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MINI-REVIEW

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COVID-19 under spotlight: A close look at the origin, transmission, diagnosis, and treatment of the 2019-nCoV disease

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Abstract

Months after the outbreak of a new flu-like disease in China, the entire world is now in a state of caution. The subsequent less-anticipated propagation of the novel coronavirus disease, formally known as COVID-19, not only made it to headlines by an overwhelmingly high transmission rate and fatality reports, but also raised an alarm for the medical community all around the globe. Since the causative agent, SARS-CoV-2, is a recently discovered species, there is no specific medicine for downright treatment of the infection. This has led to an unprecedented societal fear of the newly born disease, adding a psychological aspect to the physical manifestation of the virus. Herein, the COVID-19 structure, epidemiology, pathogenesis, etiology, diagnosis, and therapy have been reviewed.

KEYWORDS

2019-nCoV or COVID-19 or SARS-CoV-2, diagnosis, epidemiology, etiology, pathogenesis, therapy

1 | INTRODUCTION

CoVs were recognized as "novel respiratory tract viruses" over half a century ago. The title was conferred in 1962, following the examination of samples collected from individuals who had manifested symptoms of respiratory tract infection (Hamre & Procknow, 1966). Initially, CoVs were not considered as highly pathogenic for humans. That was until 2002, however, that CoVs emerged in the form of Severe Acute Respiratory Syndrome (SARS) in the Guangdong state of China (Sahin et al., 2020). Almost a decade later, another highly pathogenic CoV appeared in the Middle East countries, which similarly led to severe respiratory symptoms of acute onset. The then-novel species was named Middle East Respiratory Syndrome Coronavirus (MERS-CoV; Zaki, Van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012).

In December 2019, a cluster of insidious Coronavirus infections was reported in the Huanan Seafood Market, located in Wuhan State of Hubei Province in China. Unlike the name, livestock animals were also traded in the market alongside their marine relatives. Days later, the cluster turned into a local network and set off the alarm for the Chinese government. It was then that a pneumonia epidemic of unknown cause became the focus of global attention (Sahin et al., 2020). Chinese authorities announced on January 7, 2020 that a new type of CoV (novel CoV, nCoV) was isolated (Imperial College London, 2020; World Health Organization, 2020). On December 12, 2019, a pneumonia case of unknown origin was reported in Wuhan, China. Initial laboratory tests ruled out Influenza and infection with recognized CoVs. Following the incident, 27 new cases of pneumonia of viral origin were officially reported on December 31, 2019. A week later on January 7, 2020, the Chinese authorities announced that a new species of CoV was isolated in the country (Zumla, Hui, Azhar, Memish, & Maeurer, 2020).

Given the whereabouts of the first case ever reported, the infection was speculated to have been contracted from a zoonotic agent. Etiologic investigations on patients who had been hospitalized with a similar medical history supported the likelihood of a viral infection transmitted from animals to humans (Sahin et al., 2020; World Health Organization, 2020; Yin & Wunderink, 2018). nCoV was duly reported to have been originated from wild bats. Falling in the category of group 2 β-CoVs, the novel Coronavirus only shares a 70% similarity in genetic sequence with its predecessor, SARS-CoV, which also belongs to the exact same family (Gralinski & Menachery, 2020).

The tantalizing surge in the number of cases infected with SARS-CoV-2 in China, despite the closure of markets and evacuation of the vicinity, fulfilled the burden of proof that the virus can also be transmitted from human to human. Soon thereafter, peculiar cases of acute respiratory syndrome started appearing in other Asian countries, ultimately spreading to North America and Europe. (Sahin et al., 2020; World Health Organization, 2020; Yin & Wunderink, 2018). Following an emergent briefing on January 30, 2020, The World Health Organization (WHO) declared the outbreak of COVID-19 as a Public Health Emergency of International Concern (Organization, 2020).

The epidemic began to emerge with the advent of the Chinese New Year, a traditionally important festival that is heavily celebrated across the country. The coincidence paved the way for SARS-CoV-2 to turn into an unprecedented massive Coronavirus outbreak, which required extensive measurements to be contained. With a population of 10 million, Wuhan City also served as an important pathway for millions of people traveling in celebration of the Spring Festival. Accordingly, the number of cases to be diagnosed with COVID-19 showed an overwhelming increase between January 10–22, 2020 (Chen, Zhang et al., 2020).

Despite the arbitrary speculations, not only did the recent outbreak of COVID-19 egress the country of origin, it also proceeded to become a global concern in the form of a pandemic (Yang et al., 2020). COVID-19 is an acute self-resolving respiratory disease in most of the cases, however, it can also be fatal in some cases. The disease was initially reported to have a mortality rate of 2%. If severe, COVID-19 might result in death as a result of the preceding extensive alveolar damage, and failure of the lungs (Xu et al., 2020). As of February 15, 2020, a total of 66,580 cases had been confirmed, with over 1,524 deaths. However, there have no specific reports on pathology, as performing an autopsy or biopsy was not possible in most of the cases (Chan et al., 2020; Huang et al., 2020). Table 1. Represents the WHO situation reports on March 24, 2020 (www.WHO.int).

A total of 8,096 SARS cases and 774 deaths across 29 countries were reported for an overall case-fatality rate (CFR) of 9.6%. MERS is still not contained and is thus far responsible for 2,494 confirmed cases and 858 deaths across 27 countries for a CFR of 34.4%. Despite the much higher CFR of 9.6% and 34.4% for SARS and MERS, the novel Coronavirus epidemic has led to a larger death toll. The Chinese government had reported 72,528 confirmed cases, with 1,870 deaths, as of February 18, 2020. These statistics yield a crude CFR of 2.6%. However, one should not haste to generalize this number, as most possibly the total number of patients with COVID-19 is much higher. That is, because the cases are not readily identifiable, as many asymptomatic patients are missed during the process (Wu et al., 2020; Yan et al., 2020). Despite the higher transmissibility than SARS and MERS, COVID-19 is still a relatively unknown disease and requires further investigations to be fully understood (Yan et al., 2020).

TABLE 1 The number of cases and death of Covid-19 outbreak according to World Health Organization statistics (April 13, 2020)

Region	Total (new) cases in last 24 hr	Total (new) death in last 24 hr
Globally	1,773,084 confirmed (76,498)	111,652 deaths (5,702)
Western Pacific Region	121,426 confirmed (1,310)	4,125 deaths (67)
European Region	913,349 confirmed (33,243)	77,419 deaths (3,183)
South-East Asia Region	16,883 confirmed (842)	766 deaths (38)
Eastern Mediterranean Region	99,713 confirmed (3,768)	5,107 deaths (164)
American Region	610,742 confirmed (36,804)	23,759 deaths (2,228)
African Region	10,259 confirmed (531)	464 deaths (21)

2 | PATHOGENESIS

Initially, the virus interacts with sensitive human cells that exhibit distinct receptors for the viral Spike protein. After making a successful entry, the RNA-based genome starts replicating itself, and expressing specific sequences that results in production of useful accessory proteins; facilitating the adaptation of CoV to its human host (ViralZone., 2019). Alterations in genetic make-up that result from recombination, exchange, insertion, or deletion of genes, are frequently reported among CoVs; a phenomenon that might have played a part in the past epidemics (Sahin et al., 2020). Therefore, the classification of CoVs is continuously being changed. Based on the most recent classification provided by The International Committee on Taxonomy of Viruses, there are four genera of CoVs, that comprise a total of 38 unique species (Subissi et al., 2014). Thus, variable mechanisms could be involved in the process of pathogenesis. For instance, SARS-CoV binds to angiotensin I converting enzyme 2 (ACE2). On the other hand, MERS-CoV is more inclined to attach the cellular receptor of dipeptidyl peptidase 4 (Lambeir, Durinx, Scharpé, & De Meester, 2003). Following a cascade of signals after binding, the viral genome is successfully injected into the target cell. The genomic RNA that regulates the expression of structural and nonstructural polyproteins, is polyadenylated and encapsulated. These proteins are then cleaved by certain proteases that exhibit chymotrypsin-like activity (Lambeir et al., 2003; ViralZone, 2019). Through replication and transcription, the resulting protein complex drives the production of negative-sense RNA or (−) RNA. Full-length (−)RNAs produced by replication are ultimately used as templates for generation of positive-sense RNA or (+) RNA (Luk, Li, Fung, Lau, & Woo, 2019; ViralZone, 2019). All of the structural proteins are then translated from a subset of 7–9 subgenomic RNAs, which are products of discontinuous transcription. The resulting protein complex is the assembled together to envelope the viral genome, making a nucleocapsid in the process, that will bud into the lumen of the endoplasmic reticulum to finally complete the intracellular cycle. Newly formed virions are then expelled from the infected cell through exocytosis. The CoVs released thereafter are now capable to infect a wide spectrum of human cells, including lung, renal, hepatic, intestinal, and lower respiratory tract cells, as well as T lymphocytes (Chhikara, Rathi, Singh, & Poonam, 2020; Lambeir et al., 2003). Figure 1 presents a schematic of viral structure and the entry mechanism of SARS-CoV-2.

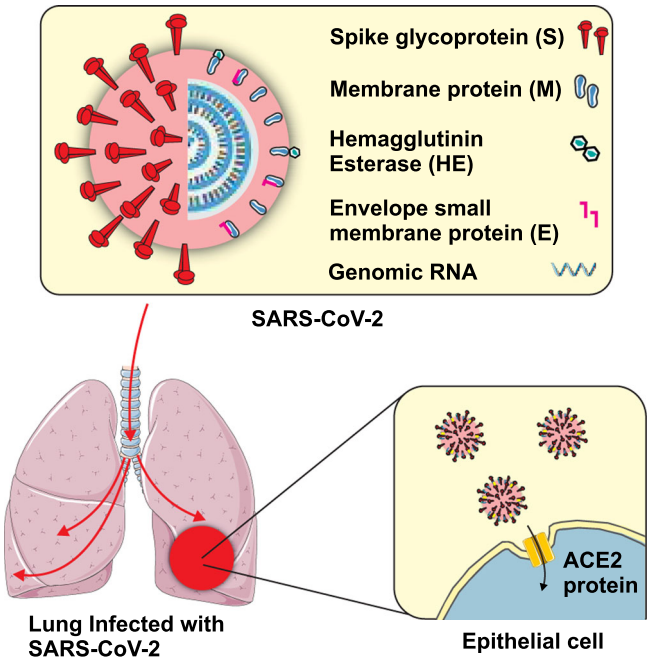

FIGURE 1 Presents a schematic of viral structure and the entry mechanism of SARS-CoV-2

2.1 | Respiratory system

SARS-CoV-2 tends to infect the respiratory tract, thus, pneumonia is a primary clinical finding in patients with COVID-19 (Huang et al., 2020; Li, Guan, et al., 2020; Zhu et al., 2020). However, pneumonia is only a component of the SARS that might develop in some cases. The resulting SARS may then be aggravated and lead to serious conditions that are extremely difficult to control, for example, septic shock, metabolic acidosis, and coagulation dysfunction (Kofi Ayittey, Dzuvor, Kormla Ayittey, Bennita Chiwero, & Habib, 2020).

