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Review Article

Past and current coronavirus outbreaks; Focusing on coronavirus disease 2019 in comparison with severe acute respiratory syndrome and middle east respiratory syndrome.

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) is currently the most significant public health concern globally, having affected more than 24 million patients and caused an excess of 0.83 million deaths since its emergence in December 2019 in the city of Wuhan, China. There have been similar Coronavirus outbreaks in the past, namely Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). In this review article, we discussed the epidemiology, virology, clinical presentation, diagnostic approaches, and effective treatment modalities for COVID-19 in light of existing literature.

Methodology: The aim of conducting this systematic review was to compare the three human coronavirus outbreaks: Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Corona Virus Disease 2019 (COVID-19). Multiple search engines were used and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were referenced.

Results: The findings suggest that COVID-19 shares substantial characteristics with both SARS and MERS, SARS being more closely related to COVID-19 in terms of epidemiological characters, particularly their viral reservoirs. SARS-CoV-1 and SARS-CoV-2 use the same receptor to gain access to the host cells, while MERS-CoV uses a different entry point. The radiological manifestations of SARS, MERS and COVID-19 are similar as well.

Conclusion: The recurrent appearance of coronaviruses in the human population makes it crucial to study them in great details. Furthermore, owing to its similarity to previous coronavirus outbreaks, the lasting effects of COVID-19 on pulmonary tissue must be investigated. Moreover, at the time of writing this paper, no vaccines are available against COVID-19, a facet that requires extensive global research.

Keywords

Coronavirus, COVID-19, SARS-CoV2, MERS, SARS-CoV1, Pandemic.

Introduction

In December 2019, reports started emerging about clusters of patients being affected by a pneumonia-like febrile illness in Wuhan, China. Initially considered an illness of unknown origin, the disease was later attributed to a novel mutation of coronavirus following the isolation of the strain (SARS-CoV-2) from the bronchoalveolar secretions of the affected patients[1]. As of 30th August 2020, COVID-19 has affected 24,854,140 people across 216 countries with a death toll of 838,924 globally[2].

Coronaviruses have been identified as a family of enveloped RNA viruses that are responsible for a vast array of respiratory tract infections in humans, with variable manifestations ranging from mild, self-limiting upper respiratory tract symptoms to more critical lower respiratory tract manifestations like Acute Lung Injury also known as ALI and Acute Respiratory Distress Syndrome also termed as ARDS[3,4]. Moreover, in the last two decades, additional strains belonging to the coronavirus family have been implicated in two similar and sizeable epidemics: The Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS) in 2012[5]. This mini review aims to compare SARS-CoV-2 to SARS-CoV-1, and MERS-CoV in terms of epidemiological characteristics, virology, clinical course, diagnostic approaches, and treatment modalities in light of existing literature.

Epidemiological Characteristics

Origin, reservoirs and hosts

The first clinical case of COVID-19 was reported in Wuhan, a city of Hubei province, China, in December 2019[6]. About 66% of the initial cluster of 41 confirmed cases could be traced back to the seafood market in Huanan, Wuhan, China, that was considered ground zero for the COVID-19 outbreak[7]. Many of these index patients worked at the market or were regular patrons. Moreover, SARS-CoV-2 RNA was detected in the environmental samples acquired from the Huanan seafood market in December of 2019, further strengthening the hypothesis of the Huanan seafood market being the source of COVID-19[6].

Previously, the SARS-CoV-1 outbreak of 2002 originated in southern China and, more specifically, in the city of Foshan, Guangdong province[8]. Subsequent studies found that bats were the natural reservoir for SARS-CoV-1 with Himalayan palm civets (Gem-faced civets or masked palm civets), Raccoon dogs, and Chinese-ferret-badgers acting as intermediate hosts[9]. Recently, viral genomic sequencing has determined that SARS-CoV-2 is almost 80% identical to SARS-CoV-1. Owing to this fact as well as the evolutionary analysis of the virus, bats are being postulated as the natural reservoir of SARS-CoV-2[2,6,7], while pangolins, snakes, and turtles are thought to be potential intermediate hosts[10].

Conversely, the earliest clinical case of MERS was reported in a different geographical setting, the Kingdom of Saudi Arabia in 2012 with infected Dromedary camels being implicated as the primary host. However, in light of the virus's genomic analysis, it is postulated that the virus may have chiropteran (bat) origins and was transmitted to camels at some point in the past[11].

