A comparison of COVID-19, SARS and MERS

Tingting Hu1,*, Ying Liu1,*, Mingyi Zhao1, Quan Zhuang2, Linyong Xu3 and Qingnan He1

1 Department of Pediatrics, The Third Xiangya Hospital, Central South University, Changsha, China
2 Transplantation Center, The Third Xiangya Hospital, Central South University, Changsha, China
3 Department of Biomedical Informatics, School of Life Sciences, Central South University, Changsha, China
* These authors contributed equally to this work.

ABSTRACT

In mid-December 2019, a novel atypical pneumonia broke out in Wuhan, Hubei Province, China and was caused by a newly identified coronavirus, initially termed 2019 Novel Coronavirus and subsequently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 19 May 2020, a total of 4,731,458 individuals were reported as infected with SARS-CoV-2 among 213 countries, areas or territories with recorded cases, and the overall case-fatality rate was 6.6% (316,169 deaths among 4,731,458 recorded cases), according to the World Health Organization. Studies have shown that SARS-CoV-2 is notably similar to (severe acute respiratory syndrome coronavirus) SARS-CoV that emerged in 2002–2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) that spread during 2012, and these viruses all contributed to global pandemics. The ability of SARS-CoV-2 to rapidly spread a pneumonia-like disease from Hubei Province, China, throughout the world has provoked widespread concern. The main symptoms of coronavirus disease 2019 (COVID-19) include fever, cough, myalgia, fatigue and lower respiratory signs. At present, nucleic acid tests are widely recommended as the optimal method for detecting SARS-CoV-2. However, obstacles remain, including the global shortage of testing kits and the presentation of false negatives. Experts suggest that almost everyone in China is susceptible to SARS-CoV-2 infection, and to date, there are no effective treatments. In light of the references published, this review demonstrates the biological features, spread, diagnosis and treatment of SARS-CoV-2 as a whole and aims to analyse the similarities and differences among SARS-CoV-2, SARS-CoV and MERS-CoV to provide new ideas and suggestions for prevention, diagnosis and clinical treatment.

INTRODUCTION

A large concentration of pneumonia cases in Wuhan city, Hubei Province, China (World Health Organization (WHO), 2020), was first reported by the Wuhan Municipal Health
Commission on 31 December 2019 (Paules, Marston & Fauci, 2020). Subsequently, on 30 January 2020, the director-general of the World Health Organization (WHO) proclaimed that the outbreak of the new virus constitutes a Public Health Emergency of International Concern (Liu et al., 2020). The virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can lead to severe pneumonia, and the evidence shows that it can be transmitted from human to human (Huang et al., 2020). By 22 July 2020, SARS-CoV-2 had been detected in approximately 216 countries and regions. Epidemiologists and doctors advised that the infection could be well controlled if people reduce exposure, block transmission and volunteer to isolate themselves while infected. Nevertheless, a number of barriers must be overcome to fight SARS-CoV-2. Accordingly, it is especially necessary to develop stronger preventative measures, improve the public’s awareness of protection, and stop the disease from becoming a pandemic.

Coronaviruses (CoVs) consist of four genera: Alphacoronavirus (α), Betacoronavirus (β), Gammacoronavirus (γ) and Deltacoronavirus (δ). Among these, α and β only infect mammals, whereas γ and δ mainly infect birds. Betacoronaviruses are further divided into four lineages: A, B, C and D. Previously, there have been six human coronaviruses: 229E, HKU1, OC43, NL63, middle east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). Among these lineages, 229E, HKU1, OC43 and NL63 are low pathogenic CoVs, whereas SARS-CoV and MERS-CoV are highly pathogenic CoVs (Cui, Li & Shi, 2019). Prior to the SARS-CoV-2 epidemic, there was a devastating outbreak of SARS in 2003 and a similarly devastating outbreak of MERS in 2012, both resulting in up to thousands of deaths; additionally, these outbreaks resulted from zoonotic coronavirus, leading to high morbidity and mortality in the infected population (Liu et al., 2020; Otter et al., 2016).

In this review, we summarize recent research in the field of SARS-CoV-2, especially the biological and epidemiological characteristics, symptoms, laboratory diagnosis, radiological features, treatment and pathology of this virus and present our recommendations. Some of the biological and epidemiological characteristics of SARS-CoV-2 and the clinical presentations that it causes resemble those of SARS-CoV and MERS-CoV; thus, a comparison of the similarities and differences among the three coronaviruses might greatly help minimize the number of deaths caused by SARS-CoV-2 and guide future studies on the new virus.

**SURVEY METHODOLOGY**

First, we set up an independent literature review team to searched for and referred to the guidelines related to SARS-CoV, MERS-CoV and SARS-CoV-2. We also consulted the newly released guidelines for SARS-CoV-2 composed by the National Health Commission of People’s Republic of China and the WHO. Then we confirmed the question which we would focus on: Are there similarities and differences among COVID-19, SARS and MERS? In addition, recent research in the field of SARS-CoV-2 are also in the spotlight by us. Databank and online books were searched on 22 July 2020. During the literature review, we searched the following bibliographic databases: PubMed (mostly), Wiley Online Library and Elsevier/Science Direct. We also searched the following websites: the Centers
for Disease Control and Prevention (CDC, https://www.cdc.gov/), the WHO (https://www.who.int/), the National Administration of Traditional Chinese Medicine (http://www.satcm.gov.cn/) and the National Health Commission of the People’s Republic of China (http://www.nhc.gov.cn/). The following search parameters and MeSH terms “SARS-CoV-2”, “SARS-CoV”, “MERS-CoV”, “epidemiology”, “clinical presentations”, “laboratory diagnosis” and “radiological features” delivered 151 hits (see Fig. 1).

We focused on the similarities and differences of COVID-19, SARS and MERS in all respects to be clinically relevant to a great extent. Thus, inclusion criteria were the following:

- Diagnosis of COVID-19, SARS and MERS by medical experts
- Biological studies of SARS-CoV-2, SARS-CoV and MERS-CoV
- Collection and analysis of at least one of the following biomaterials: faecal, urinary or blood samples of confirmed/suspected individuals
- Analysis of isolated SARS-CoV-2, SARS-CoV or/and MERS-CoV by sequencing et al.
- Epidemiological investigations and studies of SARS-CoV-2, SARS-CoV and MERS-CoV

![Methodical approach of this review.](https://www.cdc.gov)

Full-size DOI: 10.7717/peerj.9725/fig-1
The latest diagnostic criteria of COVID-19, SARS and MERS including clinical presentations, laboratory diagnosis and radiological feature

Latest treatment and prevention methods of COVID-19

Published in a peer-reviewed article

Availability of the full text publication

Availability of the paper in English

Most of the included papers were published between 2005 and 2020 and the evaluation of papers was conducted in the procedure above by two experienced researchers. Among the included papers, six papers were excluded because the full texts were not available; besides, three non-English papers were excluded and five papers were also excluded for lacking of any relevance to the subject. Totally, 137 texts were selected for this literature Review.

BIOLOGICAL AND EPIDEMIOLOGIC FEATURES OF THE THREE VIRUSES

Biological features

Researchers determined the sequence of SARS-CoV-2 through high-throughput sequencing. In addition to the published references on SARS-CoV and MERS-CoV, we compared the biological features of SARS-CoV-2, SARS-CoV and MERS-CoV, which are summarized in Table 1. As shown in this table, SARS-CoV-2 can cause severe acute respiratory syndrome and has a 4.2% mortality rate; similarly, SARS-CoV and MERS-CoV can cause severe acute respiratory syndrome and have mortality rates of 11% and 34%, respectively (Yang et al., 2020).

According to previous studies, SARS-CoV-2 has been confirmed to share 79.5% sequence identity with SARS-CoV and 94.6% sequence identity with SARS-CoV in ORF1a/b; the sequencing results were used for CoV species classification and revealed that both of these viruses are lineage B betacoronaviruses (Zhou et al., 2020; Lu et al., 2020). However, SARS-CoV-2 shares only 40% sequence identity with MERS-CoV, which is a lineage C betacoronavirus (Chan et al., 2020). Civets are the intermediate hosts of SARS-CoV, whereas dromedary camels are the intermediate hosts of MERS-CoV (Zhou et al., 2020; Lu et al., 2020). However, the intermediate hosts of SARS-CoV-2 have not been determined. At present, the prevailing viewpoints suggest Malayan pangolins and turtles (Liu et al., 2020).

CoVs are RNA viruses characterized by a single-stranded, 5′-capped, positive strand RNA molecule ranging from 26 to 32 kb, and the RNA includes at least six open reading frames (ORFs). The first ORF (ORF1a/b) comprises approximately 2/3 of the genome and encodes replicase proteins, and the remaining ORFs mainly encode four structural proteins: spike (S), membrane (M), envelope (E) and nucleocapsid (N) (Perlman & Netland, 2009). The genome organization of SARS-CoV-2, SARS-CoV and MERS-CoV are described in Fig. 2, and the major distinctions between SARS-CoV-2 and SARS-CoV are in open reading frame-3b (orf3b), spike and open reading frame-8 (orf8), especially
in spike S1 and orf8 (Perlman & Netland, 2009). Orf8 is an accessory protein. The SARS-CoV orf8b can activate NLRP3 inflammasomes and trigger pyroptotic cell death, whereas the new orf8 of SARS-CoV-2 does not contain a known functional domain or motif (Shi et al., 2019). The spike protein can mediate coronavirus entry into host cells. This protein has three segments: a short intracellular tail, a single-pass transmembrane anchor (TM) and a large ectodomain (IC), which consists of two subunits (S1 and S2). The S1 subunit can recognize and bind to receptors, and when S1 binds to a host receptor, the S2 subunit is exposed and cleaved by host proteases, mediating viral and host membrane fusion (Li, 2016; Belouzard, Chu & Whittaker, 2009). The coronavirus structure is described in Fig. 3. The N protein is important for the virus capsid and modulates the initial innate immune response by inhibiting type I interferon (IFN) production (Hui, 2013). The M protein and the E protein are involved in virus morphogenesis, assembly and budding. The S protein mediates virus entry into cells. The receptor of SARS-CoV-2 is angiotensin converting enzyme II (ACE2), which is also the receptor of SARS-CoV. ACE2 binds to the SARS-CoV-2 S ectodomain with 15 nM affinity, which is approximately 10- to 20-fold higher affinity than ACE2 binding to SARS-CoV S. In contrast, the receptor of MERS-CoV is DPP4 (Wrapp et al., 2020). Both ACE2 and DPP4 are recognized by the C-terminal domain in S1 (S1-CTD) as a receptor-binding domain (RBD). As previously mentioned, S1 is one of the major distinctions between SARS-CoV-2 and SARS-CoV. These realizations lead one to wonder how these viruses can recognize the same receptor of the host cell despite their inherent differences. The RBD of SARS-CoV contains two subdomains: a core and an extended loop. The core is constructed of a five-stranded anti-parallel β sheet (β1 to β4 and β7) and three short connecting α helices (αA to αC). The extended loop subdomain is positioned to one side of the core, and a two-stranded β sheet (β5 and β6) forms a gently concave outer surface, the base of which cradles the N-terminal helix of ACE2 (Wang et al., 2013). Although only 9 out of 13 glycans in the table are described, the table provides a comprehensive comparison of biological features among SARS-CoV-2, SARS-CoV and MERS-CoV. The data are from the following studies: Zhou et al. (2020), Lu et al. (2020), Chan et al. (2020), Belouzard, Chu & Whittaker (2009), Hui (2013), Wang et al. (2013) and Yang et al. (2020).