Investigation on the radiological findings of COVID-19-associated pneumonia have yielded little, if any, information that are mostly unspecific. Progressive lung lesions are usually detected in patients with COVID-19, about 1 week after the onset of signs and symptoms (Ooi et al., 2004). The lesions then become aggravated during the 2nd week, and lead to formation of irregular reticular opacities mixed with ground glass opacities (GGOs), which can be detected by CT at the fourth week. In a recent cohort study, 85.7% (54/63) of subjects with COVID-19-associated pneumonia showed disease progression, defined by an increased extent of GGO, on early follow-up CT (Pan et al., 2020). Pulmonary fibrous cords was reported in one particular patient that displayed signs of improvement, as the inflammatory secretions had been absorbed (Pan & Guan, 2020). Long-term complications of COVID-19 in patients with severe pneumonia might include an array of fibrotic changes often observed in the late stages of lung injury, for example, reticulation, interlobular septal thickening, and traction bronchiectasis (Kim, 2020).

2.2 | Immune system

There have been several reports that indicated meager Cytolethal Distending Toxin-induced lymphocytes, with a density as low as 200 cells/mm^3 in three patients with SARS-CoV infection (Chu et al., 2014; Zhou et al., 2014). As in the case of SARS-CoV-2, it has been suspected that infection with this type of CoV might lead to

inflammatory cytokine storm (Chen, Liu, et al., 2020; Zumla et al., 2020); a life-threatening condition characterized by elevated levels of interleukin 6 (IL-6) in plasma. A number of investigations recently conducted on COVID-19 have reported that IL-6 levels was actually higher in the patients with severe disease (Cai, 2020; Chen, Liu, et al., 2020; Xiang et al., 2020). This could highlight the importance of IL-6 as a biomarker for evaluation of disease severity (Chen, Zhao, et al., 2020).

2.3 | Liver damage

Impaired liver function tests have been reported for a number of patients with SARS-CoV-2 infection, suggesting hepatic damage as an extrapulmonary complication of COVID-19 in almost one half of the patients (Chen, Zhou, et al., 2020; Wang, Hu, et al., 2020). A recent study has concluded that liver function abnormality might stem from infection of bile duct cells with SARS-CoV-2. Nonetheless, the alkaline phosphatase value, which is an index of bile duct damage, were not specific in patients with COVID-19 (Chen, Zhou, et al., 2020; Wang, Hu, et al., 2020). Investigation of liver biopsy specimens was accompanied by new pathological findings. Scientists have reported moderate microvascular steatosis, and mild lobular and portal activity in these patients, that suggests liver damage may have arisen from either SARS-CoV-2 infection or drug-induced liver (Xu et al., 2020).

2.4 | Myocardial, gastrointestinal, and renal symptoms: homeostasis of electrolytes

An essential player in maintenance of electrolyte balance and blood pressure, ACE2 is regarded by many as the principal counter-regulatory arm in the axis of renin–angiotensin-aldosterone system (RAAS; Santos, Ferreira, & Simões e Silva, 2008). Upon infection, SARS-CoV-2 binds ACE2. This results in degradation of ACE2, which subsequently dampens the counter-effect of ACE2 on RAAS. The final effect of ACE2 in an otherwise healthy adult is to increase reabsorption of sodium and the reciprocal excretion of potassium ions (K^+). The concomitant re-uptake of water with sodium reabsorption prompts an increase in blood pressure (Weir & Rolfe, 2010). Potassium is the predominant intracellular ion, that is majorly involved in regulation of cell membrane polarity. Too low levels of K+ in blood, known as hypokalemia, can result in cellular hyper-polarity. A hyper-polarized cell membrane tends to be depolarized faster than normal, causing aberrancy in the function of cardiac cells (Bielecka-Dabrowa et al., 2012).

In a recent cohort study, patients diagnosed with COVID-19 were categorized into three groups: severe hypokalemia, hypokalemia, and normokalemia. The study reported that 93% of patients with a severe clinical condition had hypokalemia. Scientists did not find a direct link between gastrointestinal symptoms and hypokalemia among 108 patients with both severe or moderate hypokalemia. Further investigations established an association between parameters such as body temperature, creatine kinase (CK), creatine kinase myocardial band (CK-MB), lactate dehydrogenase (LDH), and C-reactive protein (CRP) with the severity of hypokalemia. Reportedly, hypokalemia was most often observed with patients who had elevated levels of serum CK, CK-MB, LDH, and CRP. Potassium (K^+) loss in the urine was determined to be the primary cause of hypokalemia.

Hypokalemia requires strenuous efforts to be corrected. This is chiefly due to the incessant loss of K^+ in the urine, as a result of ACE2 degradation. In the case of COVID-19-associated hypokalemia, however, the patients seemed to respond well to potassium supplements when the critical phase had passed [49]. Therefore, one should consider the impact of hypokalemia in COVID-19 morbidity, and its effect on the outcomes of treatment. This is a condition that must be carefully addressed for, as patients with COVID-19 are more inclined to develop dysfunctions in heart, lungs, and other vital organs (Li, Hu, Su, & Dai, 2020).

3 | POSSIBLE FACTORS CORRELATED WITH COVID-19

3.1 | Sex

Several studies have sought to compare the sex differences in the clinical findings of severe COVID-19. In one study, scientists investigated 47 patients with COVID-19, 28 (59.6%) of whom were men. Procalcitonin (PCT) level was reported to be higher in men than in women. The results also showed higher amounts of serum N-terminal-pro brain natriuretic peptide, as increased levels of the molecule were detected in men 57.1% than women 26.3%. Furthermore, 17.9% of male patients were reported test-positive for influenza A antibody, whereas no such records were registered for female patients. During a 2-week stay at the hospital, 17.9% of male, and 5.3% of female patients deteriorated, and hence were reassigned to the critical-type group. There was no mortality reports among women, whereas 3.6% of male patients had deceased due to COVID-19 complications. A total of 21.1% and 3.6% of female and male patients successfully recovered, and were discharged from the hospital. Based on the current evidence, men are more likely to develop complications, and experience worse in-hospital outcomes compared with women (Li, Zhang, et al., 2020).

3.2 | Pregnancy

A group of researchers led by Chen investigated the clinical characteristics of SARS-CoV-2 infection in nine pregnant women. Their aim was to evaluate the likelihood of intrauterine/vertical transmission of SARS-CoV-2 from mother to baby. All of the women who were being investigated had cesarean section in the third trimester of their previous pregnancies. Seven patients were febrile, and variably presented other symptoms such as cough, sore throat, myalgia,

and malaise. Fetal distress was reported in two cases. Lymphopenia and increased aminotransferase activity were observed in five and three patients, respectively. There was no mortality cases, as none of the patients in the study developed severe COVID-19-associated pneumonia. Nine livebirths were recorded. The newborns displayed no signs of asphyxia. A 1-min Apgar score of 8–9, and a 5-min Apgar score of 9–10 were calculated for all nine newborns. Samples collected from six patients, including amniotic fluid, cord blood, neonatal throat swab, and breastmilk proved test-negative for SARS-CoV-2. The clinical features of COVID-19-associated pneumonia observed in these pregnant women shared a great similarity to characteristics reported for COVID-19-associated pneumonia in nonpregnant adult patients (Chen, Guo, et al., 2020).

3.3 | Blood type

In a recent investigation, scientists in China looked into the pattern of blood type distribution in 2,173 patients in three hospitals, who had been confirmed to have SARS-CoV-2 infection. Accordingly, they compared their findings regarding the blood type of patients with that of the healthy population who lived in the same area as the patients in the study. Apparently, there was a higher prevalence of blood type A among the patients with COVID-19 than in the normal population. On the contrary, it seemed that individuals with O blood type were spared somehow, as there were fewer patients with this blood type in this study (both $p < .001$). A series of meta-analyses on the available data indicated a significantly higher risk for COVID-19 in people with blood type A, relative to individuals with non-A blood types. However, an opposite scenario seemed to be true for the blood type O community, since, according to the literature, are less susceptible for contracting infectious diseases such as COVID-19 (Zhao et al., 2020).

4 | ETIOLOGY: SOURCES AND MODES OF TRANSMISSION

According to the literature, the pathogen and area of origin were similar in both SARS and COVID-19 outbreaks. However, despite this similarity, the raised public awareness and extensive interventional procedures that might have once proved effective for SARS containment, have been rendered ineffective against the 2019 novel Coronavirus; as the disease is already more widespread than SARS (Liu, Gayle, Wilder-Smith, & Rocklöv, 2020). A large family of viruses, CoVs are common among many different animal species, including cattle, civets, camels, and bats. However, these CoVs are not solely restricted to animal populations, as they can occasionally infect humans, bringing epidemics such as SARS, MERS, and in recent memory, COVID-19 (Sahin et al., 2020). Recent investigations conducted on the origins of CoVs responsible for the past epidemics have reported bats as the primary reservoir for both SARS-CoV and MERS-CoV; suggesting that other animal species were involved in the process merely as intermediate hosts. Accordingly, the majority of bat-associated CoVs belong to α-CoV and β-CoV genera, while almost all of the avian CoVs fall in the other two genera; γ-CoVs and δ-CoVs (Yin & Wunderink, 2018). It has been suggested that species responsible for the recent epidemic is reminiscent of the CoV isolated in bats. Trafficking of wild animals in Huanan Seafood Market, located in Wuhan State of Hubei Province in China, where the first cases were reported, further supports this finding. Only 10 days following the first outbreak, secondary cases started emerging. Although the new cases had no contact with the marketplace, they did have a history of social contact with the salesmen and people who had previously been there. The growing pile of confirmed cases from healthcare workers in Wuhan City is an strong indicator of human-to-human transmission in the case of SARS-CoV-2 (Sahin et al., 2020).