Mode of Transmission

According to the information currently available, there are two modes of transmission of SARS-CoV-2: Droplet-borne and fomite-borne. In certain circumstances, airborne transmission can occur as well[12]. Droplet-borne transmission can occur within 1 m of an infected person when they cough or sneeze. It can also occur through fomites in close proximity of the infected person[13]. However, the airborne transmission may occur under specific conditions only, particularly when aerosol-generating procedures are performed (CPR, endotracheal intubation, tracheostomy, airway suctioning, and nebulized medication administration NIPPV ventilation, proning the patient, disconnecting a ventilator)[12]. Isolated incidents of vertical transmission of SARS-CoV-2 as well as the virus's presence in the fecal matter have also been reported[12,14]. Similarly, the route of transmission of SARS-CoV-1 was determined to be via respiratory droplet inhalation. In some cases, transmission through the fecal-oral route through contact with contaminated fomites has been noted. A vast majority of the cases were acquired through the nosocomial route[8].

In contrast, although the transmission of MERS-CoV occurred through human-to-human contact in both community and nosocomial settings, the majority of cases occurred in healthcare settings with poor infection control practices. Sustained transmission from human-to-human has not been noted to date[11].

Infectivity

"Basic reproductive number" (Ro) determines the incidence and prevalence of contagion and is defined as the average number of secondary cases generated by an index case in a predisposed group of individuals. Furthermore, a Ro that is not much larger than 1 indicates a high chance that the infection will likely fade away instead of snowballing into a pandemic[15,16]. The Ro estimates for SARS-CoV-1 ranged between 2 and 3[17]. Conversely, the Ro for MERS-CoV was calculated to be 0.69[18]. Based on recent studies, the estimated basic reproductive number of SARS-CoV-2 is about 2.2[16].

Incubation Period

It was postulated that a longer incubation period might be the basis for the rapid spread of SARS-CoV-2 as longer incubation periods are associated with high rates of asymptomatic or subclinical infection in immunocompetent people[19]. However, the differences between estimated incubation periods of SARS-COV-2 (mean incubation period 5.2 days)[15], SARS-CoV-1 (mean incubation period 4.0 days)[20] and MERS-CoV (Incubation period 4.5 - 5.2 days)[21] were negligible, disproving this hypothesis[19].

Incidence and Case Fatality Rate

As of 30th August 2020, 24,854,140 confirmed cases of COVID-19 have been reported across 216 countries globally, with 838,924 confirmed deaths[2]. The case fatality rate varies from country to country, from less than 0.1% to over 25%[22]. In comparison, the 2002 SARS-CoV-1 outbreak had a case fatality of 9.6% and affected 8098 individuals across 29 countries[8] while MERS-CoV has had 2494 confirmed cases since 2012, spanning 27 countries with a death toll of 858. (Mortality rate: 34.4%)[23].

Virology of Coronavirus

They are enveloped, positive-sense, single-stranded RNA viruses that belong to the family of Beta-corona virus, a subfamily of Coronavirinae[24]. The virions are spherical, and the most significant feature of coronaviruses is that they possess club-shaped spiky pointed projections on their external surface. Spikes are the hallmark features of the virion and impart the semblance of a solar radiating corona, hence the name, coronaviruses. The nucleocapsids of coronaviruses are located within the viral envelope and are helically symmetrical, which is an anomaly among positive-sense RNA viruses, but a frequent occurrence in negative-sense RNA viruses[25].

The structural proteins of coronaviruses include spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The heavily N-linked glycosylated protein employed to gain entry to the endoplasmic reticulum is called the S protein (~150 kDa). It does so by an N-terminal signal sequence. Homotrimers of the S protein are attributed for the distinctive spike structure on the surface of the virus[26,27]. A fifth structural protein, named the Hemagglutinin-Esterase (HE), found only in some of β-coronaviruses mimics hemagglutinin, binding sialic acids on glycoproteins on the surface and containing acetyl-esterase activity[28]. Describing the other three structural proteins is beyond the scope of this study.

MERS-CoV enters into the host cells by binding to human receptor dipeptidylpeptidase-4 (hDPP4) on the target cell surface via its receptor-binding domain (RBD) present on its spiky glycoprotein, in contrast to SARS which gains access to the target cells via angiotensin-converting enzyme 2 (ACE2)[29-31]. Host proteases are used by MERS-CoV to enter into pulmonary cells[31]. Furin protease activates the spike protein on the viral envelope. This reaction is the mediator of membrane fusion and eventually supports the viral access to the host cell[30]. Consequently, protease inhibitors block MERS-CoV entry into cells[32].

Clinical Features

The three coronavirus infections present mainly with fever and cough, frequently leading to pneumonia with poor clinical outcomes often associated with elderly individuals, or those with associated comorbidities[33,34].