### Table 1 A comparison of biological features among SARS-CoV-2, SARS-CoV and MERS-CoV.

| Coronavirus | SARS-CoV-2 | SARS-CoV | MERS-CoV |
|-------------|-----------|----------|----------|
| Homology*   | –         | 79.5%    | 40%      |
| Possible natural reservoir | Bat (Zhou et al., 2020; Lu et al., 2020) | Bat (Zhou et al., 2020; Lu et al., 2020) | Bat (Zhou et al., 2020; Lu et al., 2020) |
| Possible intermediate host | Malayan Pangolins and turtles (Zhou et al., 2020; Lu et al., 2020) | Palm civets (Zhou et al., 2020; Lu et al., 2020) | Camel (Zhou et al., 2020; Lu et al., 2020) |
| The lineage of Betacoronaviruses | B (Zhou et al., 2020; Lu et al., 2020) | B (Zhou et al., 2020; Lu et al., 2020) | C (Zhou et al., 2020; Lu et al., 2020) |
| Predominant cellular receptor | ACE2 (Belouzard, Chu & Whittaker, 2009; Hui, 2013) | ACE2 (Belouzard, Chu & Whittaker, 2009; Hui, 2013) | Dipeptidyl peptidase 4 (DPP4, also known as CD26) (Wang et al., 2013) |
| Symptoms | Severe acute respiratory syndrome, 4.2% mortality rate (Yang et al., 2020) | Severe acute respiratory syndrome, 11% mortality rate (Yang et al., 2020) | Severe acute respiratory syndrome, 34% mortality rate (Yang et al., 2020) |

Note: * Homology with SARS-CoV-2.
S1 subunit are conserved among SARS-CoV-2 S and SARS-CoV S, their overall structures are similar, and the most notable difference is the position of the RBDs in their respective down conformations: tightly against the N-terminal domain (NTD) in SARS-CoV and angled closer to the central cavity of the trimer in SARS-CoV-2 (Wang et al., 2013).

In contrast to SARS-CoV and other SARSr-CoVs, there is a four amino acid residue insertion at the S1/S2 boundary of SARS-CoV-2 S that results in the presence of a furin cleavage site (Walls et al., 2020). The S1–S2 site cleaved during biosynthesis is not
necessary for S-mediated entry, but it may contribute to the high affinity of SARS-CoV-2 S for human ACE2 (Letko, Marzi & Munster, 2020).

Angiotensin converting enzyme II is the receptor of SARS-CoV-2 and SARS-CoV, and it is one of the enzymes in the renin angiotensin system (RAS). It can convert angiotensin I (AngI) to angiotensin 1–9 (Ang 1–9) and angiotensin II (Ang II) to angiotensin 1–7 (ANG 1–7) to decrease AngII, which can increase aldosterone and vasopressin secretion, cause vasoconstriction, and induce myocardial and renal fibrosis (Flores-Muñoz et al., 2011; Serfozo et al., 2020). As counterregulatory components of the ACE-Ang II-AT1 axis, ACE2 and (ANG 1–7) can control inflammation and fibrosis in cardiovascular and renal disease (Simões e Silva & Teixeira, 2016). Expression of the ACE2 receptor is found in many tissues, including lung, heart, kidney, liver, endothelium, intestine, oral mucosa and even testis (Xu et al., 2020; Cheng, Wang & Wang, 2020; Venkatakrishnan et al., 2020; Xu et al., 2020). ACE2 is reported to improve acute lung injury, suppress hypertension and cardiac dysfunction, reduce glomerular and biliary fibrosis, stimulate brown adipose tissue and induce browning in white adipose tissue (Minato et al., 2020; Liu et al., 2020; Rajapaksha et al., 2019; Kawabe et al., 2019; Chen et al., 2019). All these factors could be targets for SARS-CoV-2 to damage human health. In addition, the level of ACE2 was reported to be related to IL-6, which plays an important role in cytokine storm syndrome (CSS), by Long Chen1 and Li Zhong on Preprint.org. CSS is considered to increase the illness severity of SARS-CoV-2 (Huang et al., 2020).

The lungs are the main target organ of SARS-CoV-2. According to recent research, ACE2 is expressed in 0.64% of all human lung cells, and the majority of them are type II alveolar cells (AT2) (average 83%) (Huang et al., 2020). Consistent with these findings, SARS-CoV-2 presents as lesions involving mainly destruction of the distal alveoli. Other lung cells, such as type I alveolar cells (AT1), endothelial cells, airway epithelial cells, fibroblasts and macrophages, were also reported to express ACE2. Though their ratio is low and variable among individuals, they may also be the target of SARS-CoV-2 (Hamming et al., 2004).

Severe acute respiratory syndrome coronavirus 2 also causes gastrointestinal symptoms, and approximately 3% of patients develop diarrhoeal symptoms (Holshue et al., 2020). Accordingly, oesophageal upper and stratified epithelial cells as well as absorptive enterocytes from the ileum and colon were also reported to be ACE2 positive (Yang et al., 2020). SARS-CoV-2 was also reported by the Third People’s Hospital of Shenzhen to be present in faecal samples. Based on the above-mentioned studies, many researchers speculated that the faecal-oral route may be one route of SARS-CoV-2 transmission; however, it has been fairly settled by WHO that the fecal-oral route does not drive transmission and we should not read too much into this mode of transmission. According to several recent studies, acute kidney injury (AKI) has been reported in over 20% of patients who suffered from COVID-19 in China and the US (Yang et al., 2020; Richardson et al., 2020). Besides, a meta-analysis showed the prevalence of chronic kidney disease was higher in severe patients with COVID-19 (3.3% vs. 0.4%; odds ratio 3.03, 95% CI [1.09–8.47]) (Henry & Lippi, 2020). This outcome may be attributed to ACE2 because ACE2 is expressed in the kidney, especially in proximal tubular cells and bile duct
Notely, ACE2 is also expressed by endothelial cells, and other major clinical events commonly observed in COVID-19 patients including high blood pressure, thrombosis, pulmonary embolism, cerebrovascular and neurologic disorders (Lovren et al., 2008; Chen et al., 2020; Poissy et al., 2020; Aggarwal, Lippi & Michael Henry, 2020; Mao et al., 2020; Baumgartner-Parzer & Waldhausl, 2001).

Epidemiologic features of the three viruses

The SARS-CoV-2 pneumonia outbreak in Wuhan began in early December 2019. Among the first 41 laboratory-confirmed patients, 27 (66%) had been exposed to the Huanan seafood market, where wild animals are sold, suggesting that COVID-19 may be passed to humans from wild animals (Huang et al., 2020). The median incubation period of COVID-19 is 3.0 days (range, 0–24.0 days) (Chen et al., 2020). The disease is highly contagious, and the speed of the spread and the infectivity of COVID-19 dramatically exceeded those of MERS-CoV and SARS-CoV (Goh et al., 2020). The basic reproduction number (R0) reflects the rate of disease transmission. Recent data revealed an R0 for COVID-19 of 2.56 (95% CI [2.49–2.63]), indicating that one patient could transmit the disease to 2.56 other people (Zhao et al., 2020). According to recent data from the WHO, Centers for Disease Control and Prevention (CDC), and reports to the WHO from various countries and their allied agencies, as of 22 July 2020, a total of 14,562,550 individuals were reported as infected with SARS-CoV-2 among 216 countries, areas or territories with recorded cases, and the overall case-fatality rate (CFR) was 4.2% (607,781 deaths among 14,562,550 recorded cases). In a report from the WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports), Europe and the Americas became the locations of the most serious epidemics, instead of China, which had previously been the location for the most serious outbreaks. In China, people with overseas exposures have become the high-risk population, as with Wuhan-related exposures. Male sex and older age are two significant risk factors (Shen et al., 2020). According to a study among 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, the male-to-female ratio was 1.06:1, and the median age was 56 years (interquartile range, 42–68; range, 22–92 years) (Wu & McGoogan, 2020; Wang et al., 2020). Of the 1,591 patients requiring treatment in an intensive care unit (ICU) in the Lombardy region of Italy, the median (IQR) age was 63 (Richardson et al., 2020; Borghesi et al., 2020; Zheng et al., 2020; De Wit et al., 2016; Gao et al., 2016) years, and 1,304 (82%) were male (Grasselli et al., 2020). According to the data from 5,700 hospitalized patients with confirmed COVID-19 in New York City, the median age was 63 years (interquartile range, 52–75; range, 0–107 years), and 39.7% were female (Richardson et al., 2020). One study showed that males aged 50 years or older and females aged 80 years or older showed the highest risk (Borghesi et al., 2020). Health workers are one of the high-risk groups. A total of 3.8% of confirmed COVID-19 patients were health workers (Aggarwal, Lippi & Michael Henry, 2020). Diabetes could be one of the risk factors for progression to severe/critical outcomes (Zheng et al., 2020). Human–human transmission is considered a major transmission mode of COVID-19 by the sixth version of the...
Guidance for Diagnosis and Treatments for COVID-19 issued by the National Health Commission of China. And according to the latest reports from the WHO, the driving transmission of COVID-19 contains droplet transmission, contact transmission and aerosol transmission.