Transmission of the virus from human to human occurs mostly with close contact. The short distance between individuals in close social contacts makes it possible for respiratory droplets of the infected person, released by coughing and sneezing, to reach other people in the proximity. This is similar to the transmission of Influenza and other respiratory infection. It still remains unclear if the virus can be contracted by touching surfaces, and then touching mouth, nose, or even eyes (WHO, 2020). Apparently, COVID-19 is considered most contagious when individuals infected with the virus is symptomatic. However, there have been cases who reportedly had contracted the disease from asymptomatic patients in the prodrome period of COVID-19. Transmission of the novel Coronavirus has yet to be clarified by more investigations. (Rothe et al., 2020).

4.1 | Presumed asymptomatic carrier-based transmission of COVID-19

Investigation on a familial cluster of five patients concluded that SARS-CoV-2 might have actually been transmitted by an asymptomatic carrier in the family (Bai et al., 2020). Surprisingly, the first reverse transcription polymerase chain reaction (RT-PCR) test of the asymptomatic family member was reported negative; a noteworthy example of a false-negative result. Unwanted false-negative results are inevitably reported due to a number of factors, for example, quality of the test kit, sufficiency of the collected sample, or performance of the test by clinicians. To this date, RT-PCR has widely been used as a reliable diagnostic method (Corman et al., 2020). Thus, her second RT-PCR result, reported positive, was unlikely to have been a false-positive result; hence, it was accepted as the definite evidence that the suspected person had indeed been infected with SARS-CoV-2 (Bai et al., 2020).

There was also another study that reported an asymptomatic young boy with COVID-19 infection. However, CT scans obtained from the subject exhibited abnormalities, indicative of an on-going pulmonary pathology (Chan et al., 2020). If we presume that the findings regarding asymptomatic carrier-based transmission of COVID-19 can be replicated, this would prove COVID-19 an overwhelmingly challenging issue to be controlled (Bai et al., 2020).

The incubation period for the asymptomatic patient in the case of familial cluster was 19 days. Despite being a long period, it still perfectly falls in the suggested incubation period of 0–24 days (Bai et al., 2020; Guan et al., 2020).

5 | DIAGNOSIS

A proper diagnosis of COVID-19 is made based on the following criteria, which have been recently suggested based on the initial investigations: (a) clinical signs and symptoms, (b) history of traveling or close contact with people suspected to be infected, (c) positive test result for the pathogen, and (d) pathologic findings on CT images. The key clinical features of COVID-19, though nonspecific, include fever, dry cough, dyspnea, and pneumonia (Chen, Zhou, et al., 2020; Huang et al., 2020; Li, Guan, et al., 2020; Wang, Hu, et al., 2020). Rapid screening of patients with acute respiratory symptoms, initiation of an appropriate quarantine program, and development of therapeutic measures have been suggested as a top-priority strategy to control the spread of COVID-19 (Tian et al., 2020; Wang, Kang, et al., 2020). According to the data gathered by individual-level surveillance, it is strongly recommended that the elderly and male patients should be diagnosed in a timely manner, as progression of the respiratory pathology to pneumonia might result in catastrophic outcomes (Jian-ya, 2020).

5.1 | Clinical symptom spectrum

Understanding the otherwise nonspecific clinical signs and symptoms of COVID-19 is a crucial step toward appropriate management of the disease. Patients mostly complain of fever, non-productive cough, and body ache or extreme tiredness. In some cases, diarrhea and nausea precede fever by a few days, suggesting that fever might not be the initial manifestation of infection. A small number of patients reportedly had headache, or even developed hemoptysis (Guan et al., 2020; Wang, Hu, et al., 2020). Some patients remained asymptomatic, despite being tested positive for the disease (Chan et al., 2020). According to several studies, infection with SARS-CoV-2 in the elderly, especially the male community, is more likely to result in severe alveolar damage and respiratory failure (Chen, Zhou, et al., 2020). Occasionally, the disease may be demonstrated with a fulminant natural history, rapidly progressing to organ dysfunction, and even death in critical cases. Organ dysfunction includes conditions such as shock, ARDS, acute cardiac injury, and acute kidney injury (Huang et al., 2020; Wang, Hu, et al., 2020). From a laboratory point of view, lymphopenia, thrombocytopenia, impaired prothrombin time (PT), and elevated serum levels of CRP stand among the findings that can be reported for patients with COVID-19 (Chen, Zhou, et al., 2020; Guan et al., 2020; Huang et al., 2020; Wang, Hu, et al., 2020). Overall, any patient with fever and acute respiratory symptoms, who is reported to have lymphopenia or leukopenia on lab examination, should be suspected. A history of travel to Wuhan or having close contact with local residents is a strong indicator for careful management of the patient (Zu et al., 2020). Table 2 represents the criteria for diagnosis of COVID-19 infected patients (Committee, 2020b; Zu et al., 2020; WWW.ClinicalTrials.gov).

5.2 | Epidemiological history

Shortly after the onset of the epidemic, The National Health Commission of China (Committee, 2020a; Organization, 2020a) initiated the Diagnosis and Treatment Program of COVID-19-associated pneumonia, following the guidelines provided by WHO on SARS and MERS (Azhar & EI-Kafrawy, 2014; Organization, 2017, 2020b).

According to the newly formulated criteria, a "suspected case" is defined as a patient with epidemiological history, that is traveling and contact, and two clinical findings pertinent to the disease. If, however, an epidemiological history is not confirmed, then the patient must present at least three clinical findings to be considered as a suspected case. Based on the Trial, Fifth Edition (Committee, 2020b), pathologic findings indicative of viral pneumonia on chest CT scans provide enough evidence for clinical diagnosis of COVID-19. Nonetheless, as of February 17, 2020, WHO does not approve of any diagnosis based solely on radiologic findings, without obtaining an RT-PCR test from the patient (Organization, 2020c). In the more recent revision of the Chinese Diagnosis and Treatment Program, 6th Edition, the term "clinical diagnosis" was removed and replaced with "etiological diagnosis" (Organization, 2020a). According to the recent revision, it is imperative that an etiological diagnosis of COVID-19 is made at first, which can then be complemented by a positive real-time RT-PCR assay for SARS-CoV-2, which is duly performed on the sputum or blood sample of the patient. After the final diagnosis is made, confirmed patients are categorized into mild, moderate, severe, and critical types, based on the severity of disease (Zu et al., 2020).

5.3 | COVID-19 detection tests: Pathogenic laboratory testing, real-time RT-PCR, and sequencing of nucleic acid

Table 3 (Ai et al., 2020; Bai et al., 2020; Chen, Zhao, et al., 2020; Shi et al., 2020; Tian et al., 2020; Wang, Kang, et al., 2020; Wu & McGoogan, 2020; Yan et al., 2020; Yang et al., 2020) and Table 4 represent 2020 studies on diagnosis of COVID-19 infected patients and related clinical trials, respectively.

5.3.1 | Reverse transcriptase polymerase chain reaction

Despite being the diagnostic gold standard, pathogenic lab testing is a rather time-consuming procedure, with unavoidable false-positive results (Wang, Kang, et al., 2020). It is recommended that lab testing should be performed, as soon as the patient is identified as a "person

TABLE 2 Criteria for clinical severity of confirmed COVID-19 pneumonia

Patient	Clinical findings	CT (imaging findings of pneumonia)	Organ damage
Mild	Negative No dyspnea, with or without cough, fever <38°C (quelled without treatment) No history of chronic respiratory disease	None	None
Moderate	dyspnea, with or without cough SpO2 >93% without oxygen inhalation	Multifocal patchy GGOs with subpleural distribution	None
Severe	Fever Muscle ache Headache Confusion Respiratory distress: RR ≥ 30 times/min SpO2 < 93% at rest PaO2/FiO2 ≤ 300 mmHg	Diffuse heterogeneous consolidation with GGO, Rapid progression (>50%) on CT imaging within 24–48 hr	None
Critical	Shock Respiratory failure need mechanical assistance Intensive care unit is needed		"Extra pulmonary" organ failure or MODS

Abbreviations: FiO2, fraction of inspired oxygen; GGO, ground-glass opacity; MODS, multiple organ dysfunction syndrome; PaO2, partial pressure of oxygen; RR, respiratory rate, SpO2, oxygen saturation.

under investigation" (PUI). Viral nucleic acid required for an RT-PCR test is usually extracted from secretions of the lower respiratory tract, for example, bronchoalveolar lavage; however, tracheal aspirate or sputum can also be used (Chu et al., 2020; Corman et al., 2020). Since the onset of the epidemic, several factors have been found to affect the final efficiency of nucleic acid testing, that is, availability, quality, stability, and reproducibility of detection kits. In most of the cases, the tests need to be repeated for several times (Wang, Kang, et al., 2020), as the estimated detection rate of the test falls in an underwhelming range of 30–50% (Chu et al., 2020; Corman et al., 2020; Zhang et al., 2020). In spite of being a valuable asset, the undesirable false-negative results of RT-PCR have prompted careful clinical and etiological evaluation of COVID-19 in suspected cases as the first-line diagnostic method (Zu et al., 2020).

5.3.2 | Computed tomography (CT)

CT has proved to be of great value in diagnosis of the COVID-19-associated pneumonia, as it provides major evidence, that cannot readily be obtained with alternative methods. It is true that CT is a reliable imaging modality in subtle detection of viral pneumonia and screening of suspected cases; however, it should be noted that many pulmonary diseases of inflammatory nature share similar radiographic findings (Wang, Kang, et al., 2020). The majority of patients with COVID-19 present with GGO in their chest CT, which later progress into multilobar consolidations. There have been several reports of rounded opacities, which are sometimes peripherally distributed in the lung (Chung et al., 2020; Huang et al., 2020). In contrast to CT, plain chest radiography (CXR) has not been recommended as a first-line imaging method, because this modality does not provide the clarity viewed on CT scans, especially in the early stages of pulmonary infection (Ng et al., 2020). Nevertheless, CXR is capable of recording pathologic changes in patients with severely progressed COVID-19, as the bilateral multifocal consolidations present in these patients are too dense to be missed. The notorious "white lung" appearance can be optimally viewed on CXRs of critically ill patients (Zu et al., 2020). CT resulted in diagnosis of 14,840 new cases as of February 13, 2020 (Zu et al., 2020). Therefore, slice chest CT is an adequately sensitive and reliable method in early detection of pneumonia in patients with COVID-19 (Chan et al., 2020; Ng et al., 2020).