SARS CoV 2 Presentation

Patients affected by SARS CoV 2 have presented with a vast array of clinical features from mild, moderate, and severe to rapidly progressive to fulminant disease[33]. The signs and symptoms involving the upper respiratory tract include high to low-grade fever, cough, runny nose, malaise, and fatigue. Moreover, symptomatology may progress to include severe lower respiratory tract or even extra-pulmonary manifestations like severe shortness of breath, rashes, changes in the sense of smell and taste, headache, hemoptysis, diarrhea, and vomiting. The COVID-19 symptomatology is nonspecific, and clinical profile may range from asymptomatic to severe pneumonia and eventual death[33]. Zhang et al. analyzed 140 COVID-19 patients at the Hospital of Wuhan and observed that a vast majority of the patients affected were in the middle-aged and elderly age group, with an almost 1:1 male-female ratio. Fever (91.7%), fatigue (75.0%) and cough (75.0%) were the predominant symptoms in patients with COVID-19. Over a third of the described patients complained of chest tightness, dyspnea and gastrointestinal symptoms, namely nausea, anorexia, and diarrhea[35].

MERS Presentation

MERS-CoV infected patient's clinical symptoms were comparable with that of SARS but exhibited a unique clinical course and with a high mortality rate of 34.4%. Most patients had symptoms of influenza-like illness (ILI) such as pyrexia, rhinorrhea, non-productive cough, sore throat, headache, myalgia, nausea, vomiting, diarrhea, and abdominal pain [36,37].

SARS CoV 1 Presentation

A study conducted by Jann-Tay Wang et al. in one of the primary care facilities for SARS outbreak in Taiwan in the year 2003 stated the primary presenting complaints of patients with SARS were fever, myalgia, cough, dyspnea, and diarrhea[38], with the severity of the disease being dependent on the host's individual characteristics[39]. Respiratory distress was present in 90.8% of such patients during the course of their hospitalization[38]. The duration from onset of the infection to severe respiratory distress was found to be an average of 9.8 ± 3.0 days[38].

Diagnostic Investigations

As is the case with any novel pathogen, COVID-19 was initially a diagnostic dilemma for medical practitioners. However, considerable progress has been made with respect to diagnostic testing since the onset of the pandemic.

Screening

The criteria for suspected cases of COVID-19 include positive symptomatology, history of travel to "hot-spots" of SARS-CoV-2 or having close contact with probable or confirmed cases of COVID-19[40]. All patients that fulfill the criteria for suspected cases of COVID-19 should undergo screening for confirmation of the disease. For confirmation of COVID-19, clinical specimens are subjected to serological or molecular testing. Serological testing entails detecting SARS-CoV-2 specific proteins using ELISA or Western blot, while molecular analysis involves detecting SARS-CoV-2 viral nucleic using RT-PCR[41]. Clinical samples to be analyzed are acquired from the upper respiratory tract (Swabs from the nasopharynx or the oropharynx, or nasopharyngeal aspirate) or, if possible, from the lower respiratory tract [Expectorated sputum, bronchoalveolar lavage (BAL) or endotracheal tube aspirate]. Additionally, secretions from the lower respiratory tract merit a higher consideration in terms of diagnosis, but procedures like BAL are associated with a higher degree of risk to the medical personnel involved in the procedure[42]. Furthermore, the virus can also be detected in other bodily secretions, namely the blood and feces[43].

Similarly, RT-PCR targeting specific areas of SARS-CoV-1 and MERS-CoV genomes remains the mainstay for laboratory confirmation of SARS and MERS[44,45]. Moreover, over the years, a myriad of assays have been developed for the detection of anti-MERS-CoV antibodies, including ELISA, IFA, and neutralization assays[46], while serological testing for SARS-CoV-1 employs ELISA and Western blot to detect SARS-CoV-1 specific proteins[47].

Radiological Investigations

Although the diagnosis of COVID-19 and other SARS-like CoV associated illnesses depends mostly on the patient's symptomatology, serological and molecular assays, radiological imaging of the chest plays a vital role in determining the extent of pulmonary involvement as well as the progression of the disease.

SARS

Chest x-ray Manifestations

About 80% of the patients with SARS usually show abnormal manifestations on initial chest radiographs, with most cases showing unilateral and poorly-defined zones of air-space opacities predominantly involving the peripheries of the lower lung zones. The pulmonary involvement is estimated to be focal in about 50% cases and multifocal in the remaining patients. Diffuse pulmonary manifestations can be appreciated in less than 10% cases[48]. Over the next 6-12 days, the chest x-ray shows progressive multifocal areas of consolidation unilaterally or bilaterally. However, in about 25% of the cases, unilateral foci of consolidation persist[49].