From November 2002, when the first known case of SARS occurred in Foshan, China, to July 2003, when the WHO declared the SARS pandemic over, a total of 8,096 cases were reported in 27 countries, including 774 deaths for a CFR of 9.6% (De Wit et al., 2016). Among these 8,096 cases, 23.1% were health workers, the male–female ratio was 1:1.25, and the mean age was 39.9 years, ranging from 1 to 91 (Rota et al., 2003). The mean incubation period was 6.4 days (range 2–10) (Park et al., 2019). Carrying an HLACw*0801 allele is a risk factor for SARS (Chen et al., 2006). Older age and male gender were predictive of poor prognosis (Chan, Tsui & Wong, 2007). Human–human transmission is also the major transmission mode of SARS-CoV, and the primary route of transmission for SARS is contact of the mucous membranes with respiratory droplets or fomites (https://www.who.int/zh).

MERS first emerged in September 2012 in Saudi Arabia and is still not contained. According to data from the WHO (https://www.who.int/csr/don/24-february-2020-mers-saudi-arabia/zh/), as of 31 January 2020, 2,519 cases of MERS had been laboratory-confirmed, including 858 associated deaths (CFR: 34.4%) that were reported in the 27 countries globally that have had cases of MERS-CoV; the proportion of healthcare workers infected in Saudi Arabia from January 2013 to November 2019 was 19.1%. Based on the analysis of WHO data from 23 September 2012 to 18 June 2018, Ahmadzadeh et al. (2020) described the epidemiological characteristic of MERS as follows: the CFR was 32% (95% CI [29.4–34.5]); the male-to-female ratio was 2.52; the mean age was 50.21 ± 18.73 years and ranged from 2 to 109 years of age; and the risk factors for MERS included age >30 years old, Saudi nationality, comorbidities, and the interval time from symptom onset and admission to the hospital >14 days. The median incubation period was seven days (range 2–17) (Cho et al., 2016). Human–human transmission in MERS-CoV is limited and not sustained (Bernard-Stoecklin et al., 2019). Camels were thought to be involved in its spread to humans, but in what way remains unclear. According to a report from the WHO (https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)), people become infected through unprotected contact with infected dromedary camels or infected people. In conclusion, we summarized the epidemiological comparisons of COVID-19 with SARS and MERS in Table 2.

**SYMPTOMS OF COVID-19, SARS AND MERS**

COVID-19, SARS, and MERS show several similarities regarding their symptoms, which include fever, cough, myalgia, fatigue and lower respiratory signs. However, the symptoms vary with the state of the illness and in the process of disease progression. Notably, 60% of patients suffering from SARS have watery diarrhoea in addition to the abovementioned symptoms with the characteristics that there is a representative biphasic clinical course (Hui & Zumla, 2019; Monaghan, 2016). Patients who suffer from MERS
have symptoms that include fever, cough (predominantly dry), malaise, myalgia, nausea, vomiting, diarrhoea, headache and even renal failure (Arabi et al., 2014; Gao et al., 2016). Not surprisingly, the symptoms of MERS resemble SARS, but the clinical course is unpredictable and changeable. More than half of the MERS patients are reported to develop acute renal damage at an average time of approximately ten days after the onset of symptoms; additionally, the majority of the cases require renal replacement therapy (Arabi et al., 2014; Assiri et al., 2013; Memish et al., 2014). However, approximately 6.6% of patients who are infected with SARS develop acute renal failure at a median time of 20 days after onset, and only 5% call for replacement therapy (Chan, Tsui & Wong, 2007).

Direct renal injury is considered to contribute to the common symptoms of acute renal damage in MERS patients (Monaghan, 2016); namely, DPP4 is present in renal cells, and MERS-CoV can be detected in urine. The majority of patients with COVID-19 infections present with fever (98%), cough (76%), and myalgia or fatigue (44%). It has been

---

**Table 2** Epidemiological comparison of COVID-19 with SARS and MERS. The data are from the following studies: Poissy et al. (2020), Aggarwal, Lippi & Michael Henry (2020), Mao et al. (2020), Baumgartner-Parzer & Waldhausl (2001), Huang et al. (2020), Chen et al. (2020), Goh et al. (2020), Zhao et al. (2020), Shen et al. (2020), Wu & McGoogan (2020), Wang et al. (2020), Grussell et al. (2020), Richardson et al. (2020) and Borghesi et al. (2020). Other data were obtained from the World Health Organization (WHO, https://www.who.int/emergencies/diseases/novel-coronavirus-2019), the Centers for Disease Control and Prevention (CDC, https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/index.html), and reports from various countries and their allied ministries to the WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen; https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1; https://www.ecdc.europa.eu/en/covid-19-pandemic).

| Outbreak date   | 2019-nCoV | SARS-CoV | MERS-CoV |
|-----------------|-----------|----------|----------|
| Confirmed cases | 4,731,458 (19 May 2020) | 8,096 (31 July 2003) | 2,519 (31 January 2020) |
| Total death     | 316,169 (19 May 2020) | 774 (31 July 2003) | 866 (31 January 2020) |
| CRF             | 6.6%      | 9.6%     | 34.4%    |
| Countries, areas or territories with cases | 213 (19 May 2020) | 29 (31 July 2003) | 27 (31 January 2020) |
| Incubation period, days (range) | 3.0 (0–24.0) | 6.4 (2–10) | 7 (2–17) |
| Major routes of transmission | Respiratory aspirates, droplets, contacts and feces | Respiratory aspirates, droplets and contacts (World Health, 2003) | Unprotected contact with infected dromedary camels or infected people |
| Age, years (range) | 56 (22–92) (in Wuhan, China) | 39.9 (1–91) | 50.21 (2–109) |
| Proportion of health workers | 3.8% | 23.1% | 19.1% |
| Male:female ratio | 1.06:1 | 1:1.25 | 1:2.52 (Ahmadzadeh et al., 2020) |
| Risk areas      | Europe, Americas | China | Saudi Arabia |
| Risk factors    | Male, older ages | Cw*0801 HLA | Age >30 years old, Saudi nationality, comorbidities, the interval time of onset sign and the admission to the hospital >14 days |
reported that 55% of patients can present with dyspnoea, which develops a median of eight days after the onset of initial symptoms (Kanne, 2020). In light of the studies from all over the country, the symptoms suggest that the target cell is likely present in the lower respiratory tract, as patients who are infected with COVID-19 seldom have conspicuous upper respiratory symptoms such as sneezing or sore throat (Huang et al., 2020). The autopsy reports of new coronavirus pneumonia (NCP) patients indicate that the disease mainly causes distal airway inflammatory reactions and alveolar damage, which is coincidental with the abovementioned symptoms. The fibrosis and consolidation in the lungs of SARS patients are more serious than the lesions caused by COVID-19, which indicates that the chest lesions are not primarily serous inflammation; instead, the exudative reaction of SARS is less than that of COVID-19.

LABORATORY DIAGNOSIS AND RADIOLOGICAL FEATURES

Laboratory diagnosis

Specimens

Laboratory diagnosis plays a leading role in the early detection of infected individuals, which enables an earlier discovery of the source of infection and interruption of epidemic transmission (Yan, Chang & Wang, 2020). The first and crucial step for laboratory testing is the collection and processing of suitable specimens. In light of the published studies, viral RNA, considered one of the gold standards of detection, can be found in the upper respiratory tract (URT), lower respiratory tract (LRT), stool, blood, and urine of patients who are infected with SARS-CoV, MERS-CoV, and SARS-CoV-2. The detection rates of the abovementioned specimens for SARS-CoV, MERS-CoV, and SARS-CoV-2 infection are summarized in Table 3 (Zhang et al., 2020; Young et al., 2020; Peiris et al., 2003; Poon et al., 2003; Corman et al., 2016; Ng et al., 2003; Chen et al., 2020; Ling et al., 2020). We can select the specimens showing higher sensitivity in different stages.

Nucleic acid tests

Currently, nucleic acid tests (NAT) are widely considered the optimal method for diagnosis, since specific primers and standard operation procedures have been established during sequencing of the total genome of the coronavirus (Monaghan, 2016). In general, real-time polymerase chain reaction (RT-PCR) is thought to be the preferred and most widely used NAT method (Gootenberg et al., 2017). The ORF1a, ORF1b, S gene, and N gene, in addition to the M gene and 3′UTR, are all gene targets of RT-PCR assays, which can have high sensitivity. The RT-PCR methods for SARS-CoV, MERS-CoV and SARS-CoV-2 varied in genome target, sequence, assay use, etc. (Lu et al., 2014; Emery et al., 2004; Yan, Chang & Wang, 2020). As shown, most of the in-house assays, as well as commercial kits, can detect two or three regions of the virus genome. However, there are many knowledge gaps and limitations to overcome, including the difficulties of obtaining testing kits due to the global shortage, the requirements of having access to sophisticated equipment, and the management of false negatives that need to be retested (Al-Tawfiq & Memish, 2020; Loeffelholz & Tang, 2020).
The abovementioned limitations have resulted in the development in recent years of many kinds of NAT testing kits used for routine detection of SARS-CoV and MERS-CoV, such as nucleic acid sequence-based amplification (NASBA), loop-mediated isothermal amplification (LAMP), rolling-circle amplification (RCA), clustered regularly interspaced short palindromic repeats (CRISPR) system, etc., the details of which are summarized in Table 4. As shown, a real-time NASBA assay was developed by Chantratita et al. (2004) that can detect only one strand of SARS-CoV RNA. In the same year, the RT-LAMP assay for SARS-CoV can detect 0.01 PFU, which is 100-fold greater than RT-PCR sensitivity (Hong et al., 2004). Several RT-LAMP methods of MERS-CoV that can detect 3.4–15.8 copies of MERS-CoV RNA have been developed (Shirato et al., 2018; Lee et al., 2017). RT-PCR can detect SARS-CoV and MERS-CoV with sensitivities of five copies and 10 copies, respectively (Wang et al., 2005; Abd El Wahed et al., 2013).