5.3.3 | Novel approaches: Artificial intelligence-based technologies

Depp learning, as a novel AI-based modality might be able to analyze radiographic features of COVID-19, and help clinicians provide an accurate clinical diagnosis based on a precedented pattern (Wang, Kang, et al., 2020). As part of recent advancements, Convolutional Neural Network (CNN), a class of deep neural networks, has been shown to be capable of medical image analysis. To this date, CNN has been successfully employed in investigations on the nature of pulmonary nodules reported in CT images, diagnosis of pneumonia in children based on CXR, and image recognition in cystoscopy videos (Choe et al., 2019; Kermany et al., 2018; Negassi, Suarez-Ibarrola, Hein, Miernik, & Reiterer, 2020; Wang et al., 2018).

TABLE 3 Studies for diagnosis, prognosis and therapy of COVID-19 patients

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
Wu et al. (2020), China	Retrospective study/ Chinese Center for Disease Control and Prevention	72,314; subjects: confirmed cases 44,672 (62%), suspected cases 16,186 (22%), diagnosed cases 10,567 (15%), asymptomatic cases 889 (1%)/ age *N* = 44,672: 80: 3% (1,408), 30–79: 87% (38,680), 20–29: 8% (3,619), 10–19: 1% (549), <10: 1% (416)	PCR	Throat swab samples	Confirmed cases based on positive PCR, suspected cases based on symptoms and exposures only, clinically cases based on symptoms, exposures, and CT, asymptomatic cases diagnosis by positive PCR	Spectrum of disease: (*N* = 44,415); mild: 81% (36,160), severe: 14% (6,168), critical: 5% (2,087)	Cardiovascular disease: 10.5%, diabetes: 7.3%, chronic respiratory disease: 6.3%, hypertension: 6.0%, cancer: 5.6%	About a week	2.3% (1,023 of 44,672 confirmed cases), 14.8% aged >80 years (208 of 1,408), 8.0% aged 70–79 years (312 of 3,918) 49.0% in critical cases (1,023 of 2,087)	Next step: to help "buy time" for more diagnostic and therapeutic research before COVID-19 becomes too widespread
Tian et al. (2020), China	Retrospective study/ Beijing Emergency Medical Service	262/47.5/48.5% male	Real-time RT-PCR	Respiratory specimens	COVID-19 infected patients/ residents of Beijing: 92 (73.3%), patients had been to Wuhan: 50 (26.0%), close contact with confirmed cases: 116 (60.4%), no contact history: 21 (10.9%)	Spectrum of disease: sever: 46 (17.6%); common: 216; (82.4%); mild: 192 (73.3%); nonpneumonia: 11 (4.2%); asymptomatic:13 (5.0%)	Fever (82.1%), cough (45.8%), fatigue (26.3%), dyspnea (6.9%), headache (6.5%)/pulmonary infection, chronic cardiovascular disease and heart failure: 1, pulmonary infection and multiple chronic diseases: 1	Incubation: 6.7 days, illness onset to visit hospital: 4.5 days	3 (0.9%)	Results: As of February 10, 45 (17.2%) patients have discharged For COVID-19 control: first step is prevent transmission at early stage, next steps is early isolation and quarantine of suspected subjects
Wang et al. (2020), China	Retrospective cohort/ Xi'an Jiaotong University First Affiliated Hospital, Nanchang University First Hospital and Xi'an No.8 Hospital of Xi'an Medical College	99	CT, artificial intelligence, inception migration-learning model	–	Pathogen-confirmed COVID-19 patients	Spectrum of disease: typical viral pneumonia or negative group: 55, confirmed nucleic acid testing or positive group: 44. CT (453 CT images): negative: 258, positive: 195	Viral pneumonia symptoms	–	–	Screening: The internal validation; accuracy: 82·9%, specificity: 80·5%, sensitivity: 84% The external testing; accuracy: 73·1%, specificity: 67%, sensitivity: 74% Algorithm prediction: a rate of 2 s per case on the graphic processing unit

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
										Interpretation: the early diagnosis through fast, accurate, safe and noninvasive methods is crucial for control of virus
Yan et al. (2020), China	Retrospective study/ Tongji Hospital	375, 58.83, 58.7% males	CT, machine learning model (a supervised XGBoost classifier)	–	Validated or suspected COVID-19 patient/Wuhan residents (37.9%), familial cluster (6.4%), health workers (1.9%)	Spectrum of disease: critical patients: 46.1%, severe cases: RR ≥ 30bpm or SPO2 ≤93% on rest	Fever: 49.9%, cough: 13.9%, fatigue 3.7%, dyspnea 2.1%, shock: 2		174 16 + 1	Interpretation: the three indices-based prognostic prediction model might predict themortality risk, recognition of critical cases, help to early identification, on time intervention, reducing mortality rate
Shi et al. (2020), China	Retrospective/ hospitals in Wuhan	81, 49–5, 42 (52%) men and 39 (48%) women	Next-generation sequencing or RT-PCR, serial chest CT	Throat swab specimens	Confirmed COVID-19 pneumonia patients/direct exposure to Huanan seafood market: 31 (38%), health-care workers: 15 (19%), familial clusters: 7 (9%), any obvious history of exposure: 28 (35%)	Spectrum of disease: mean number of involved lung segments: 10.5 (SD 6.4): group 1: subclinical patients (CT before symptom onset): 2.8 (3.3), group 2: ≤1 week after symptom onset/11.1 (5.4), group 3: >1–2 weeks/13.0 (5.7), group 4: >2–3 weeks/12.1 (5.9). CT: ALL: bilateral abnormality: 64 [79%], peripheral 44 [54%], Ill-defined 66 [81%], GGO: 53 [65%], mainly	Fever: 59 [73%], dry cough: 48 [59%] nonspecific symptoms: dizziness: 2 [2%], diarrhea: 3 [4%], vomiting: 4 [5%], headache: 5 [6%], generalised weakness: 7 [9%]/chronic pulmonary disease (tuberculosis): 1, T2D: 1, hypertension/ cardiovascular/ erebrovascular disease: 1	Symptom onset and discharge of 23–2 days	3 (4%)	By February 8, 2020, 62 (77%) patients discharged Interpretation: COVID-19 pneumonia include CT abnormalities that rapidly progress from focal unilateral to diffuse bilateral GGO coexisted with consolidations within 1–3 weeks (even in asymptomatic patients). Early diagnosis through combined CT with clinical and laboratory findings

(Continues)

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						involving the right lower lobes: 225 [27%] of 849. Group 1 (*n*=15): unilateral: 9 [60%]/multifocal 8 [53%]/GGO: 14 [93%]; Group 2 (*n* = 21): bilateral 19 [90%]/diffuse 11 [52%]/GGO predominance 17 [81%]; Group 3 (*n* = 30): GGO 17 [57%], consolidation/ mixed patterns: 12 [40%]; Group 4 (*n*=15): consolidation/ mixed patterns: 8 [53%]. Blood: Group1: Lower CRP and AST				
Bai et al. (2020), China	Case study/The Fifth People's Hospital of Anyang	6, Patient 1: 20-year-old woman, patients 2–6: four women 42–57 years old	CT, RT-PCR	Nasopharyn-geal swabs	Patient 1: met with Patients 2 and 3, and accompanied five relatives (Patients 2–6), Patients 2–6: no visited Wuhan or been in contact with any other people traveled to Wuhan	Spectrum of disease: severe pneumonia: 2, moderate: others. A familial cluster of five patients with respiratory symptoms, 1 asymptomatic family member. Blood: all symptomatic patients: increased CRP, reduced lymphocyte. CT: multifocal GGO: in all symptomatic patients,	Fever: patients 2–6	19 days for patient 1	–	Transmission: COVID-19 transmission could transmit by an asymptomatic carrier S

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						subsegmental consolidation/ fibrosis: 1. Patient 1: normal CT, CRP and lymphocyte count, RT-PCR: negative, positive, negative. Patients 2–6: COVID-19 confirmed. PCR: positive for patients 2–6 within 1 day				
Ai et al. (2020), China	Cohort/Tangji hospital of Tongji Medical College Huazhong University of Science and Technology, Wuhan, Hubei	1,014/51 ± 15/ 46% man	Laboratory test, chest CT (7 day interval), RT-PCR (Taq man one step): multiple assays (3 day interval)	Throat swab	Suspected of nCoV/ China	Positive CT: 88% (888/1,014), positive RT-PCR: 59% (601/1,014). Sensitivity of CT based on positive RT-PCR: 97% (95%CI, 95–98%, 580/601). Negative RT-PCR/ positive CT: 75% (308/413). Initial positive CT consistent with COVID-19 before the initial positive RT-PCR: 60–93%. Improvement in follow-up CT before the RT-PCR turning negative: 42% (24/57), CT: GGO: 46% [409/888], consolidations: 50% [447/888], bilateral findings: 90% [801/888]	Fever, dry cough	Initial + to − PCR: 5.1 ± 1.5 days, Initial − to + PCR: 6.9 ± 2.3 days	–	Diagnosis: chest CT, as a highly sensitive method, could be considered as a primary tool for infection diagnosis in epidemic areas

(Continues)