CT Chest Manifestations

The most common findings on CT chest involve the lower zones of the lungs. These radiological manifestations include bilateral peripheral lesions showing ground glass opacifications or mixed ground-glass opacifications with consolidation, predominantly in the lower lobes of the lungs. Other manifestations of clinical significance include interlobular septal thickening and interlobular interstitial thickening[50]

MERS

Chest X-ray Manifestations

Similarly, early chest radiographs will show a certain degree of abnormality in 83% of the cases of MERS with unifocal peripheral ground-glass opacities being the commonest radiological manifestation to be noted. Although the lesions initially have a predilection to the middle and the lower zones' peripheries, progression to the upper and perihilar zones with the advancement of the disease. Other findings of clinical interest include consolidation, mixed ground-glass opacification with consolidation, and consolidation with air-bronchogram[51].

CT Chest Manifestations

The CT chest of MERS patients will frequently show peripheral ground-glass opacification, predominantly involving the basal lung zones. Moreover, mixed ground-glass opacities and consolidation, pleural effusion, interlobular thickening may also be observed[52]. Rarely, tree-in-bud opacities and cavitation be appreciated as well[53].

COVID-19

Chest X-ray Manifestations

Typically, the chest radiographs of patients with COVID-19 show manifestations similar to other CoV pneumonia: Patchy or diffuse asymmetric areas of air-space consolidation involving the lower lung zones. However, the findings in COVID-19 are bilateral as opposed to other CoV pneumonia and usually peak in severity about 10-12 days after the onset of symptoms[54,55].

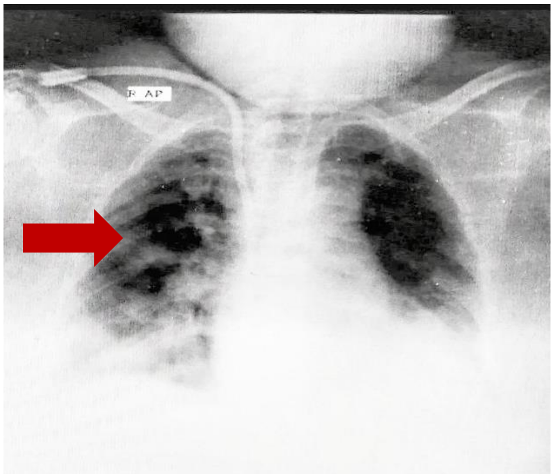

Figure 1: X-ray Chest AP view showing bilateral patchy non-homogenous opacities more prominent in the lower lung zones with bilateral pleural effusion.

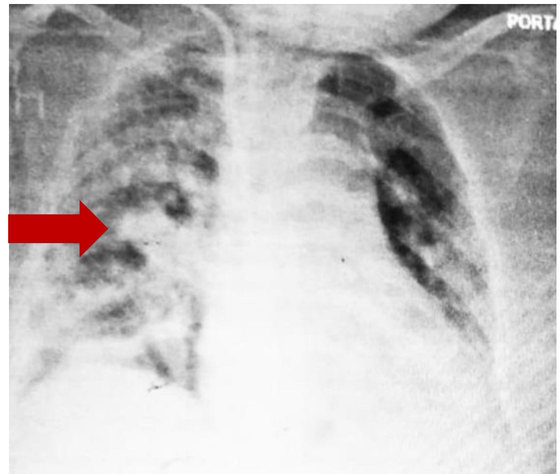

Figure 2: Portable X-ray Chest AP view of the same pt done 2 days later showing worsening of radiological picture (diffuse non-homogenous opacities).

CT Chest Manifestations

Of the initial cluster of SARS-CoV-2 positive patients reported, bilateral lung involvement was noted in 40 out of 41 cases on CT chest. The majority of the ICU patients showed consolidation while ground-glass appearance was observed in non-ICU patients[56]. A recent study (Chung M. et al.) analyzed the CT scans of 21 patients with COVID-19 and noted the findings in the table 1[57].

Table 1: Reported Chest CT findings in COVID-1956

Normal CT	14%
Ground Glass Opacities	86%
Consolidation	29%
Crazy Paving Pattern	19%
Linear Pattern	14%
Cavitation	0%
Pleural Effusion	0%
Lymphadenopathy	0%
Bilateral Manifestations	76%
Peripheral Distribution	33%
Multi-Lobular (≥ 2 Lobes) Distribution	71%

Moreover, CT chest appears to be a valuable tool for the initial screening of suspected COVID-19 cases, owing to its high sensitivity of (false-negative rate: 3.9%)[58]. Its usefulness was further highlighted when reports emerged of five confirmed COVID-19 patients who initially tested negative on RT PCR but had radiographic manifestations suggestive of COVID-19 and later tested positive on repeat swab test[59].