At present, many NAT kits have been developed for SARS-CoV-2, especially RT-PCR. However, according to previous studies, the currently available RT-PCR kits are variable

---

### Table 3: The detection rates of SARS-CoV-2, MERS-CoV, and SARS-CoV infection.

| Sample type                  | Time of illness (days) | SARS-CoV-2 | MERS-CoV (Memish et al., 2014; Huang et al., 2020) | SARS-CoV | Other URT specimens |
|------------------------------|------------------------|------------|-----------------------------------------------------|----------|---------------------|
| URT                          | 7                      | Throat swabs | Nasopharyngeal swabs | Throat swabs | Nasopharyngeal swabs | NP aspirates | Other URT specimens |
|                             |                        | 50% (Arabi et al., 2014) | 100% (Gao et al., 2016) | 75.5% | 33.3% | 32% (Arabi et al., 2014) | 39% (Memish et al., 2014) |
|                             | 14                     | 25% (Arabi et al., 2014) | 94.4% (Gao et al., 2016) | 45.8% | 23.5% | 68% (Arabi et al., 2014) | 32% (Hui & Zumla, 2019) |
|                             | 21                     | N/A         | 69.2% (Gao et al., 2016) | 0 | 5.88% | 39% (Arabi et al., 2014) | 25% (Hui & Zumla, 2019) |
| LRT (sputum or tracheal aspirate) | 7                      | N/A        | 100% | 100% (Hui & Zumla, 2019) |
|                             | 14                     | N/A        | 93% | 100% (Hui & Zumla, 2019) |
|                             | 21                     | N/A        | 66.7% | 67% (Hui & Zumla, 2019) |
| Blood                        | 7                      | 40% (Arabi et al., 2014) | 10% | 50% (Assiri et al., 2013) |
|                             | 14                     | 25% (73) | 29.4% | 50% (72) |
|                             | 21                     | N/A        | 17.6% | 25% (Assiri et al., 2013) |
| Urine                        | 7                      | 6.9% (74) | 9% | 33% (67) |
|                             | 14                     | N/A        | 0 | 25% (Hui & Zumla, 2019) |
|                             | 21                     | N/A        | 0 | 14% (Hui & Zumla, 2019) |
| Stool                        | 7                      | 53% (Monaghan, 2016) | 16.7% | 47% (Hui & Zumla, 2019) |
|                             | 14                     | 37.5% (69) | 14.3% | 97% (Arabi et al., 2014) |
|                             | 21                     | N/A        | 0 | 54% (Hui & Zumla, 2019) |

Notes:
- Conventional RT-PCR.
- RT-PCR assay.
N/A, not applicable, that is, the lack of data in a form or table.
Other URT specimens: Throat swabs and nasopharyngeal swabs.
and offer sensitivities ranging between 45 and 60% (Yi, 1990; Al-Tawfiq & Memish, 2020). In addition, these methods are not satisfactory, especially in resource-limited regions. There is no doubt that NAT based on clinical manifestations and epidemiology can be an early and rapid screening diagnosis. If NAT is not available, CT imaging also plays a vital role in the diagnosis.

Radiological features

Medical imaging technology that is commonly used to diagnose SARS, MERS and COVID-19 includes chest X-ray (CXR), computed tomography (CT) and high resolution computed tomography (HRCT). The spatial resolution of CXR is high, but the density resolution is not very good, which leads to a relatively high omission diagnostic rate. Instead, CT has a higher density resolution because it can quantitatively evaluate images. Not surprisingly, HRCT has a high spatial and density resolution and can detect small parenchymal lesions early.

The radiological features of SARS

CXR findings

The earliest radiographic abnormalities were described as GGOs, and in the majority of patients, the radiographic abnormalities progressed rapidly to focal, multifocal or diffuse consolidation. Airspace shadowing is the most common abnormality found on the CXR at presentation but it is nonspecific because, according to the survey, 10–40% of symptomatic patients in published reports, irrespective of age, have normal initial CXRs, and the findings may be indistinguishable from pneumonia of other causes (Ooi & Daqing, 2003). In approximately two-thirds of patients, unilateral lung involvement is found at presentation, and as the condition progresses, it can become bilateral with maximal lung involvement. In addition, consolidation tends to be peripheral in distribution with lower zone predominance (Ooi & Daqing, 2003). Moreover, CXR obtained in most SARS patients at initial presentation is abnormal, and the disease progression in these patients can be monitored with serial chest radiography (Paul et al., 2004).

CT findings

Ground-glass opacification, consolidation, and inter-lobular interstitial and intralobular septal thickening are the most common findings in HRCT scans, mainly with predominant involvement of the periphery and lower lobe. According to a previous study,
high-resolution CT scans (HR-CT) may be useful in detecting opacities in patients with normal CXR (Paul et al., 2004; Groneberg et al., 2003). In early stages, abnormalities described on CT include ground-glass opacification, consolidation, interlobular interstitial and intralobular septal thickening (Wang et al., 2003). When in the progressive stage, the disease findings by HRCT, including lesion size, range and severity, progressed steadily. When in the late stages, consolidation can be indistinguishable from acute respiratory distress syndrome (ARDS). Above all, CT is more sensitive in depicting SARS than conventional CXR, and CT images obtained in patients with normal chest radiographs may show extensive disease and airspace consolidation (Hong et al., 2004).

The radiological features of MERS

CXR findings

A study by Das et al. (2016) indicated that abnormalities can be detected on initial CXR in 83% of patients who suffered from MERS-CoV, and the main CXR findings of MERS-CoV include ground-glass opacity (66%) and consolidation (18%), both of which are distinct in 16% of infection cases. The consolidation can be patchy, coalesced or show opaque rounded nodules. The primary CXR of infected cases appears as lung parenchymal abnormalities with the dominating images of a peripheral mid-lung zone and peripheral lower lung zone. Involvement of multifocal lung parenchymal abnormalities is less common than unifocal involvement. Furthermore, serial CXR obtained during the progression of the disease can be used to evaluate the degree of radiographic deterioration. In general, the progression of MERS can be divided into four types (i.e., types 1–4). Type 1 is the disease development period that appears as initial radiographic deterioration with improvement. Type 2 is the quiet period that shows no apparent changes in CXR. Type 3 manifests as fluctuating radiographic changes with at least two radiographic peaks divided by a stage of soft remission. Type 4 is the progression of radiographic deterioration (Das et al., 2016).

CT findings

On the basis of the statistics and the published references, MERS CT imaging findings are more sensitive than CXR; unquestionably, CT is used to confirm or assess the progress of highly suspected MERS (Das et al., 2016). The most common CT findings of MERS are that of bilateral, predominantly subpleural and basilar airspace changes, with more extensive GGOs than consolidation (Ajan, 2015). CT scans were also assessed for the presence of consolidation, cavitation, centrilobular nodules, tree-in-bud pattern, septal thickening, peribronchial opacities, reticulation, architectural distortion, subpleural bands, traction bronchiectasis, bronchial wall thickening, intrathoracic lymph node enlargement, interlobular thickening and pleural effusions (Das et al., 2015). Generally speaking, ground-glass opacities, consolidation and a combination of the above-mentioned image results are commonly found during the first week of infection; additionally, pleural effusion and interlobular thickening can also be seen on CT imaging findings of some infected cases (Das et al., 2015). Other CT imaging findings can be seen in different stages with the development of the disease. Interestingly, Petruzzi, Shanthly & Thakur (2009)
proposed that PET/CT, a new imaging technology, can be more sensitive and specific than traditional imaging technology such as CT and CXR. Their research also confirmed that PET/CT can quantitatively describe pulmonary infections. In 2016, a study by Das et al. (2016) proposed that distinctly increased β-2-(18F)-Fluoro-2-deoxy-D-glucose (18F-FDG) might be seen in patients who are infected with MERS (Wang et al., 2005).

The radiological features of COVID-19

CXR findings
In the early phase, CXR of COVID-19 patients is not highly recommended for clinical diagnosis because of its low sensitivity in detecting SARS-CoV-2 pneumonia. Nevertheless, in some areas with limited resources, CXR, as a radiological technology, might have some practical applicability (Paul et al., 2004). The earliest radiographic abnormalities can be negative or only a few patchy increased density shadows. As the disease progresses, CXR can detect double lung patterns and patchy increased density shadows, which are mainly in the lower bilateral lung fields. Furthermore, severely ill patients can exhibit diffuse consolidation of both lungs, even showing a “white lung” (Yang et al., 2020; Pan et al., 2020; Jakobsson et al., 2014).

CT findings
The imaging findings of COVID-19 are different regarding the age of the patients, the stages of disease, etc. (Li & Xia, 2020). The CT imaging findings of COVID-19 are divided into early stage, progressive stage and severe stage considering the scope and evolution of lesions, and the characteristics of each stage are as follows: (1) Early stage: single or multiple scattered patchy or conglomerate GGO, mainly in the middle and lower lungs and along the bronchovascular bundles; (2) Progressive stage: increase of imaging findings in density; Extent coexisting with the new areas of disease; Consolidation growing with air bronchograms.; (3) Severe stage: diffuse consolidation of the lungs of varying density; The fibrous exudating; Air-bronchograms; Bronchial dilation.; (4) Dissipation stage: gradual resolution of the GGO; Consolidation in the lungs with some residual curvilinear opacities compatible with fibrosis (Kanne, 2020; Wu et al., 2020; Jin et al., 2020). The CT imaging features of lesions are as follows: (1) The predominant distribution is in the subpleural region along the bronchial tract; (2) Single and double lesions are rarely seen on CT scans, instead, multiple lesions are more common; (3) The lesions can be patchy, nodular, lumpy, honeycomb-like, etc.; (4) The density is commonly uneven, and GGOs, interlobular thickening, consolidation, crazy-paving change, etc. can be seen on CT scans; and (5) Pleural effusion is rarely seen, but concomitant signs, such as air bronchogram, in addition to mediastinal lymph node enlargement, are common. Many published studies have indicated that chest CT should be considered as a major role in the diagnosis and management of COVID-19. For instance, research by Li. Y found that chest CT has a low false negative rate in detecting COVID-19 (3.9% 2/51 cases); thus, a negative chest CT might aid in the management of COVID-19, that is, guide the doctors to make a decision whether the patient should be isolated during the incubation window (Das et al., 2016). However, some researchers still raise objections that a negative chest CT does not ensure
that a person is not infected with SARS-CoV-2; equally, the abnormalities of the chest CT are not exclusive for COVID-19 (Adair & Ledermann, 2020). In general, we should use chest CT reasonably, and there is doubt that early diagnosis based on chest CT can contribute to overcoming the outbreak as soon as possible.