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
Chen et al. (2020), China	General Hospital of Central Theater Command, PLA	48/age; critically ill: 79.6 ± 12, sever: 63.9 ± 15, mild: 45.8 ± 14/31 males (77.1%) and 17 females (22.9%)	Real-time RT-PCR, CT, GLMs analysis	Serum, throat-swab specimens	Laboratory confirmed cases	Spectrum of disease: mild: 21 (43.7%), severe 10 (20.8%), critically ill 17 (35.4%). Blood: low/lower lymphocytes: severe and critically ill, higher neutrophils: critically ill, higher PCT: critically ill. Parameters stand for the organ dysfunction; TnT, AST, ALT, CRE, and BUN: higher in critically ill patients. PCR: positive RNAaemia: (a) serum: 5 (10.4%) of critically ill, (b) throat-swab: 48 positive. IL-6: value ≥100: 35.3% in critically ill, 10-folds higher IL-6 (cytokine storm): critically ill, RNAaemia positive: IL-6 ≥100 (R = 0.902)	Mild: fever, respiratory symptoms Severe: shortness of breath, RR ≥ 30 times/ min, oxygen saturation (resting state) ≤93%, PaO2/ FiO2 ≤300 mmHg Critically ill: respiratory failure, shock, multiple organ failure/diabetes: 12 [25%], hypertension: 23 [49.7%], heart disease: 8 [16.7%], mixed fungal infection: 27.1%, bacterial infection: (2.1%)	–	3	Diagnosis; RNAaemia positive test confirmed critically ill patients Prognosis: strong association between RNAaemia with cytokine storm can be applied to predict the poor prognosis Therapeutic approach: in critically patients, IL-6 should be considered as a therapeutic target
Fan et al. (2020), China	Retrospective cohort study/three tertiary hospitals of Wenzhou	149/45.11 ± 13.35/81 (54.4%) males	Laboratory test, PCR, CT	Blood	RT-PCR confirmed patients: Hubei travel/residence history: N=85, contact with people of Hubei: N=49, no traceable exposure history: N=15	Blood: decreased oxygen saturation: 14(9.4%), leukopenia: 33 (24.2%), lymphopenia: 53 (35.6%), low platelets: 20	Fever: 114/149, 76.5%, Cough: 87/ 149, 58.4%, Expectoration: 4 8/149, 32.2%, mild infection/ cerebrovascular	Negative CT: 10 days, 6.8 (5.0) days	0 (0.0%)	Diagnosis: a normal CT cannot exclude the diagnosis of COVID-19

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						(13.4%), elevated CRP: 82 (55.0%), ALT/AST/CK and D-dimer: less common. CT: most involved lung segments: 6 and, GGO: 287 segments, mixed opacity: 637 segments, consolidation: 170 segments, lesions: more in the peripheral lung with a patchy form, normal CT on admission: *N*=17, negative CT: *N*=12, no significant difference between patients with or without exposure history	or digestive diseases: 52 (34.9%)			
Fan et al. (2020), China	Retrospective, case series/Chongqing University Three Gorges Hospital	51/45/32 (62.7%) men	Laboratory test, CT	Blood	Confirmed COVID-19: patients had been to Wuhan: 43 (84.3%), contact history of COVID-19 patients: 4 (7.7%), no clear contact history:4 (7.7%)	Spectrum of disease: nonsevere patients: *n* = 44, severe patients: 7 (13.7%) Blood: lymphopenia: 26 (51.0%), elevated CRP: 32 (62.7%). CT: GGO: 41 [80.4%], local consolidation of pneumonia: 17 [33.3%], pleural thickening: 20 (39.2%), small amount of pleural effusion:	Fever: 43 [84.3%], cough: 38 [74.5%], dry cough with expectoration: 16 (31.4%), fatigue: 22 [43.1%], asthenia: 22 (43.1%), dyspnea: 11/DM: 4 [57.1%]	2–5 days	1	Therapy: TCM decoction: 28 [54.9%], aerosol inhalation of recombinant human Interferon a-1b: 51 (100%), Lopinavir/ Ritonavir: 51 [100%], *Bacillus licheniformis* capsules: 44 [86.3%], glucocorticoid treatment: 10 (19.6%) Older patients with server COVID-19 (*N* = 7)

(Continues)

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						7 (13.7%), streak shadow of lung: 8 (15.7%), multiple solid nodular shadow: 4 (7.8%), air bronchogram: 2 (3.9%), single lobe lesions: 2 (3.9%), multiple lobe lesions: 49 (96.1%)				Antibiotic treatment: 7 [100%], nutritional diet: 6 [85.7%], human albumin infusion: 4 (57.1%), immunoglobulin treatment: 4 (57.1%), mechanical ventilation: 6 [85.7%] Results and interpretation: discharged 50 patients after 12 days, without the common clinical symptoms, with the significant increased lymphocyte ($p = .008$) and significant decreased CRP significantly ($p < .001$)
Fan et al. (2020), China	Retrospective/ Shanghai Public Health Clinical Center	148/50.5/49.3% females and 50.7% males	Laboratory test, RT-PCR and CT scanning	Sera	Confirmed SARS-CoV-2-infected patients/a history of related epidemiology	Blood: elevated LDH, AST, ALT, GGT, TB, ALP: 35.1%, 21.6%, 18.2%, 17.6%, 6.1%, 4.1% in all patients; lower CD4+ and CD8+ T cells: (62.67%)/ (56.1%) patients with abnormal liver function received more treatment compared with normal liver	Fever: (70.1%), cough: (45.3%), expectoration at admission: (26.7%), Abnormal liver functions at admission: 75 patients (50.7%) with moderate-high degree fever (44%) in males,/ chronic hepatitis B or C: $N = 8$	5 days (3–7)	1	Therapy: Antibiotics (Levofloxacin, Meropenem, Moxifloxacin, Cephalosporin), interferon, antiviral drugs (Arbidol, Lopinavir/ ritonavir, Dnrunavir) Results and interpretation: all patients discharged from the hospital. Lopinavir/Ritonavir treatment can

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						function (25%) ($p = .009$)				significantly alleviate the SARS-CoV-2-induced liver function damage
Chen et al. (2020) China	Retrospective/ Zhongnan Hospital of Wuhan University, Wuhan	9/26–34/female	Clinical records, laboratory results, CT scans	Amniotic fluid, cord blood, and neonatal throat swab, breastmilk samples	Pregnant women with laboratory-confirmed COVID-19 pneumonia and caesarean section in their third trimester/a history of epidemiological exposure to COVID-19	Blood: lymphopenia: $N = 5$, elevated CRP: $N = 6$, increased ALT and AST: $N = 3$, normal WBC count: $N = 7$, lower WBC: $N = 1$. Nine mothers: none developed severe COVID-19 pneumonia or dying as of Feb4. Six mothers: amniotic fluid, cord blood, neonatal throat swab, and breastmilk: negative for COVID-19. Nine livebirths: with 1-min Apgar score of 8–9 and a 5-min Apgar score of 9–10, No neonatal asphyxia. CT: multiple patchy ground-glass shadows: $N=8$	Fever: $N = 7$, cough $N = 4$, myalgia $N = 3$, sore throat: $N = 2$, malaise: $N = 2$, fetal distress: $N = 2$/gestational hypertension: $N = 1$, pre-eclampsia: $N = 1$, influenza virus infection: $N = 1$	Short	None	Therapy: oxygen support (nasal cannula) and empirical antibiotic treatment: $N = 9$, antiviral therapy: $N = 6$ Interpretation: no evidence for intrauterine infection caused by vertical transmission in late pregnancy
Lim et al. (2020), Korea	Public health center, Myongji Hospital	1/54/male	PCR, CT	Throat swab, sputum	A Korean man living in Wuhan China/ Virus transmission; from index patient Patient A to	Spectrum of disease: mild respiratory symptoms. CT: small consolidation in right upper lobe,	Chills, muscle pain	5–7 days	–	Therapy: Lopinavir/Ritonavir Results and interpretation: significant decrease in β-coronavirus viral loads due to

(Continues)

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
					Patients B, C, D@@	GGO in both lower lobes				the natural course of the healing process rather than administration of Lopinavir/ Ritonavir, or both
Wu et al. (2020), China	Retrospective/three Grade IIIA hospitals of Jiangsu	80/46.1/41 female (51.25%)	Laboratory testing, real time RT-PCR, CT	Throat swab and/or nose swab, blood	Confirmed COVID-19 patients/with a history of epidemic in Wuhan and without contact with the seafood market	Spectrum of disease: mild: 28 (35.00%), moderate: 49 (61.25%), severe: 3 (3.75%), critically ill: none Laboratory: lower WBC: 36 (45.00%), lymphocytopenia: 26 (32.50%), lower platelets: 11 (13.75%), high CRP: 62 (77.50%), high ESR: 59 (73.75%), elevated PCT: 1 (1.25%). Liver function: increased ALT/AST: 3 (3.75%), lower albumin: 2 (2.50%). Abnormal myocardial enzyme spectrum and increase of CK: 18 (22.50%). Increased LDH: 17 (21.25%). Renal function damage: 2 (2.50%). Serious renal function damage: 1. Hyperglycemia: 19 (23.17%). Increased D-dimer: 3 (3.75%).	Fever: 63 (78.75%), cough: 51 (63.75%), shortness of breath: 30 (37.50%), muscle ache: 18 (22.50%), headache: 13 (16.25%) liver dysfunction: 3 (3.75%)/ cardiovascular/ cerebrovascular, endocrine, digestive, respiratory, malignancies and nervous system diseases: 38 (47.50%)	8.0	Not now	Therapy: all patients: single antibiotic mainly Moxifloxacin and Ribavirin antiviral therapy, 12 (14.63%) patients: methylprednisolone sodium succinate or methylpredniso-lone, 35 (43.75%) patients: noninvasive ventilator, 1 patient: hemodialysis, 3 patients: TCM Interpretation: 21 cases discharged from the hospital: With no obvious gender susceptivity, lower proportion of liver dysfunction, abnormal CT and higher frequency nucleic acid detection

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						9 kinds of respiratory pathogens and influenza A/B nucleic acids: all patients. CT: abnormal: 55 (68.75%), bilateral pneumonia: 36 (45.00%), unilateral pneumonia: 19 (23.75%), normal: 25 (31.25%). Organ damage: acute respiratory injury: 10 (12.50%), renal injury: 2 (2.50%)				
Li et al. (2020), China	Retrospective study/ hospital in Wenzhou	175/46/92 women, 83/men	Real-time PCR, CT	Respiratory tract samples or blood samples	Confirmed COVID-19/a history of exposure to the epidemic area: 57 (33%) patients	Spectrum of disease: COVID-19: mild: mild clinical manifestations, no pneumonia; moderate: respiratory symptoms, mild pneumonia, severe (37): pneumonia, ARDS with RR >30 times/min, oxygen saturation <93%; critical (3): pneumonia, shock, respiratory failure, and failures in other organs, nearly all patients: GGO K^+: severe hypokalemia: 39 (higher body temperature, higher heart rate	Cough, fever, pneumonia/ hypertension: 28, diabetes: 12, other conditions:31	6	–	Therapy: 1 severe hypokalemia patients; 3 g/day K^+, 34 ($SD = 4$) g potassium during hospital stay Good response of patients to K+ supplements when they inclined to recovery Interpretation: hypokalemia is prevailing in COVID-19 patients