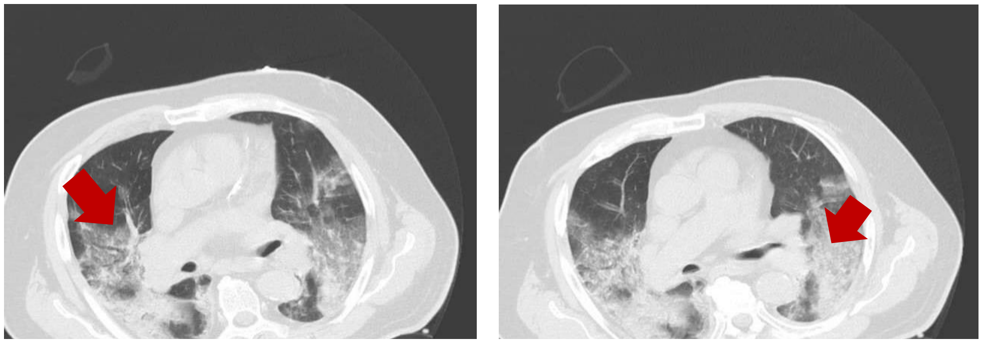

Figure 3 and 4: CT chest axial lung window of a COVID-19 patient showing bilateral prominent areas of ground glass opacities, crazy paving pattern and areas of consolidation more prominent at the lung bases.

Long-Term Follow-up Imaging

Follow-up CT chest in recovered SARS patients may show transient interlobular septal thickening and reticulation over weeks to months in addition to areas of air trapping from injury to the ciliated respiratory epithelium[60,61]. Evidence of fibrosis (intra-lobular and inter-lobular reticulation, traction, honey-combing, bronchiectasis) might be observed in about 33% of persistent pulmonary symptoms[62]. Likewise, MERS' post-recovery cases may show transient interlobular septal thickening and radiological findings consistent with fibrosis[63,64].

Although long-term manifestations of COVID-19 have yet to be reported, follow-up imaging using CT chest is highly recommended to evaluate long-term or permanent lung changes in light of SARS and MERS' experiences.

Treatment

Management of SARS CoV 2

At this point in time, there are no specific antiviral drugs formulated against COVID-19. As such, the mainstay of treatment is still supportive care and invasive and non-invasive ventilation modalities[65]. For prevention and timely management, viral testing should be initiated early for disease confirmation[65]. Based on experiences of MERS, if the patient's tests show a negative result despite strong suspicion of having SARS-CoV-2 infection, a second test is recommended from various respiratory sites including sputum, nose, and endotracheal aspirate[64].

Isolation

As soon as the COVID-19 suspected patient is confirmed positive, he/she must be shifted to a single occupancy room, and infection prevention and control principles (IPC) must be undertaken. The patient ideally, should be shifted to an isolated room with negative pressure. Providers must practice contact, airborne and droplet precautions[64].

Supportive Management

Empirical therapy for community-acquired pneumonia should be considered, utilizing antibiotics which are active against typical as well as atypical respiratory pathogens and clinical usage of fluids for hydration. Currently, there is no known treatment or vaccine effective for combating the disease. However, individual experimental medications and drug combinations, including Remdesivir, Lopinavir-Ritonavir, or Lopinavir-Ritonavir, and Interferon Beta-1b, are under clinical trials around the world and may be considered for sympathetic use in critically ill patients[65,66]. Given the enormous cytokine exodus induced by SARS-CoV-1, MERS-CoV, and SARS-CoV-2 infections[67], corticosteroids have been frequently utilized to treat patients at critical stages of the diseases, under the pretext of reducing inflammation induced lung damage. Despite the justified use, current evidence suggests that corticosteroids do not affect mortality, rather they delayed the clearance of the virus[68]. Moreover, the increased viral load and consequent viremia indicate against the usage. Therefore, systemic corticosteroids should be avoided as a routine, according to WHO interim guidance[65]. Mechanical ventilation is the primary supportive treatment for severely ill patients and has shown a good prognosis if used early on in the disease[68].

Also, Convalescent plasma refined from already recovered patients has proven to be an effective means of treatment till Remdesivir trials and vaccination development are under process. A meta-analysis by Mair-Jenkins et al. proved that mortality reduced after providing the patients with differing doses of convalescent plasma in case of severe acute respiratory infections, while no negative effects or complications occurred after treatment.