**A summary and a comparison of the three kinds of coronavirus pneumonia**

COVID-19 pneumonia tends to show similarities with SARS and MERS pneumonia on CXR, with a predominance of bilateral ground-glass opacities and consolidative lesions in the peripheral lung. COVID-19 seems radiologically milder than SARS and MERS despite the similarities in CT findings (Yoon et al., 2020). Each disease undoubtedly has unique radiological features, and the summary data are in Table 5 (Kanne, 2020; Das et al., 2015; Wang et al., 2003). In addition, changes in radiographic scores of SARS in general tended to reflect temporal changes in clinical and laboratory parameters such as oxygen saturation (SaO2). Moreover, there were significant inverse relationships between radiographic scores and SaO2. In a study involving a cohort of patients with serologically confirmed SARS, all patients with diffuse consolidation at maximal radiographic change required oxygen supplementation, including mechanical ventilation (Yang et al., 2020). Therefore, we can speculate that it may also be suitable for COVID-19.

**OVERLAPPING AND DISCRETE ASPECTS OF THE PATHOLOGY OF SARS, MERS AND COVID-19**

The available pathology data for SARS and MERS infections mainly rely on limited numbers of autopsy and biopsy cases. According to previous studies, oedematous lungs with increased gross weights and multiple areas of congestion are the predominant visceral

| CT findings                          | COVID-19 | SARS   | MERS  |
|--------------------------------------|----------|--------|-------|
| Ground-glass opacity                 | 86%      | 81.8%  | 86.6% |
| Consolidation                        | 29%      | 45.5%  | 33.3% |
| Crazy-paving                         | 19%      | 36.4%  | 27%   |
| Linear                               | 14%      | 0      | 0     |
| Bronchiectasis                       | 0        | 18.2%  | 0     |
| Interlobular thickening               | 0        | N/A    | 40%   |
| Pleural effusion                     | 0        | 22.7%  | 60%   |
| Pulmonary fibrosis with emphysema    | 0        | 0      | 6.6%  |
| Position on CT                        |          |        |       |
| Peripheral distribution              | 33%      | 69%    | 54%   |
| Central distribution                 | 76%      | 31%    | 24%   |
| Mixed                                | 0        | 0      | 22%   |

Note:

N/A, not applicable, that is, the lack of data in a form or table.
macroscopic changes in fatal SARS cases. Moreover, enlargement of the lymph nodes in
the pulmonary hila and the abdominal cavity, as well as diminished spleen size and
reduced spleen weights, are also the most common changes (Nicholls et al., 2003).
Morphological changes of SARS include bronchial epithelial denudation, loss of cilia, and
squamous metaplasia (Nicholls et al., 2003; Ding et al., 2003; Liu et al., 2020). In the early
phase, the histological features of pulmonary SARS infections may be commonly
connected with acute diffuse alveolar damage; on the contrary, a combination of diffuse
alveolar damage and acute fibrinous and organizing pneumonia are demonstrated in the
later phases of the disease (Gu et al., 2005). Some studies suggest that the pathological
features of MERS infection are varied and include exudative diffuse alveolar damage with
hyaline membranes, pulmonary oedema, type II pneumocyte hyperplasia, interstitial
pneumonia (which is predominantly lymphocytic), and multinucleate syncytial cells.
Moreover, bronchial submucosal gland necrosis was also observed, and it includes the
pathologic basis for respiratory failure and radiologic abnormalities of MERS infection
(Alsaad et al., 2018). Ultra-structurally, viral particles could be found in the pneumocytes,
pulmonary macrophages, macrophages infiltrating the skeletal muscles, and renal
proximal tubular epithelial cells (Walker, 2016). On 17 February 2020, the team of
academician Wang of PLA General Hospital performed a pathologic dissection on a
patient who died of COVID-19. Tissue samples were taken from the patient's lung, liver
and heart tissues, and histological examination of the lung revealed bilateral diffuse
alveolar injury with fibrous mucinous exudation. In the right lung tissue, prominent
alveolar epithelial exfoliation and clear membrane formation suggested ARDS, and in the
left lung, tissue pulmonary oedema and clear membrane formation suggested the early
stage of ARDS. Mononuclear inflammatory infiltrations of lymphocytes in the stroma were
manifested in both lungs, multinucleated giant cells and uncharacteristically enlarged
alveolar cells were found in the alveolar exudate, and the latter contained larger nuclei,
bi-tropic intracytoplasmic granules and prominent nucleoli, which showed viral
cytopathic-like changes. Additionally, no obvious intracytoplasmic or nuclear virus
inclusion bodies were found. The severity of pulmonary lesions in SARS, MERS and
COVID-19 is different, especially the destruction of alveoli and the degree of necrotic lung.
According to the comparison of the pathology, COVID-19 seems to be not as severe as
SARS. Indeed, they show some similarities in pathology in that they all have type II
pneumocyte hyperplasia. However, they also have some differentia. In general, the
pathological features of SARS are that a large proportion of type II pneumocytes fall off into
the alveolar cavity, while the pathological features of SARS are that there are many cells
proliferating and active in the alveolar walls, and some cells even fall into the lumen in
clumps, especially in the late stage (Qu et al., 2020; Xu et al., 2020; Barrett et al., 2020).
Indeed, the degree and progression of alveolar fibrosis are varied. In summary, these results
suggest that pathology may also play a relevant role in the development of disease severity.

**TREATMENTS OF SARS, MERS AND COVID-19**

During the SARS-CoV epidemic, there were no treatments available to reduce
SARS-related diseases and deaths. The earliest treated patients received intravenous
injection (IV) ribavirin, which was based on its broad-spectrum antiviral activity, because there was insufficient time to perform efficacy studies (Poutanen et al., 2003). After confirming that SARS-CoV was the causative agent, many studies on treatments for SARS were started. The most commonly used treatments for SARS include ribavirin, LPV/r, corticosteroids, interferon (IFN) and convalescent plasma or immunoglobulins. Unfortunately, the abovementioned treatments are associated with adverse effects, including avascular necrosis and osteoporosis (Stockman et al., 2006). Therapeutically, MERS therapies resemble SARS therapies, among which antiviral therapy has been widely studied. Broad spectrum antiviral drugs with low toxicity, including interferon, ribavirin and cyclophilin inhibitors, which were used effectively for SARS, were also proven to be effective in MERS patients (De Wilde et al., 2013; Omrani et al., 2014). Severe studies tested and compared the activity of SARS-CoV and MERS-CoV to antiviral drugs. For instance, De Wilde et al. (2013) and De Wit et al. (2016) indicated that SARS-CoV was fifty to one hundred times less sensitive to IFN-α treatment than MERS-CoV (Gu et al., 2005). The therapy of using antibodies targeting the virus was widely recognized during the epidemic of SARS-CoV (Ter Meulen et al., 2004). To date, many antibodies targeting SARS-CoV and MERS-CoV have been identified. However, the difficulties of use worldwide relate to the emergence of possible escape mutants.

At present, no approved antiviral therapy is available for SARS or MERS, nor for COVID-19. The drugs available for COVID-19 contain broad-spectrum antiviral drugs such as nucleoside analogues and HIV-protease inhibitors (Lu, 2020). In light of recent studies, broad-spectrum antivirals, including lopinavir, neuraminidase inhibitors, peptides (EK1), and RNA synthesis inhibitors, are considered reasonable for treatment (Rothan & Byrareddy, 2020). To date, a randomized, controlled clinical trial by Ledford et al. found that dexamethasone is first drug shown to save lives and reduce deaths from the COVID-19 (Ledford, 2020). The other drug shown to benefit people who suffered from COVID-19 is the antiviral drug remdesivir. Surprisingly, Remdesivir was testified to have the function of shortening the length of stay (LOS) of people with COVID, but it did not have significant effects on deaths (Oh et al., 2016). In general, both Remdesivir and Dexamethasone are approved in the united states (USA) to treat COVID-19. Besides, many scientists are working diligently to study COVID-19 to gain a better understand of virus-host interactions, in addition to creating novel therapeutics and testing potential vaccines.

CONCLUSIONS AND OUTLOOK

The novel atypical pneumonia that emerged in Wuhan, Hubei Province has been proven to be caused by SARS-CoV-2, which has homology with SARS-CoV and MERS-CoV to some extent (Liu et al., 2020). The outbreaks of SARS-CoV and MERS-CoV provide us with significant lessons, including valuable experiences and clinical opinions, on how to better fight the SARS-CoV-2 epidemic. Furthermore, the previous treatments can be used as the basis to begin to control the condition. Given the above findings, we present our suggestions. To fully control the situation, we first need to confirm the transmission of
SARS-CoV-2 by performing well-designed large-scale case-control studies; then, proper interventions can be taken to control the cause of disease. Second, monitoring signs of viral genome mutations will play a major role in future research. Third, assessing the effects of antiviral drugs by conducting a randomized controlled study (RCT) is also important. Finally, further research on animal vaccines is especially necessary.

**ACKNOWLEDGEMENTS**

We thank the language modification of this review by company AJE.

**ADDITIONAL INFORMATION AND DECLARATIONS**

**Funding**

This study was supported by grants from the Hunan Innovative Provincial Construction Project (2019SK2211) and the Changsha Science and Technology Plan Project (kq2001044). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Grant Disclosures**

The following grant information was disclosed by the authors:
Hunan Innovative Provincial Construction Project: 2019SK2211.
Changsha Science and Technology Plan Project: kq2001044.

**Competing Interests**

The authors declare that they have no competing interests.

**Author Contributions**

- Tingting Hu conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Ying Liu conceived and designed the experiments, performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Mingyi Zhao conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Quan Zhuang conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Linyong Xu conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Qingnan He analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.

**Data Availability**

The following information was supplied regarding data availability:

This is a review article; there is no raw data.
REFERENCES

Abd El Wahed A, Patel P, Heidenreich D, Hufert FT, Weidmann M. 2013. Reverse transcription recombinase polymerase amplification assay for the detection of middle East respiratory syndrome coronavirus. *PLOS Currents* 5:e8364 DOI 10.1371/currents.outbreaks.62df1c7c75ff96cd59034531e2e8364.

Adair LN, Ledermann EJ. 2020. Chest CT findings of early and progressive phase COVID-19 infection from a US patient. *Radiology Case Reports* 15(7):819–824 DOI 10.1016/j.radcr.2020.04.031.

Aggarwal G, Lippi G, Michael Henry B. 2020. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature. *International Journal of Stroke* 15(4):385–389 DOI 10.1177/1747493020921664.