(Continues)

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						and RR, higher prevalence of dyspnea or tachypnea ($p < .05$)), hypokalemia 69, normokalemia patients 67. Correlations: severity of hypokalemia with body temperature, CK, CK-MB, LDH, and CRP ($p < .01$), 93% of severe/ critically ill patients showed hypokalemia				
Lan et al. (2020), China	Case study/Zhongnan Hospital of Wuhan University, Wuhan	4, 30–36 years, 2 male	RT-PCR, thin-section CT	Throat swabs	Medical personnel quarantined at home with COVID-19	Spectrum of disease: mild to moderate Results: (at admission); PCR positive: for all CT positive: for all GGO, or mixed GGO/ consolidation (after therapy); 2 consecutive negative RT-PCR: all (after discharge); repeated RT-PCR 5–13 days later: all positive	Fever:3, cough: 3, both: 3	Symptom onset to recovery: 12–32 days	–	Therapy: antiviral treatment (75 mg of oseltamivir every 12 hr) Resolved clinical symptoms and CT abnormalities: 3 Delicate patches of GGO: 1 Interpretation: possibility of at least a proportion of recovered patients act as virus carriers
Li et al. (2020), China	Retrospective study/ Sino-French New Town area Tongji Hospital	47, 62, 28 (59.6%) men	Real-time RT-PCR	Throat-swab specimens, sputum or endotra-cheal aspirates	Patients with severe COVID-19	Spectrum of disease: severe: 41 critical: 5(17.9%) men and 1 (5.3%) women Common: oxygen saturation <93% after routine	Fever: 34 [72.3%], cough: 36 [76.6%], myalgia: 5 [10.6%], fatigue: 7 [14.9%]/ comorbidities: 30 (63.8%):	–	3.6% in men and 0 in women	Therapy: antibiotics applied more in the men than the women Results and interpretation: 4 (21.1%) women/1 man (3.6%) discharged.

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
						Nasal oxygen supply: 3 men/1 woman Blood: PCT: higher in men, N-terminal-pro brain natriuretic peptide: Higher in 16(57.1%) men/5 (26.3%) women, Positive influenza A antibody: 5 men (17.9%)	COPD, hypertension/ CVD lower in men			Possibility of sex differences in severe COVID-19 patients, Men with more complicated clinical condition and worse outcomes
Han et al. (2020)	Case study/People's Hospital in Wuwei	A 47-year-old man/ smoking for 20 years/no alcohol abuse	RT-PCR, CT	Nasopharyn-geal swab specimens	Confirmed SARS-CoV-2/returned to Wuwei city on January 18 from Wuhan city by car	Blood: decreased lymphocytes, increased CRP, slightly elevated fibrinogen, neutrophil, LDH, and fibrinogen PCR: positive for expression of RdRPN, N and E genes CT: multiple patchy high-density shadows scattered mainly in the border regions of lungs, solid changes, GGO changes, slightly thickened pleura	Fever, cough productive of white phlegm, bosom frowsty, stuffy/runny noses, vertigo, fatigue, chest tightness, nausea, expiratory dyspnea, poor diet, lethargy/ hypertension grade 2 and T2D	–	–	Therapy: combination therapy including: Lopinavir/Ritonavir (800/200 mg daily), methylpredniso-lone (40 mg daily), recombinant human interferon α-2b (10 million IU daily), ambroxol hydrochloride (60 mg daily) moxifloxacin hydrochloride (0.4 g daily), high flow humidification oxygen inhalation therapy, treatment of blood glucose, blood pressure, and rehydration therapy Results interpretation: the persistent negative results of SARS-CoV-2 on days 6 and 7, normal TLC, lung

(Continues)

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
										lesions partially absorbed, The patient discharged. Laboratory tests like TLC are necessary, CT combined with RT-PCR is helpful, Lopinavir/ Ritonavir are effective after failure of methylpredniso-lone/interferon alfa-2b
Liu et al. (2020), China	Retrospective cohort and case study/ Zhongnan Hospital of Wuhan University Dawu County People's Hospital	124 patients, 22 patients: 12 therapy (mean age 53), 10 control (mean age 58)	CT, PCR	Serum	124 confirmed COVID-19 cases, 12 HCOV infected patients	Blood: (Study 1) decreased platelet: 25 (20.2%), prolonged PT: 77 (62.1%), increased FIB: 27 (21.8%), and increased D-dimer: 26 (21.0%) Spectrum of disease: (study 2) severe cases: 6 mild cases: 4 critically ill: 2 CT: (study 2) Bilateral pneumonia: all	Study 1: hypercoagul-ability Study 2: cough: all shortness of breath: most of them, nausea and vomiting: 60.0%/ DM, cardiovascular and cerebrovascular diseases: 4 patients from the DIP, 5 patients control group	–	1	Therapy: Dipyridamole (150 mg in three separate doses for 7 consecutive days), antiviral (ribavirin, 0.5 g, Q12hr), corticoid (methylpredniso-lone sodium succinate, 40 mg, qd), oxygen therapy, nutritional support Results and interpretation: significant increase in platelet/ lymphocyte, significant decrease in D-dimer levels Discharged patients: 50% of severe cases and all 4 mild cases. Dipyridamole adjunctive

TABLE 3 (Continued)

Study/region	Study type/ medical team	Patient/median age/sex	Diagnostic test	Sample	Inclusion criteria/ residency	Test results	Most common symptoms/chronic disease	Incubation period (day)	Case fatality rate	Diagnosis/prognosis/ therapy
										therapy could significantly reduce viral replication, inhibits hypercoagulability and improves immune recovery

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase myocardial band; COPD, chronic obstructive pulmonary disease; CRE, serum creatinine; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; FIB, fibrinogen; FiO2, fraction of inspired oxygen; GGO, ground-glass opacity; GGT, γ-glutamyltransferase; GLM, Generalized Linear Model; LDH, lactate dehydrogenase; nCoV, novel coronavirus; PaO2, partial pressure of oxygen; PCT, procalcitonin; PT, prothrombin time; RNAaemia, SARS-CoV-2 nucleic acid; RR, respiratory rate; RT-PCR, reverse transcriptase polymerase chain reaction; SpO2, oxygen saturation; T2D, type 2 diabetes; TB, total bilirubin; TCM, traditional Chinese medicine; TCM, traditional Chinese medicine; TLC, total lymphocyte count; TnT, troponin T; WBC, white blood cell.

The 21st century has seen many AI-based models to be incorporated in several scientific fields, particularly imaging studies. Diagnostic AI-based models might actually be a forward leap in tasks that simply cannot be handled by manpower, especially risk prioritization, that can greatly help improve patient turnaround time. Given the shortage of human resources and inadequate number of hospital beds in a country like China, AI-based models for analysis of CXR and CT scans can be useful in ruling out irrelevant cases, and resource-wise admission of patients to the hospitals (Kim, 2020).

6 | PREDICTION

Recent studies focused on prognosis of COVID-19 concluded that the load of SARS-CoV-2 RNA in blood (RNAemia) is correlated with Cytokine Release Storm (CRS) and poor prognosis of the disease. In one particular study, scientists used Generalized Linear Models to generate a prediction model for natural history of disease based on the C_t value of real-time RT-PCR results. They reported that traceable amounts of SARS-CoV-2 RNA was detected in blood plasma of 15% of COVID-19 positive patients enrolled at the study. Their findings drew a direct link between serum markers and disease severity, as RNAemia and high levels of IL-6 (nearly 10-fold) were exclusively reported in critically ill patients. Interestingly, there was also an association between the extremely high levels of IL-6 with the incidence of RNAemia ($R = 0.902$) in patients. Findings also suggested that vital signs of patients were also affected by high levels of both serum markers ($R = 0.682$). According to this study, IL-6 might be of clinical value in identification and treatment of patients with an excessive inflammatory response (Chen, Zhao, et al., 2020). Table 3 (Chen, Zhao, et al., 2020; Yan et al., 2020) and Table 4 represent 2020 studies on prognosis of COVID-19 infected patients and related clinical trials, respectively.

7 | THERAPY

Scientists have made strenuous efforts to come up with an effective regimen for successful treatment of COVID-19 (Gao, Tian, & Yang, 2020). Table 3 (Chen, Guo, et al., 2020; Fan et al., 2020; Han et al., 2020; Lan et al., 2020; Li, Zhang, et al., 2020; Li, Hu, et al., 2020; Lim et al., 2020; Liu et al., 2020; Liu et al., 2020; Wu et al., 2020; Wu & McGoogan, 2020), Tables 4 and 5 (Zhang & Liu, 2020) represent 2020 studies on treatment of COVID-19 infected patients, related clinical trials and available therapeutic options, respectively.