Management of MERS-CoV

From the time of 2012 outbreak in the Middle East to the largest known MERS outbreak in 2015 in the Republic of Korea, there is currently no accepted vaccine or specific antiviral therapy available for MERS-CoV[69,70]. Controlling MERS-CoV mainly places reliance on case-based surveillance; early diagnosis becomes a necessity when the suspicion of infection is present[71].

Omrani et al. (2014) revealed that in severe MERS-CoV infection, ribavirin and pegylated interferon alfa- 2a therapy greatly increased survival at 14 days[71]. For patients in the hospital, the untested convalescent-phase plasma is suggested as supportive therapy to reduce the magnitude of infection[72].

Management of SARS CoV 1

According to reports, SARS-CoV-2 shares around 80% of its genome with SARS-CoV-1, so the line of treatment is very similar to SARS-CoV-2[73]. So et al. conducted a study in March 2003 at Pamela Youde Nethersole Eastern Hospital, Hong Kong found that patients that received treatment with lopinavir/ritonavir and ribavirin had a reduced risk of acute respiratory distress syndrome (ARDS), with prophylactic antibiotics (piperacillin and tazobactam) use in patients who had a fever and raised white[74,75].

Conclusion

In conclusion, the frequent emergence of CoV-diseases along with their spontaneous mutations, high transmissibility and pathogenicity has made it imperative for investigating them in greater detail. This is not only to elucidate their propensity for inter-specie transmission, reservoirs, replication process, and pathogenesis as well as the long term pulmonary effects of the disease on radiological imaging. Numerous clinical trials are underway to develop newer drugs and determine the efficacy of existing modalities in treating COVID-19, including previous antiviral drugs and convalescent plasma, each of which has its pros and cons. Moreover, rapid vaccine development follows the drastic mutations in the viral genome and penetrance in hosts' cells over a large scale; this aspect of the disease needs substantial funding and research globally.

Conflicts of Interest

None.

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References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virology, 2020;92(4):401–402.
2. World Health Organization (WHO), Emergency diseases dashboard, Numbers at a glance.

[Accessed 30th August 2020]. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

3. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y, Gao GF. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiology, 2016;24: 490–502.
4. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. J Pathol. 2015;235(2):185-195.
5. Al-Tawfiq JA, Zumla A, Memish ZA. Coronaviruses: severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus in travelers. Curr Opin Infect Dis. 2014;27(5):411-417.
6. World Health Organization (WHO).Coronavirus disease 2019 (COVID-19) Situation Report – 94, Data as received by WHO from national authorities by 10:00 CEST, 23 April 2020. Available at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200423-sitrep-94-covid-19.pdf?sfvrsn=b8304bf0_4
7. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J. Xing F, Liu J, Yip CCY, Poon RWS, Tsoi HW, Lo SKF, Chan KH, Poon VKM, Chan WM, Daniel Ip J, Cai JP, Cheng VCC, Chen H, Hui CKM, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet 2020; 395: 514–523
8. Hui DSC, Zumla A. Severe Acute Respiratory Syndrome: Historical, Epidemiologic, and Clinical Features. Infect Dis Clin N Am. 2019;33(4):869-889.
9. Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, Wong SS, Leung SY, Chan KH, Yuen KY. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(39):14040-14045.
10. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, Zhu J, Zhang Q, Wu J, Liu L. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J. Med. Virol. 2020; 92(6):595-601.
11. World Health Organization. Middle East Respiratory Syndrome Corona Virus (MERS-COV).2019 March 11. Available at https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)
12. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020. Available at http://webcache.googleusercontent.com/search?q=cache:1BRetychZMMJ:www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf+&cd=1&hl=en&ct=clnk&gl=pk
13. Ong SW, Tan YK, Chia PY, Lee TH, Ng OT, Wong MS, Marimuthu K. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. Jama. 2020;323(16):1610-1612.
14. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, Xia S, Zhou W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl. Pediatr. 2020;9(1):51-60.
15. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J. Travel Med. 2020 Mar 13.
16. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KS, Lau EH, Wong JY, Xing X. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N. Engl. J. Med. 2020 Jan 29.
17. Riley S, Fraser C, Donnelly CA, Ghani AC, Abu-Raddad LJ, Hedley AJ, Leung GM, Ho LM, Lam TH, Thach TQ, Chau P. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science. 2003; 300(5627):1961-1966.
18. Breban R, Riou J, Fontanet A. Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. The Lancet. 2013;382(9893):694-699.
19. Jiang X, Rayner S, Luo MH. Does SARS-CoV-2 has a longer incubation period than SARS and MERS? J. Med. Virol. 2020;92(5):476-478.
20. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. The Lancet. Infectious diseases. 2009;9(5):291-300.
21. Park JE, Jung S, Kim A, Park JE. MERS transmission and risk factors: a systematic review. BMC Pub Health. 2018;18(1):574.
22. World Health Organization. Estimating mortality from COVID-19: scientific brief, 4 August 2020. World Health Organization; 2020.
23. Harcourt JL, Rudoler N, Tamin A, Leshem E, Rasis M, Giladi M, Haynes LM. The prevalence of Middle East

respiratory syndrome coronavirus (MERS-CoV) antibodies in dromedary camels in Israel. Zoonoses Public Hlth. 2018;65(6):749-754.