Ahmadzadeh J, Mobaraki K, Mousavi SJ, Aghazadeh-Attari J, Mirza-Aghazadeh-Attari M, Mohebbi I. 2020. The risk factors associated with MERS-CoV patient fatality: a global survey. *Diagnostic Microbiology and Infectious Disease* 96(3):114876 DOI 10.1016/j.diagmicrobio.2019.114876.

Ajlan AM. 2015. Reply to “Chest CT findings in MERS”. *AJR: American Journal of Roentgenology* 204:W112 DOI 10.2214/AJR.14.13367.

Al-Tawfiq JA, Memish ZA. 2020. Diagnosis of SARS-CoV-2 infection based on CT scan vs RT-PCR: reflecting on experience from MERS-CoV. *Journal of Hospital Infection* 105(2):154–155 DOI 10.1016/j.jhin.2020.03.001.

Alsaad KO, Hajeer AH, Al BM, Al MM, Al ON, Al AA, AlJohani S, Alsolamy S, Gmati GE, Balkhy H, Al-Jahdali HH, Baharoon SA, Arabi YM. 2018. Histopathology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection—clinicopathological and ultrastructural study. *Histopathology* 72:516–524 DOI 10.1111/his.13379.

Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, Hawa H, Alothman A, Khalidi A, Al RB. 2014. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Annals of Internal Medicine* 160:389–397 DOI 10.7326/M13-2486.

Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, Flemban H, Al-Nassir WN, Balkhy HH, Al-Hakeem RF, Makhdoom HQ, Zumla AI, Memish ZA. 2013. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infectious Diseases* 13:752–761 DOI 10.1016/S1473-3099(13)70204-4.

Barrett CD, Moore HB, Moore EE, McIntyre RC, Moore PK, Burke J, Hua F, Apgar J, Talmor DS, Sauaia A, Liptzin DR, Veress LA, Yaffe MB. 2020. Fibrinolytic therapy for refractory COVID-19 acute respiratory distress syndrome: scientific rationale and review. *Research and Practice in Thrombosis and Haemostasis* 4:524–531 DOI 10.1002/rth2.12357.

Baumgartner-Parzer SM, Waldhaeusl WK. 2001. The endothelium as a metabolic and endocrine organ: its relation with insulin resistance. *Experimental and Clinical Endocrinology and Diabetes* 109(Suppl. 2):S166–S179 DOI 10.1055/s-2001-18579.

Belouzard S, Chu VC, Whittaker GR. 2009. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proceedings of the National Academy of Sciences* 106(14):5871–5876 DOI 10.1073/pnas.0809524106.

Bernard-Stoecklin S, Nikolay B, Assiri A, Bin SA, Ben EP, El BH, Ki M, Malik MR, Fontanet A, Cauchemez S, Van Kerkhove MD. 2019. Comparative analysis of eleven healthcare-associated
outbreaks of middle east respiratory syndrome coronavirus (Mers-Cov) from 2015 to 2017. *Scientific Reports* 9:7385 DOI 10.1038/s41598-019-43586-9.

Borghesi A, Zigliani A, Mascullo R, Golemi S, Maculotti P, Farina D, Maroldi R. 2020. Radiographic severity index in COVID-19 pneumonia: relationship to age and sex in 783 Italian patients. *La Radiologia Medica* 125(5):461–464 DOI 10.1007/s11547-020-01202-1.

Chan JF-W, Kok K-H, Zhu Z, Chu H, To KK-W, Yuan S, Yuen K-Y. 2020. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections* 9(1):221–236 DOI 10.1080/22221751.2020.1719902.

Chan JC, Tsui EL, Wong VC. 2007. Prognostication in severe acute respiratory syndrome: a retrospective time-course analysis of 1312 laboratory-confirmed patients in Hong Kong. *Respirology* 12:531–542 DOI 10.1111/j.1440-1843.2007.01102.x.

Chantratita W, Pongtanapisit W, Piroj W, Srichunrasmi C, Seesuai S. 2004. Development and comparison of the real-time amplification based methods—NASBA-Beacon, RT-PCR taqman and RT-PCR hybridization probe assays—for the qualitative detection of sars coronavirus. *Southeast Asian Journal of Tropical Medicine and Public Health* 35:623–629.

Chen YM, Liang SY, Shih YP, Chen CY, Lee YM, Chang L, Jung SY, Ho MS, Liang KY, Chen HY, Chan YJ, Chu DC. 2006. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. *Journal of Clinical Microbiology* 44:359–365 DOI 10.1128/JCM.44.2.359-365.2006.

Chen Q, Liu J, Wang W, Liu S, Yang X, Chen M, Cheng L, Lu J, Guo T, Huang F. 2019. Sini decoction ameliorates sepsis-induced acute lung injury via regulating ACE2-Ang (1-7)-Mas axis and inhibiting the MAPK signaling pathway. *Biomedicine & Pharmacotherapy* 115:108971 DOI 10.1016/j.biopha.2019.108971.

Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, Li F, Xu Q, Zhang Y, Xu S, Song Z, Zeng Y, Shen Y, Shi Y, Zhu T, Lu H. 2020. Clinical progression of patients with COVID-19 in Shanghai, China. *Journal of Infection* 80:e1–e6 DOI 10.1016/j.jinf.2020.03.004.

Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. 2020. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 368:m1091 DOI 10.1136/bmj.m1091.

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. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395:507–513 DOI 10.1016/S0140-6736(20)30211-7.

Cheng H, Wang Y, Wang G-Q. 2020. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *Journal of Medical Virology* 92:726–730 DOI 10.1002/jmv.25785.

Cho SY, Kang JM, Ha YE, Park GE, Lee JY, Ko JH, Lee JY, Kim JM, Kang CI, Jo IJ, Ryu JG, Choi JR, Kim S, Huh HJ, Ki CS, Kang ES, Peck KR, Dhong HJ, Song JH, Chung DR, Kim YJ. 2016. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. *Lancet* 388:994–1001 DOI 10.1016/S0140-6736(16)30623-7.

Corman VM, Albarrak AM, Omrani AS, Albarrak MM, Farah ME, Almasri M, Muth D, Sieberg A, Meyer B, Assiri AM, Binger T, Steinhagen K, Lattwein E, Al-Tawfiq J, Muller MA, Drosten C, Memish ZA. 2016. Viral shedding and antibody response in 37 patients with middle
east respiratory syndrome coronavirus infection. Clinical Infectious Diseases 62:477–483
DOI 10.1093/cid/civ951.

Cui J, Li F, Shi ZL. 2019. Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology 17:181–192 DOI 10.1038/s41579-018-0118-9.

Das KM, Lee EY, Enani MA, AlJawder SE, Singh R, Bashir S, Al-Nakshbandi N, AlDossari K, Larsson SG. 2015. CT correlation with outcomes in 15 patients with acute Middle East respiratory syndrome coronavirus. American Journal of Roentgenology 204(4):736–742 DOI 10.2214/AJR.14.13671.

Das KM, Lee EY, Langer RD, Larsson SG. 2016. Middle east respiratory syndrome coronavirus: what does a radiologist need to know? American Journal of Roentgenology 206(6):1193–1201 DOI 10.2214/AJR.15.15363.

De Wilde AH, Raj VS, Oudshoorn D, Bestebroer TM, Van Nieuwkoop S, Limpens R, Posthuma CC, Van der Meer Y, Barcena M, Haagmans BL, Snijder EJ, Van den Hoogen BG. 2013. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-alpha treatment. Journal of General Virology 94:1749–1760 DOI 10.1099/vir.0.052910-0.

De Wit E, Van Doremalen N, Falzarano D, Munster VJ. 2016. SARS and MERS: recent insights into emerging coronaviruses. Nature Reviews Microbiology 14(8):523–534 DOI 10.1038/nrmicro.2016.81.

Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, Cai J, Li X, Kang W, Weng D, Lu Y, Wu D, He L, Yao K. 2003. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. Journal of Pathology 200:282–289 DOI 10.1002/path.1440.

Emery SL, Erdman DD, Bowen MD, Newton BR, Winchell JM, Meyer RF, Tong S, Cook BT, Holloway BP, McCaustland KA, Rota PA, Bankamp B, Lowe LE, Ksiazek TG, Bellini WJ, Anderson LJ. 2004. Real-time reverse transcription-polymerase chain reaction assay for SARS-associated coronavirus. Emerging Infectious Diseases 10:311–316 DOI 10.3201/eid1002.030759.

Flores-Muñoz M, Smith NJ, Haggerty C, Milligan G, Nicklin SA. 2011. Angiotensin1–9 antagonises pro-hypertrophic signalling in cardiomyocytes via the angiotensin type 2 receptor. Journal of Physiology 589(4):939–951 DOI 10.1113/jphysiol.2010.203075.

Gao H, Yao H, Yang S, Li L. 2016. From SARS to MERS: evidence and speculation. Frontiers in Medicine 10:377–382 DOI 10.1007/s11684-016-0466-7.

Goh GK-M, Dunker AK, Foster JA, Uversky VN. 2020. Rigidity of the outer shell predicted by a protein intrinsic disorder model sheds light on the COVID-19 (Wuhan-2019-nCoV) infectivity. Biomolecules 10(2):331 DOI 10.3390/biom10020331.

Gootenberg JS, Abudayyeh OO, Lee JW, Eslsletzbichler P, Dy AJ, Joung J, Verdine V, Dongbia N, Daringer NM, Freije CA, Myhrvold C, Bhattacharyya RP, Livny J, Regev A, Koonin EV, Hung DT, Sabeti PC, Collins JJ, Zhang F. 2017. Nucleic acid detection with CRISPR-Cas13a/C2c2. Science 356:438–442 DOI 10.1126/science.aam9321.