7.1 | Chloroquine phosphate

Chloroquine phosphate is an old medicine, that has been widely used for treatment of malaria in endemic regions. It is also a salutary treatment of choice for certain progressive anti-inflammatory diseases, for example, rheumatoid arthritis, and systemic lupus

TABLE 4 Clinical trials for COVID-19 or SARS-nCoV2

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
The efficacy and safety of huaier in the adjuvant treatment of COVID-19	Drug: Huaier Granule	COVID-19	550, all, 18–75	Treatment	Experimental group: standard therapy + Huaier granule 20 g, po, tid for 2 weeks (or until discharge) Control group: standard therapy	II, III	Primary (up to 28 days): all cause mortality Secondary (up to 28 days): clinical status, differences in oxygen intake methods, supplemental oxygenation, mechanical ventilation, mean PaO2/FiO2, length of hospital stay, Length of ICU stay (days), pulmonary function (up to 3 months after discharge)	NCT04291053/Not yet recruiting, Apr1-Sep1 2020
Clinical trial on regularity of TCM syndrome and differentiation treatment of COVID-19	Drug: TCM prescriptions	China/COVID-19	340, all, 18–75	Treatment	Exposure group: integrated TCM and western medicine cohort (routine treatment + one or two of the following antiviral drugs + the following TCM regimens: take decocted or granule, one dose a day) Control group: western medicine cohort (routine treatment + one or both of the following antiviral drugs)	Not applicable	Primary (9 days): The relief/disappearance rate of main symptoms, chest CT absorption Secondary (9 days): virus antigen negative conversion rate, Clinical effective time: the average effective time. The number of severe and critical conversion cases, Incidence of complications, Traditional Chinese Medicine Syndrome Score Other outcome measures (9 days): CRP changes, ESR changes, PCTchanges, The index of T cell subsets changed	NCT04306497/ Recruiting, Mar2-May 2020
Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19	Drug: Recombinant human angiotensin-converting enzyme 2 (rhACE2)	China/COVID-19	24, all, 18–80	Treatment	Experimental group: 0.4 mg/kg rhACE2 IV BID for 7 days and standard of care Control group: standard of care	Not applicable	Primary (14 days): time course of body temperature, viral load over time Secondary (14 days): P/F ratio over time, sequential organ failure assessment score over time, Pulmonary Severity Index, image examination of chest over time, proportion of subjects who progressed to critical illness or death, Time from first dose to conversion to normal or mild pneumonia, T-lymphocyte counts over time, C-reactive protein levels over time, angiotensin II (Ang II) changes over time, angiotensin 1–7 (Ang 1–7) changes over time, angiotensin 1–5 (Ang 1–5) changes over time, renin changes over time, aldosterone changes over time, angiotensin-converting enzyme changes over time, angiotensin-converting enzyme 2 (ACE2) changes over time, IL-6 changes over time, IL-8 changes over time,	NCT04287686/ Withdraw, Feb-Apr 2020

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							soluble tumor necrosis factor receptor type II (sTNFrII) changes over time, Plasminogen activator inhibitor type-1 changes over time, Von willebrand factor changes over time, tumor necrosis factor-α changes over time, soluble receptor for advanced glycation end products (sRAGE) changes over time, surfactant protein-D changes over time, angiopoietin-2 changes over time, frequency of adverse events and severe adverse events	
The COVID-19 mobile health study (CMHS)	nCapp, a cell phone-based autodiagnosis system	China/COVID-19	450, all, 18–90	Diagnosis	Training: nCapp, a cell phone-based autodiagnosis system, combined with 15 questions online, and a predicated formula to autodiagnosis of the risk of COVID-19 Validation: nCapp, a cell phone-based autodiagnosis system, combined with 15 questions online, and a predicated formula to auto-diagnosis of the risk of COVID-19	–	Primary (1 day): accuracy of nCapp COVID-19 risk diagnostic model	NCT04275947/ Recruiting, Feb 14-May 31 2020
A Pilot Study of Sildenafil in COVID-19	Drug: Sildenafil citrate tablets (G1)	China/COVID-19	10, all, 18 years and older	Treatment	Experimental group: sildenafil citrate tablet 0.1 g/day for 14 days	Not applicable	Primary (14 days): rate of disease remission, rate of entering the critical stage, time of entering the critical stage Secondary (14 days): rate of no fever, rate of respiratory symptom remission, rate of lung imaging recovery, rate of C-reactive protein (CRP) recovery, rate of Biochemical criterion (CK, ALT, Mb) recovery, rate of undetectable viral RNA (continuous twice), time for hospitalization, rate of adverse event	NCT04304313/ Recruiting, Feb 9-Nov 9 2020
Critically Ill patients with COVID-19 in Hong Kong: a multicentre observational cohort study	–	Hong Kong/ COVID-19	8	descriptive	A case series of 41 hospitalized patients with confirmed infection 30% required critical care admission: developed severe respiratory failure, 10%	–	Primary (28 days): 28 day mortality Secondary (28 days): vasopressor days, days on mechanical ventilation, sequential organ function assessment score, ECMO use, percentage nitric oxide use,	NCT04285801/ Completed, Feb 14-Feb 25 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					required mechanical ventilation, 5% needed extracorporeal membrane oxygenation support mortality rate: 15%		percentage free from oxygen supplement	
Treatment of mild cases and chemoprophylaxis of contacts as prevention of the COVID-19 epidemic	Drug: antiviral treatment and prophylaxis, Standard Public Health measures	COVID-19	3,040, All, 18 Years and older	Treatment	Experimental: antiviral treatment and prophylaxis: darunavir 800 mg/cobicistat 150 mg tablets (oral, 1 tablet q24h, taking for 7 days) and hydroxychloroquine (200 mg tablets) 800 mg on Day 1, and 400 mg on days 2, 3, 4. Contacts: a prophylactic regimen of hydroxychloroquine (200 mg tablets) 800 mg on Day 1, and 400 mg on days 2,3,4. Other: standard public health measures Active comparator: standard public health measures	III	Primary (up to 14 days after start of treatment): effectiveness of chemoprophylaxis assessed by incidence of secondary COVID-19 cases Secondary: the virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at days 3, the mortality rate of subjects at weeks 2, proportion of participants that drop out of study (up to 14 days after start of treatment), proportion of participants that show noncompliance with study drug (up to 14 days after start of treatment)	NCT04304053/Not yet recruiting, Mar15-Jul15 2020
Comparison of lopinavir/ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19)	Drug: lopinavir/ritonavir, Drug: hydroxychloroquine sulfate	Korea/COVID-19	150, all, 16 years to 99 years	Treatment	Experimental: lopinavir/ritonavir 200 mg/100 mg 2 tablets by mouth, every 12 hr for 7–10 days Active comparator: hydroxychloroquine 200 mg 2 tablets by mouth, every 12 hr for 7–10 days No intervention: control, no lopinavir/ritonavir and hydroxychloroquine	II	Primary: viral load (hospital Day 3, 5, 7, 10, 14, 18) Secondary viral load change (hospital Day 3, 5, 7, 10, 14, 18), time to clinical improvement (time frame: up to 28 days), percentage of progression to supplemental oxygen requirement by Day 7, Time to NEWS2 (National Early Warning Score 2) of 3 or more maintained for 24 hr by Day 7, time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission (up to 28 days), rate of switch to lopinavir/ritonavir or hydroxychloroquine by Day 7, adverse effects (up to 28 days), concentration of lopinavir/ritonavir and hydroxychloroquine (1, 2, 4, 5, 12 hr after taking intervention medicine)	NCT04307693/ Recruiting, Mar11-May 2020
Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in	Drug: remdesivir, standard of care	United States, Hong Kong/ COVID-19	400, all, 18 years and older	Treatment	Experimental: demdesivir (RDV), 5 days participants will receive continued standard of care	III	Primary: proportion of participants with normalization of fever and oxygen saturation through day 14	NCT04292899/ Recruiting, Mar6-May 2020

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
participants with severe coronavirus disease (COVID-19)					therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5 Experimental: remdesivir, 10 days participants will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10		Secondary: proportion of participants with treatment emergent adverse events leading to study drug discontinuation (first dose date up to 10 days)	
Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment	Drug: remdesivir, standard of care	United States, Hong Kong,	600, all, 18 years and older	Treatment	Experimental: remdesivir, 5 days participants will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5. Experimental: remdesivir, 10 days participants will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10. Active comparator: continued standard of care therapy	III	Primary (up to 14 days): proportion of participants discharged by day 14-secondary (up to 10 days): proportion of participants with treatment emergent adverse events leading to study drug discontinuation	NCT04292730/ Recruiting, Mar-May 2020
Bevacizumab in severe or critical patients with COVID-19 pneumonia-RCT	Drug: bevacizumab	China/COVID-19 Pneumonia	118, all, 18–80	Treatment	Experimental; bevacizumab, group: bevacizumab 500 mg + 0.9% NaCl 100 ml, intravenous drip No intervention: control group	Not applicable	Primary: proportion of patients whose oxygenation index increased by 100 mmHg on the 7th day after admission	NCT04305106/Not yet recruiting, Mar12-May31 2020
The efficacy and safety of thalidomide in the adjuvant treatment of moderate new coronavirus (COVID-19) pneumonia	Drug: thalidomide, placebo	COVID-19 thalidomide	100, all, 18 years and older	Treatment	Placebo comparator: control group: placebo 100 mg, po, qn, for 14 days Experimental: thalidomide group 100 mg, po, qn, for 14 days. Other name: fanyingting	II	Primary (up to 28 days): time to clinical recovery time to clinical recovery (up to 28 days) Secondary (up to 28 days): all cause mortality (up to 28 days), frequency of respiratory progression, Time to defervescence Others(up to 28 days): time to cough reported as mild or absent, respiratory improvement time, frequency of requirement for supplemental oxygen or noninvasive ventilation, Time to 2019-nCoV RT-PCR negative in upper	NCT04273529/Not yet recruiting, Feb20-Jun30 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							respiratory tract specimen, change (reduction) in 2019-nCoV viral load in upper respiratory tract specimen as assessed by area under viral load curve, frequency of requirement for mechanical ventilation, frequency of serious adverse events, Serum TNF-α, IL-1β, IL-2, IL-6, IL-7, IL-10, GSCF, IP10, MCP1, MIP1α and other cytokine expression levels before and after treatment	
The efficacy and safety of thalidomide combined with low-dose hormones in the treatment of Severe COVID-19	Placebo, drug: thalidomide	COVID-19 thalidomide	40, all, 18 years and older	Treatment	Placebo comparator: control group α-interferon: nebulized inhalation, 5 million U or equivalent dose added 2 ml of sterile water for injection, 2 times a day, for 7 days; abidol, 200 mg/time, 3 times a day, for 7 days; methylprednisolone: 40 mg, q12h, for 5 days. placebo: 100 mg/d, qn, for 14 days Experimental: thalidomide group α-interferon: nebulized inhalation, 5 million U or equivalent dose added 2 ml of sterile water for injection, 2 times a day, for 7 days; abidol, 200 mg/time, 3 times a day, for 7 days; methylprednisolone: 40 mg, q12h, for 5 days. thalidomide: 100 mg/d qn for 14 days	II	Primary (up to 28 days): time to clinical improvement Secondary (up to 28 days): clinical status (days 7, 14, 21, and 28), time to hospital discharge or NEWS2 (National Early Warning Score 2) of ≤2 maintained for 24 hr, all cause mortality, duration (days) of mechanical ventilation, duration (days) of extracorporeal membrane oxygenation, duration (days) of supplemental oxygenation, length of hospital stay (days), time to 2019-nCoV RT-PCR, change (reduction) in 2019-nCoV viral load in upper and lower respiratory tract specimens as assessed by area under viral load curve, frequency of serious adverse drug events, Serum TNF-α, IL-1β, IL-2, IL-6, IL-7, IL-10, GSCF, IP10#MCP1, MIP1α, and other cytokine expression levels before and after treatment	NCT04273581/Not yet recruiting, Feb18-May30 2020
Tetrandrine tablets used in the treatment of COVID-19	Drug: tetrandrine	China/COVID-19	60, all, 18–75	Treatment	Experimental: tetrandrine cohort after the subjects were enrolled, they were given "Tetrandrine 60 mg QD" for a course of 1 week (take 6 days, stop using for 1 day) No intervention: control cohort treatment according to standard protocols without intervention	IV	Primary (12 weeks): survival rate secondary (2 weeks): body temperature	NCT04308317/ Enrolling by invitation, Mar5-May1 2020