24. de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, Fouchier RA, Galiano M, Gorbalenya AE, Memish ZA, Perlman S. Commentary: Middle east respiratory syndrome coronavirus (mers-cov): announcement of the coronavirus study group. J Virology. 2013;87(14):7790-7792.
25. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. InCoronaviruses 2015 (pp. 1-23). Humana Press, New York, NY.
26. Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. Natur Struc Molecular Biology. 2006;13(8):751-752.
27. Delmas B, Laude H. Assembly of coronavirus spike protein into trimers and its role in epitope expression. J Virology. 1990;64(11):5367-5375.
28. Klausegger A, Strobl B, Regl G, Kaser A, Luytjes W, Vlasak R. Identification of a coronavirus hemagglutinin-esterase with a substrate specificity different from those of influenza C virus and bovine coronavirus. J Virology. 1999;73(5):3737-43.
29. Shirato K, Kawase M, Matsuyama S. Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2. J Virology. 2013;87(23):12552-12561.
30. Eckerle I, Müller MA, Kallies S, Gotthardt DN, Drosten C. In-vitro renal epithelial cell infection reveals a viral kidney tropism as a potential mechanism for acute renal failure during Middle East Respiratory Syndrome (MERS) Coronavirus infection. J Virology. 2013; 10(1):359.
31. Song W, Wang Y, Wang N, Wang D, Guo J, Fu L, Shi X . Identification of residues on human receptor DPP4 critical for MERS-CoV binding and entry. Virology. 2014; 471-473:49-53.
32. Shirato K, Yano T, Senba S, Akachi S, Kobayashi T, Nishinaka T, Notomi T, Matsuyama S. Detection of Middle East respiratory syndrome coronavirus using reverse transcription loop-mediated isothermal amplification (RT-LAMP). Virology J. 2014;11(1):139.
33. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: what we know. Int J Infect. Dis. 2020 Mar 12.
34. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–1242.
35. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741
36. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M, Al Nakhli D, Al Aidaroos AY, Al Sherbeeni N, Al-Khashan HI, Memish ZA, Albarrak AM. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect. Dis. 2014; 29:301-306
37. Alghamdi IG, Hussain II, Almalki SS, Alghamdi MS, Alghamdi MM, El-Sheemy MA. The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. Int. J. Gen. Med. 2014; 7:417-423.
38. Wang JT, Sheng WH, Fang CT, Chen YC, Wang JL, Yu CJ, Chang SC, Yang PC. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg. Infect. Dis. 2004;10(5):818-824.
39. Fehr AR, Channappanavar R, Perlman S. Middle East respiratory syndrome: emergence of a pathogenic human coronavirus. Ann Review Med. 2017;68.
40. General Office of National Health Committee. Office of State Administration of Traditional Chinese Medicine. Notice on the issuance of a programme for the diagnosis and treatment of novel coronavirus (2019-nCoV) infected pneumonia (Trial Version 4). Updated on 2020. Available at: http://bgs. satcm. gov. cn/zhengcewenjian/2020-02-06/12847.
41. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, Bleicker T, Brünink S, Schneider J, Schmidt ML, Mulders DG. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020;25(3):2000045.
42. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. Intensive Care Med. 2020;46(4):579-582.
43. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020;323(18):1843–1844.