Grasselli G, Zanrillo 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, Naielsucu A, Corona A, Zangrillo A, Protti A, Albertin A, Forastieri MA, Lombardo A, Pezzi A, Benini A, Scandroglio AM, Malara A, Castelli A, Coluccello A, Micucci A, Pesenti A, Sala A, Alborghetti A, Antonini B, Capra C, Troiano C, Roscita C, Radrizzani D, Chiumento D, Coppini D, Guzzon D, Costantini E, Malpetti E, Zoia E, Catena E, Agosteo E, Barbara E, Beretta E, Boselli E, Storti E, Harizay F, Della MF, Lorini FL, Donato SF, Marino F, Mojoli F,
Rasulo F, Grasselli G, Casella G, De Filippi G, Castelli G, Aldegheri G, Gallioli G, Lotti G, Albano G, Landoni G, Marino G, Vitale G, Battista PG, Evasi G, Citerio G, Foti G, Natalini G, Merli G, Sforzini I, Bianciardi L, Carnevale L, Grazioli L, Cabrini L, Guatteri L, Salvi L, Dei PM, Galletti M, Gemma M, Ranucci M, Riccio M, Borelli M, Zambon M, Subert M, Cecconi M, Mazzoni MG, Raimondi M, Panigada M, Belliato M, Bronzini N, Latronico N, Petrucci N, Belgioioso N, Tagliaabue P, Cortellazzi P, Gnesin P, Grosso P, Gritti P, Perazzo P, Severgnini P, Ruggeri P, Sebastiano P, Covello RD, Fernandez-Olmos R, Fumagalli R, Keim R, Rona R, Valsecchi R, Viola U, Cattaneo S, Colombo S, Cirri S, Bonazzi S, Greco S, Muttini S, Langer T, Alaimo V. 2020. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 323(16):1574–1581 DOI 10.1001/jama.2020.5394.

Groneberg DA, Zhang L, Welte T, Zabel P, Chung KF. 2003. Severe acute respiratory syndrome: global initiatives for disease diagnosis. QJM: An International Journal of Medicine 96:845–852 DOI 10.1093/qjmed/hcg146.

Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, Zou W, Zhan J, Wang S, Xie Z, Zhuang H, Wu B, Zhong H, Shao H, Fang W, Gao D, Pei F, Li X, He Z, Xu D, Shi X, Anderson VM, Leong AS. 2005. Multiple organ infection and the pathogenesis of SARS. Journal of Experimental Medicine 202:415–424 DOI 10.1084/jem.20050828.

Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. Journal of Pathology 203:631–637 DOI 10.1002/path.1570.

Henry BM, Lippi G. 2020. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. International Urology and Nephrology 52:1193–1194 DOI 10.1007/s11255-020-02451-9.

Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK. 2020. First case of 2019 novel coronavirus in the United States. New England Journal of Medicine 382:929–936 DOI 10.1056/NEJMoa2001191.

Hong TC, Mai QL, Cuong DV, Parida M, Minekawa H, Notomi T, Hasebe F, Morita K. 2004. Development and evaluation of a novel loop-mediated isothermal amplification method for rapid detection of severe acute respiratory syndrome coronavirus. Journal of Clinical Microbiology 42:1956–1961 DOI 10.1128/jcm.42.5.1956-1961.2004.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506 DOI 10.1016/S0140-6736(20)30183-5.

Hui DS. 2013. Severe acute respiratory syndrome (SARS): lessons learnt in Hong Kong. Journal of Thoracic Disease 5(Suppl. 2):S122–S126 DOI 10.3978/j.issn.2072-1439.2013.06.18.

Hui D, Zumla A. 2019. Severe acute respiratory syndrome: historical, epidemiologic, and clinical features. Infectious Disease Clinics of North America 33:869–889 DOI 10.1016/j.idc.2019.07.001.

Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, Bjorksten B, Engstrand L, Andersson AF. 2014. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. GUT 63:559–566 DOI 10.1136/gutjnl-2012-303249.
Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang YY, Wang XH. 2020. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Medical Research 7:4 DOI 10.1186/s40779-020-0233-6.

Kanne JP. 2020. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist. Radiology 295(1):16–17 DOI 10.1148/radiol.2020200241.

Kawabe Y, Mori J, Morimoto H, Yamaguchi M, Miyagaki S, Ota T, Tsuma Y, Fukuhara S, Nakajima H, Oudit GY, Hosoi H. 2019. ACE2 exerts anti-obesity effect via stimulating brown adipose tissue and induction of browning in white adipose tissue. American Journal of Physiology: Endocrinology and Metabolism 317:E1140–E1149 DOI 10.1152/ajpendo.00311.2019.

Ledford H. 2020. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature 582:469 DOI 10.1038/d41586-020-01824-5.

Lee SH, Baek YH, Kim Y-H, Choi Y-K, Song M-S, Ahn J-Y. 2017. One-pot reverse transcriptional loop-mediated isothermal amplification (RT-LAMP) for detecting MERS-CoV. Frontiers in Microbiology 7:2166 DOI 10.3389/fmicb.2016.02166.

Letko M, Marzi A, Munster V. 2020. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nature Microbiology 5:562–569 DOI 10.1038/s41564-020-0688-y.

Li F. 2016. Structure, function, and evolution of coronavirus spike proteins. Annual Review of Virology 3(1):237–261 DOI 10.1146/annurev-virology-110615-042301.

Li Y, Xia L. 2020. Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management. American Journal of Roentgenology 214(6):1280–1286 DOI 10.2214/AJR.20.22954.

Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, Wu F, Song ZG, Huang W, Chen J, Hu BJ, Wang S, Mao EQ, Zhu L, Zhang WH, Lu HZ. 2020. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chinese Medical Journal 133:1039–1043 DOI 10.1097/CMJ.0000000000000774.

Liu Q, Lv S, Liu J, Liu S, Wang Y, Liu G. 2020. Mesenchymal stem cells modified with angiotensin-converting enzyme 2 are superior for amelioration of glomerular fibrosis in diabetic nephropathy. Diabetes Research and Clinical Practice 162:108093 DOI 10.1016/j.diabres.2020.108093.

Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, Zhu J, Zhang Q, Wu J, Liu L. 2020. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. Journal of Medical Virology 92:595–601 DOI 10.1002/jmv.25726.

Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, Trilling M, Lu M, Dittmer U, Yang D. 2020. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. Journal of Medical Virology 92:491–494 DOI 10.1002/jmv.25709.

Loeffelholz MJ, Tang Y-W. 2020. Laboratory diagnosis of emerging human coronavirus infections—the state of the art. Emerging Microbes & Infections 9(1):747–756 DOI 10.1080/22221751.2020.1745095.

Lovren F, Pan Y, Quan A, Teoh H, Wang G, Shukla PC, Levitt KS, Oudit GY, Al-Omran M, Stewart DJ, Slutsky AS, Peterson MD, Backx PH, Penninger JM, Verma S. 2008. Angiotensin
converting enzyme-2 confers endothelial protection and attenuates atherosclerosis. *American Journal of Physiology: Heart and Circulatory Physiology* 295:H1377–H1384 DOI 10.1152/ajpheart.00331.2008.

Lu H. 2020. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *BioScience Trends* 14(1):69–71 DOI 10.5582/bst.2020.01020.

Lu X, Whitaker B, Sakhivel SK, Kamili S, Rose LE, Lowe L, Mohareb E, Elssal EM, Al-sanouri T, Haddadin A, Erdman DD. 2014. Real-time transcription-PCR assay panel for Middle East respiratory syndrome coronavirus. *Journal of Clinical Microbiology* 52:67–75 DOI 10.1128/JCM.02533-13.

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 395:565–574 DOI 10.1016/S0140-6736(20)30251-8.

MacParland SA, Liu JC, Ma XZ, Innes BT, Bartczak AM, Gage BK, Manuel J, Khuu N, Echeverri J, Linares I, Gupta R, Cheng ML, Liu LY, Camat D, Chung SW, Seliga RK, Shao Z, Lee E, Ogawa S, Ogawa M, Wilson MD, Fish JE, Selzner M, Ghanekar A, Grant D, Greig P, Sapiochin G, Selzner N, Winegarden N, Adeyi O, Keller G, Bader GD, McGilvray ID. 2018. Single cell RNA sequencing of human liver reveals distinct intrahepatic macrophage populations. *Nature Communications* 9:4383 DOI 10.1038/s41467-018-06318-7.

Monaghan NP. 2016. Emerging infections–implications for dental care. *British Dental Journal* 221(1):13–15 DOI 10.1038/sj.bdj.2016.486.
2016. Viral load kinetics of MERS coronavirus infection. New England Journal of Medicine 375:1303–1305 DOI 10.1056/NEJMc1511695.

Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, Almakhlafi GA, Albarrak MM, Memish ZA, Albarrak AM. 2014. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infectious Diseases 14:1090–1095 DOI 10.1016/S1473-3099(14)70920-X.

Ooi GC, Daqing M. 2003. SARS: radiological features. Respirology 8:S15–S19 DOI 10.1046/j.1440-1843.2003.00519.x.

Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. 2016. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. Journal of Hospital Infection 92(3):235–250 DOI 10.1016/j.jhin.2015.08.027.

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

Park S, Park JY, Song Y, How SH, Jung K-S. 2019. Emerging respiratory infections threatening public health in the Asia-Pacific region: a position paper of the Asian Pacific Society of Respirology. Respirology 24(6):590–597 DOI 10.1111/resp.13558.

Paul NS, Roberts H, Butany J, Chung T, Gold W, Mehta S, Rao A, Provost Y, Hong HH, Zelovitsky L, Weisbrod GL. 2004. Radiologic pattern of disease in patients with severe acute respiratory syndrome: the Toronto experience. Radiographics 24:553–563 DOI 10.1148/rg.242035193.

Paules CI, Marston HD, Fauci AS. 2020. Coronavirus infections—more than just the common cold. JAMA 323(8):707 DOI 10.1001/jama.2020.0757.

Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY. 2003. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361:1767–1772 DOI 10.1016/s0140-6736(03)13412-5.

Perlman S, Netland J. 2009. Coronaviruses post-SARS: update on replication and pathogenesis. Nature Reviews Microbiology 7:439–450 DOI 10.1038/nrmicro2147.

Petruzzi N, Shanthly N, Thakur M. 2009. Recent trends in soft-tissue infection imaging. Seminars in Nuclear Medicine 39(2):115–123 DOI 10.1053/j.semnuclmed.2008.10.005.

Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S, Cousin N, Durand A, El Kalouby A, Favory R, Girardie P, Houard M, Jaillet E, Jourdain M, Ledoux G, Mathieu D, Moreau A-S, Niles C, Nseir S, Onimus T, Préau S, Robriquet L, Rouzé A, Simonnet A, Six S, Toussaint A, Dupont A, Bauters A, Zawadzki C, Paris C, Trillot N, Wibaut B, Hochart A, Marichez C, Dalibard V, Vanderz estate S, Bourgeois L, Gaul A, Jospin A, Stepina N, Pradines B, Tournys A, Brousseau T, Rémy M, Hutt A. 2020. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation 142:184–186 DOI 10.1161/CIRCULATIONAHA.120.047430.

