joh J-S, Lee JY, Shin H-S, et al. A case report of a Middle East respiratory syndrome survivor with kidney biopsy results. 2016;31(4):635.

[41] Yeung M-L, Yao Y, Jia L, Chan JF, Chan K-H, Cheung K-F, et al. MERS coronavirus induces apoptosis in kidney and lung by upregulating Smad7 and FGF2. 2016;1(3):1-8.

[42] Kim SY, Park SJ, Cho SY, Cha R, Jee H-G, Kim G, et al. Viral RNA in blood as indicator of severe outcome in Middle East respiratory syndrome coronavirus infection. 2016;22(10):1813.

[43] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. 2020

[44] Merianos AL, Fevrier B, Mahabee-Gittens EM. Telemedicine for Tobacco Cessation and Prevention to Combat COVID-19 Morbidity and Mortality in Rural Areas. 2020;8.

[45] Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. 2020;369.

[46] Zhu Z, Lian X, Su X, Wu W, Marraro GA, Zeng Y. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. 2020;21(1):1-14.

[47] Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. 2020;7(1):1-10.

[48] Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? 2020;20(5):e102-7.

[49] Maugeri G, Castrogiovanni P, Battaglia G, Pippi R, D'Agata V, Palma A, et al. The impact of physical activity on psychological health during Covid-19 pandemic in Italy. 2020;6(6):e04315.

[50] Suri JS, Agarwal S, Gupta SK, Puvvula A, Biswas M, Saba L, et al. A narrative review on characterization of acute respiratory distress syndrome in COVID-19-infected lungs using artificial intelligence. 2021;104210.

[51] Lesser IA, Nienhuis CP. The impact of COVID-19 on physical activity

behavior and well-being of Canadians. 2020;17(11):3899.

[52] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. 2020;20(5):533-4.

[53] Elezkurtaj S, Greuel S, Ihlow J, Michaelis EG, Bischoff P, Kunze CA, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. 2021;11(1):1-9.

[54] Ziegler CG, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. 2020;181(5):1016-1035. e19.

[55] Hamming I, Timens W, Bulthuis M, Lely AT, Navis G van, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. 2004;203(2):631-637.

[56] Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. 2020;323(14):1406-7.

[57] Nishiura H, Jung S, Linton NM, Kinoshita R, Yang Y, Hayashi K, et al. The extent of transmission of novel coronavirus in Wuhan, China, 2020.

[58] Barbeta E, Motos A, Torres A, Ceccato A, Ferrer M, Cilloniz C, et al. SARS-CoV-2–induced Acute Respiratory Distress Syndrome: Pulmonary Mechanics and Gas-Exchange Abnormalities. 2020;17(9):1164-8.

[59] Gatto M, Bertuzzo E, Mari L, Miccoli S, Carraro L, Casagrandi R, et al. Spread and dynamics of the COVID-19 epidemic in Italy: Effects of emergency containment measures. 2020;117(19):10484-91.

[60] Heydarloo H, Alizadeh Z. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. 2020;4(7):262-71.

[61] Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. 2020;80(6):656-65.

[62] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. 2020;579(7798):270-273.

[63] Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. 2020;323(22):2249-51