44. Feikin DR, Alraddadi B, Qutub M, Shabouni O, Curns A, Oboho IK, Tomczyk MS, Wolff B, Watson JT, Madani TA. Association of higher MERS-CoV virus load with severe disease and death, Saudi Arabia, 2014. Emerg. Infect. Dis. 2015; 21(11):2029–2035.
45. Poon LLM, Chan KH, Wong OK, Yam WC, Yuen KY, Guan Y, Lo YMD, Peiris JSM. Early diagnosis of SARS Coronavirus infection by real time RT-PCR. J Clin Virol. 2003;28(3):233–238.
46. Al Johani S, Hajeer AH. MERS-CoV diagnosis: An update. J Infect Public Heal. 2016;9(3):216-219.
47. Wang YD, Li Y, Xu GB, Dong XY, Yang XA, Feng ZR, Tian C, Chen WF. Detection of antibodies against SARS-CoV in serum from SARS-infected donors with ELISA and Western blot. Clincl Immunol. 2004;113(2):145-150.
48. Paul NS, Roberts H, Butany J, Chung T, Gold W, Mehta S, Konen E, Rao A, Provost Y, Hong HH, Zelovitsky L. Radiologic pattern of disease in patients with severe acute respiratory syndrome: the Toronto experience. Radiographics. 2004;24(2):553-563.
49. Wong KT, Antonio GE, Hui DS, Lee N, Yuen EH, Wu A, Leung CB, Rainer TH, Cameron P, Chung SS, Sung JJ. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. Radiology. 2003;228(2):401-406.
50. Wong KT, Antonio GE, Hui DS, Lee N, Yuen EH, Wu A, Leung CB, Rainer TH, Cameron P, Chung SS, Sung JJ. Thin-section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. Radiology. 2003;228(2):395-400.
51. Das KM, Lee EY, Al Jawder SE, Enani MA, Singh R, Skakni L, Al-Nakshabandi N, AlDossari K, Larsson SG. Acute Middle East Respiratory Syndrome Coronavirus: Temporal Lung Changes Observed on the Chest Radiographs of 55 Patients. AJR. 2015;205(3): W267-S274.
52. Das KM, Lee EY, Langer RD, Larsson SG. Middle East Respiratory Syndrome Coronavirus: What Does a Radiologist Need to Know? AJR. 2016;206(6), 1193–1201.
53. Ajlan AM, Ahyad RA, Jamjoom LG, Alharthy A, Madani TA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: chest CT findings. AJR. 2014;203(4):782-787.
54. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
55. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. Radiology. 2020;296(2): E72-E78.
56. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.
57. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A, Li K, Li S, Shan H. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology. 2020;295(1):202-207.
58. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. AJR. 2020;214(6):1280-1286.
59. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. Radiology. 2020;296(2): E41-E45.
60. Ooi GC, Khong PL, Müller NL, Yiu WC, Zhou LJ, Ho JC, Lam B, Nicolaou S, Tsang KW. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. Radiology. 2004;230(3):836-844.
61. Chang YC, Yu CJ, Chang SC, Galvin JR, Liu HM, Hsiao CH, Kuo PH, Chen KY, Franks TJ, Huang KM, Yang PC. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology. 2005;236(3):1067-1075.
62. Ketai L, Paul NS, Wong KT. Radiology of severe acute respiratory syndrome (SARS): the emerging pathologic-radiologic correlates of an emerging disease. J Thorac Imag. 2006;21(4):276-283.
63. Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, Larsson SG, Langer RD. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J. Radiol. Imaging. 2017; 27(3):342-349.
64. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. Intens. Care Med. 2020;46(4):579-582.

65. Yee J, Unger L, Zadravecz F, Cariello P, Seibert A, Johnson MA, Fuller MJ. Novel coronavirus 2019 (COVID-19): Emergence and implications for emergency care. JACEP open. 2020:10.1002/emp2.12034.
66. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Natural Communi. 2020;11(1):222.
67. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Resp. Med. 2020;8(5):475-481.
68. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, Jose J, Alraddadi B, Almotairi A, Al Khatib K, Abdulmomen A. Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study. Clincl Infect Dis. 2020;70(9):1837-1844.
69. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, Almakhlafi GA, Albarrak MM, Memish ZA, Albarrak AM. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis. 2014;14(11):1090-1095.
70. Memish ZA, Al-Tawfiq JA. Middle East respiratory syndrome coronavirus infection control: the missing piece?. Am. J. Infect. Con. 2014;42(12):1258-1560.
71. Kemp M, Høgh SV, Skov MN, Stenvang S, Gahrn-Hansen B. Quick simultaneous analyses are important when MERS-coronavirus infection is suspected. Ugeskrift for laeger. 2014;176(39).
72. Yao Y, Bao L, Deng W, Xu L, Li F, Lv Q, Yu P, Chen T, Xu Y, Zhu H, Yuan J, Gu S, Wei Q, Chen H, Yuen KY, Qin C. An animal model of MERS produced by infection of rhesus macaques with MERS coronavirus. J. Infect. Dis. 2014;209(2):236-242.
73. Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, Johnson RF, Olinger GG, Jahrling PB, Laidlaw M, Johansen LM. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob. Agents Chemother. 2014;58(8):4885-4893.
74. Moriguchi H, Sato C. Treatment of SARS with human interferons. The Lancet. 2003;362(9390):1159.
75. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS, Yuen KY. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59(3):252-256.