Poon LLM, Chan KH, Wong OK, Yam WC, Yuen KY, Guan Y, Lo YMD, Peiris JSM. 2003. Early diagnosis of SARS coronavirus infection by real time RT-PCR. Journal of Clinical Virology 28(3):233–238 DOI 10.1016/j.jcv.2003.08.004.
Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, Tellier R, Draker R, Adachi D, Ayers M, Chan AK, Skowronski DM, Salit I, Simor AE, Slutsky AS, Doyle PW, Krajden M, Petric M, Brunham RC, McGeer AJ. 2003. Identification of severe acute respiratory syndrome in Canada. New England Journal of Medicine 348:1995–2005 DOI 10.1056/NEJMoa030634.

Qu W, Wang Z, Hare JM, Bu G, Mallea JM, Pascual JM, Caplan AI, Kurtzberg J, Zubair AC, Kubrova E, Engelberg-Cook E, Nayfeh T, Shah VP, Hill JC, Wolf ME, Prokop LJ, Murad MH, Sanfilippo FP. 2020. Cell-based therapy to reduce mortality from COVID-19: systematic review and meta-analysis of human studies on acute respiratory distress syndrome. STEM CELLS Translational Medicine. Epub ahead of print 29 May 2020 DOI 10.1002/sctm.20-0146.

Rajapaksha IG, Gunarathe LS, Asadi K, Cunningham SC, Sharland A, Alexander IE, Angus PW, Herath CB. 2019. Liver-targeted angiotensin converting enzyme 2 therapy inhibits chronic biliary fibrosis in multiple drug-resistant gene 2-knockout mice. Hepatology Communications 3:1656–1673 DOI 10.1002/hep4.1434.

Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. 2020. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 323(20):2052 DOI 10.1001/jama.2020.6775.

Rota PA, Oberste MS, Monroe SS, Nix WA, Campagnoli R, Icenogle JP, Penaranda S, Bankamp B, Maher K, Chen MH, Tong S, Tamin A, Lowe L, Frace M, DeRisi JL, Chen Q, Wang D, Erdman DD, Peret TC, Burns C, Ksiazek TG, Rollin PE, Sanchez A, Liffick S, Holloway B, Limor J, McCaustland K, Olsen-Rasmussen M, Foucher R, Gunther S, Osterhaus AD, Drosten C, Pallansch MA, Anderson LJ, Bellini WJ. 2003. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 300:1394–1399 DOI 10.1126/science.1085952.

Rothan HA, Byrareddy SN. 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 109:102433 DOI 10.1016/j.jaut.2020.102433.

Serfozo P, Wysocki J, Gulua G, Schulze A, Ye M, Liu P, Jin J, Bader M, Myohanen T, Garcia-Horsman JA, Batlle D. 2020. Ang II (Angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (Prolyloligopeptidase)-dependent and ACE2 (Angiotensin-converting enzyme 2)-independent. Hypertension 75:173–182 DOI 10.1161/HYPERTENSIONAHA.119.14071.

Shen N, Zhu Y, Wang X, Peng J, Liu W, Wang F, Lu Y, Cheng L, Sun Z. 2020. Characteristics and diagnosis rate of 5630 subjects receiving SARS-CoV-2 nucleic acid tests from Wuhan, China. JCI Insight 5(10):e137662 DOI 10.1172/jci.insight.137662.

Shi CS, Nabar NR, Huang NN, Kehrl JH. 2019. SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discovery 5:101 DOI 10.1038/s41420-019-0181-7.

Shirato K, Semba S, El-Kafrawy SA, Hassan AM, Tolah AM, Takayama I, Kageyama T, Notomi T, Kamitani W, Matsuyama S, Azhar EI. 2018. Development of fluorescent reverse transcription loop-mediated isothermal amplification (RT-LAMP) using quenching probes for the detection of the Middle East respiratory syndrome coronavirus. Journal of Virological Methods 258:41–48 DOI 10.1016/j.jviromet.2018.05.006.
Simões e Silva AC, Teixeira MM. 2016. ACE inhibition, ACE2 and angiotensin-(1-7) axis in kidney and cardiac inflammation and fibrosis. *Pharmacological Research* **107**:154–162 DOI 10.1016/j.phrs.2016.03.018.

Soler MJ, Batlle M, Riera M, Campos B, Ortiz-Perez JT, Anguiano L, Roca-Ho H, Farrero M, Mont L, Pascual J, Perez-Villa F. 2019. ACE2 and ACE in acute and chronic rejection after human heart transplantation. *International Journal of Cardiology* **275**:59–64 DOI 10.1016/j.ijcard.2018.10.002.

Stockman LJ, Bellamy R, Garner P, Low D. 2006. SARS: systematic review of treatment effects. *PLOS Medicine* **3**(9):e343 DOI 10.1371/journal.pmed.0030343.

Ter Meulen J, Bakker AB, Van den Brink EN, Weverling GJ, Martina BE, Haagmans BL, Kuiken T, De Kruif J, Preiser W, Spaan W, Gelderblom HR, Goudsmitt J, Osterhaus AD. 2004. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. *Lancet* **363**(2139–2141) DOI 10.1016/S0140-6736(04)16506-9.

Venkatakrishnan AJ, Puranik A, Anand A, Zemmour D, Yao X, Wu X, Chilaka R, Murakowski DK, Standish K, Raghunathan B, Wagner T, Garcia-Rivera E, Solomon H, Garg A, Barve R, Anyanwu-Ojihi A, Khan N, Soundararajan V. 2020. Knowledge synthesis of 100 million biomedical documents augments the deep expression profiling of coronavirus receptors. *eLife* **9**:199 DOI 10.7554/eLife.58040.

Walker DH. 2016. Value of autopsy emphasized in the case report of a single patient with Middle East respiratory syndrome. *American Journal of Pathology* **186**:507–510 DOI 10.1016/j.ajpath.2015.11.001.

Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. 2020. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* **181**(2):281–292.e6 DOI 10.1016/j.cell.2020.02.058.

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. 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* **323**(11):1061 DOI 10.1001/jama.2020.1585.

Wang B, Potter SJ, Lin Y, Cunningham AL, Dwyer DE, Su Y, Ma X, Hou Y, Saksena NK. 2005. Rapid and sensitive detection of severe acute respiratory syndrome coronavirus by rolling circle amplification. *Journal of Clinical Microbiology* **43**:2339–2344 DOI 10.1128/JCM.43.5.2339-2344.2005.

Wang N, Shi X, Jiang L, Zhang S, Wang D, Tong P, Guo D, Fu L, Cui Y, Liu X, Arledge KC, Chen YH, Zhang L, Wang X. 2013. Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4. *Cell Research* **23**:986–993 DOI 10.1038/cr.2013.92.

Wang R, Sun H, Song L, Song W, Cui H, Li B, Wang G, Xu X, Li N, Nie L, Na J. 2003. Plain radiograph and CT features of 112 patients with SARS in acute stage. *Beijing Da Xue Xue Bao Yi Xue Ban* **35**:29–33.

World Health Organization (WHO). 2020. Coronavirus disease (COVID-19) pandemic. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS. 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* **367**(6483):1260–1263 DOI 10.1126/science.abb2507.

Wu J, Feng LC, Xian XY, Qiang J, Zhang J, Mao QX, Kang SF, Chen YC, Pan JP. 2020. Novel coronavirus pneumonia (COVID-19) CT distribution and sign features. *Zhonghua Jie He He Hu Xi Za Zhi* **43**:321–326 DOI 10.3760/cma.j.cn112147-20200217-00106.
Wu Z, McGoogan JM. 2020. 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 323(13):1239 DOI 10.1001/jama.2020.2648.

Wu H, Uchimura K, Donnelly EL, Kirita Y, Morris SA, Humphreys BD. 2018. Comparative analysis and refinement of human PSC-derived kidney organoid differentiation with single-cell transcriptomics. Cell Stem Cell 23:869–881.e8 DOI 10.1016/j.stem.2018.10.010.

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. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respiratory Medicine 8:420–422 DOI 10.1016/S2213-2600(20)30076-X.

Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. 2020. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International Journal of Oral Science 12:8 DOI 10.1038/s41368-020-0074-x.

Yan Y, Chang L, Wang L. 2020. Laborotory testing of SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV): Current status, challenges, and countermeasures. Reviews in Medical Virology 30(3):e2106 DOI 10.1002/rmv.2106.

Yang Y, Peng F, Wang R, Guan K, Jiang T, Xu G, Sun J, Chang C. 2020. The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. Journal of Autoimmunity 109:102434 DOI 10.1016/j.jaut.2020.102434.

Yang W, Sirajuddin A, Zhang X, Liu G, Teng Z, Zhao S, Lu M. 2020. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). European Radiology. Epub ahead of print 15 April 2020 DOI 10.1007/s00330-020-06827-4.

Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng O-T, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui I, Said Z, Kurupatham L, Chen M-C, Chan M, Vasoo S, Wang L-F, Tan BH, Lin RTP, Lee VJM, Leo Y-S, Lye DC, for the Singapore 2019 Novel Coronavirus Outbreak Research Team. 2020. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 323(15):1488 DOI 10.1001/jama.2020.3204.

Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, Wang YY, Xiao GF, Yan B, Shi ZL, Zhou P. 2020. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerging Microbes & Infections 9:386–389 DOI 10.1080/22221751.2020.1729071.

Zhao S, Musa SS, Lin Q, Ran J, Yang G, Wang W, Lou Y, Yang L, Gao D, He D, Wang MH. 2020. Estimating the unreported number of novel coronavirus (2019-nCoV) cases in China in the first half of January 2020: a data-driven modelling analysis of the early outbreak. Journal of Clinical Medicine 9(2):388 DOI 10.3390/jcm9020388.
Zheng Y, Xiong C, Liu Y, Qian X, Tang Y, Liu L, Leung EL-H, Wang M. 2020. Epidemiological and clinical characteristics analysis of COVID-19 in the surrounding areas of Wuhan, Hubei Province in 2020. *Pharmacological Research* 157:104821 DOI 10.1016/j.phrs.2020.104821.

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. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579:270–273 DOI 10.1038/s41586-020-2012-7.