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
Fingolimod in COVID-19	Biological: UC-MSCs, other: placebo	China/COVID-19	30, all, 18–80	Treatment	Experimental: treatment group: each patient in the fingolimod treatment group was given 0.5 mg of fingolimod orally once daily, for three consecutive days No Intervention: control group	II	Primary (5 day after treatment): the change of pneumonia severity on X-ray images	NCT04280588/ Recruiting, Feb22-Jul1 2020
Therapy for pneumonia patients infected by 2019 novel coronavirus	Biological: UC-MSCs, other: placebo	China/COVID-19	48, all, 18–75	Treatment	Experimental: UC-MSCs treatment group, participants will receive conventional treatment plus four times of 0.5*10E6 UC-MSCs/kg body weight intravenously at Day1, Day3, Day5, Day7) Placebo comparator: control group, participants will receive conventional treatment plus 4 times of placebo intravenously at Day1, Day3, Day5, Day7	Not applicable	Primary (at baseline, Day 1, Weeks 1, 2, 4, 8): size of lesion area by chest imaging, blood oxygen saturation Secondary (at baseline, Day 1, Weeks 1, 2, 4, 8): rate of mortality within 28-days, sequential organ failure assessment, side effects in the UC-MSCs treatment group, Electrocardiogram, the changes of ST-T interval mostly, Concentration of C-reactive protein C-reactive protein, immunoglobulin, CD4 + and CD8 + T cells count, Concentration of the blood cytokine (IL-1β, IL-6, IL-8,IL-10,TNF-α), Concentration of the myocardial enzymes	NCT04293692/ Recruiting, Feb24-Feb1 2020–2021
The Use PUL-042 inhalation solution to prevent COVID-19 in adults exposed to SARS-CoV-2	Drug: PUL-042 inhalation solution, drug: placebo	COVID-19	200, all, 18 years and older	Treatment	Experimental: PUL-042 inhalation solution, PUL-042 inhalation solution (20.3 μg Pam2: 29.8 μg ODN/mL) given by nebulization on study days 1,3, 6, and 10 Placebo comparator: sterile normal saline for inhalation, sterile normal saline for inhalation given by nebulization on study days 1, 3, 6, and 10	II	Primary (14 days): Prevention of COVID-19	NCT04313023/Not yet recruiting, Apr-Oct 2020
Treatment of COVID-19 patients using Wharton's jelly-mesenchymal stem cells	Biological: WJ-MSCs	Arabia Amman, Jordan/use of stem cells for COVID-19 treatment	5, all, 18 years and older	Treatment	Experimental: WJ-MSCs WJ-MSCs will be derived from cord tissue of newborns, screened for HIV1/2, HBV, HCV, CMV, mycoplasma, and cultured to enrich for MSCs. WJ-MSCs will be counted and suspended in 25 ml of saline solution containing 0.5% human serum albumin, and will	I	Primary (3 weeks): Clinical outcome, CT Scan, RT-PCR results Secondary (8 weeks): RT-PCR results	NCT04313322/ Recruiting, Mar16-Sep30 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					be given to patient intravenously			
Myocardial damage in COVID-19	Non	China/COVID-19 cardiovascular diseases	500, all, 18 years and older	Prognostic	Discharged group (no intervention) the individual which is defined as patient discharged from hospital Dead group (no intervention) The individual which is defined as patient with all-cause death	–	Primary (75 days): the myocardial injury incidence, the risk factors analysis for the death Secondary (75 days): clinical characteristics, clinical course, cardiovascular comorbidity, Analysis of causes of death	NCT04312464/ Enrolling by invitation, Jun1-Mar18 2020
Treatment with mesenchymal stem cells for severe corona virus disease 2019(COVID-19)	Biological: MSCs, biological: saline containing 1%, human serum albumin (solution of MSC	China/COVID-19	60, all, 18–70	Treatment	Experimental: mesenchymal stem cells (MSCs), conventional treatment plus MSCs participants will receive conventional treatment plus 3 times of MSCs ((4.0*10E7 cells per time) intravenously at Day 0, Day 3, Day 6) Placebo comparator: placebo conventional treatment plus placebo participants will receive conventional treatment plus 3 times of placebo (saline containing 1% human serum albumin (solution of MSC) 3 times of placebo (intravenously at Day 0, Day 3, Day 6)	I, II	Primary (28 days): improvement time of clinical critical treatment index, side effects in the MSCs treatment group Secondary: proportion of patients in each classification of clinical critical treatment index (baseline, Days 7, 14, 28), all cause mortality on Day 28, invasive mechanical ventilation rate (Day 28), duration of oxygen therapy (Day 28), duration of hospitalization (Day 28), incidence of nosocomial infection (Day 28), CD4+ T cell count by flow cytometry in two groups (baseline, Day, 3, 6, 10, 14, 21, 28)	NCT04288102/ Recruiting, May5-Dec31 2020–2021
The clinical study of carrimycin on treatment patients with COVID-19	Drug: carrimycin, drug: lopinavir/ritonavir tablets or arbidol or chloroquine phosphate, Drug: basic treatment	–	520, all, 18–75	Treatment	Experimental: carrimycin basic treatment + carrimycin Active comparator: lopinavir/ ritonavir or arbidol or chloroquine phosphate any of basic treatment + lopinavir/ ritonavir tablets or arbidol or chloroquine phosphate	IV	Primary (30 days): fever to normal time (day), pulmonary inflammation resolution time (HRCT) (day), negative conversion (%) of 2019-nCOVRNA in gargle (throat swabs) at the end of treatment	NCT04286503/Not yet recruiting, Feb23-Feb28 2020–2021
Efficacy and safety of corticosteroids in COVID-19	Drug: methylprednisolone	China/COVID-19	400, all, 18 years and older	Treatment	Experimental; Pred group: methylprednisolone 1 mg/kg/ day ivgtt for 7 days No intervention: con group	Not applicable	Primary (14 days): the incidence of treatment failure in 14 days Secondary: clinical cure incidence (14 days), the duration of virus change to negative (14 days), mortality at Day 30, ICU admission rate in 30 days	NCT04273321/ Recruiting, Feb14-May30 2020
Evaluation of the efficacy and safety of sarilumab in	Drug: sarilumab, drug: placebo	United States/ COVID-19	400, all, 18 years and older	Treatment	Experimental: sarilumab high dose: single intravenous (IV) dose of sarilumab, other names:	II, III	Primary: time to resolution of fever for at least 48 hr without antipyretics for 48 hr (Up to Day 29), percentage	NCT04315298/ Recruiting,

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
hospitalized patients with COVID-19					Kevzara®, REGN88, SAR153191 Experimental: sarilumab low dose: single intravenous (IV) dose of sarilumab Other Names: Kevzara®, REGN88, SAR153191 Placebo comparator: single intravenous (IV) dose of placebo to match sarilumab administration		of patients reporting each severity rating on a 6-point ordinal scale (Day 15) Secondary (up to Day 29): time to improvement in oxygenation for at least 48 hr, mean change in the 6-point ordinal scale, clinical status using the 6-point ordinal scale, time to improvement in one category from admission using the 6-point ordinal scale, time to resolution of fever for at least 48 hr without antipyretics by clinical severity, time to resolution of fever for at least 48 hr without antipyretics by baseline IL-6 levels, time to improvement in oxygenation for at least 48 hr by clinical severity, time to improvement in oxygenation for at least 48 hr by baseline IL-6 levels, time to resolution of fever and improvement in oxygenation for at least 48 hr, time to change in National Early Warning Score 2 (NEWS2) scoring system, time to score of <2 maintained for 24 hr in NEWS2 scoring system, mean change in NEWS2 scoring system, number of days with fever, number of patients alive off oxygen, number of days of resting respiratory rate >24 breaths/min, number of days with hypoxemia, number of days of supplemental oxygen use, time to saturation ≥94% on room air, number of ventilator free days in the first 28 days, number of patients requiring initiation of mechanical ventilation, number of patients requiring noninvasive ventilation, number of patients requiring the use of high flow nasal cannula, number of patients admitted into an intensive care unit, number of days of hospitalization among survivors, number of deaths due to any cause (up to Day 60), incidence of serious	Mar16-Mar16 2020–2021

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							adverse events (Up to Day 60), incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infection, Incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infection in patients with grade 4 neutropenia, Incidence of hypersensitivity reactions, incidence of infusion reactions, incidence of gastrointestinal perforation, white blood cell count, hemoglobin levels, platelet count, creatinine levels, total bilirubin level, alanine aminotransferase level, aspartate aminotransferase level	
Washed microbiota transplantation for patients with 2019-nCoV infection	Other: washed microbiota transplantation, other: placebo	China/COVID-19 complicated with refractory intestinal infections	0, all, 14–70 complicated with refractory intestinal infections	Treatment	Experimental: observational group 5 u washed microbiota suspension administered via nasogastric tube, nasojejunal tube or oral, combining with standard therapy Placebo comparator: control group 5 u placebo (edible suspension of the same color as the washed microbiota suspension) administered via nasogastric tube, nasojejunal tube or oral, combining with standard therapy	Not applicable	Primary (2 weeks): number of participants with improvement from severe type to common type	NCT04251767/ Withdrawn, Feb5-Apr30 2020
Safety and immunity of Covid-19 aAPC vaccine	Biological: pathogen-specific aAPC	China/Covid-19 infection	100, all, 6 months to 80 years	Treat and Prevent Covid-19 Infection	Experimental: the subjects will receive three injections of 5×10^6 each Covid-19/aAPC vaccine via subcutaneous injections	I	Primary (0–28 day): frequency of vaccine events, frequency of serious vaccine events, proportion of subjects with positive T cell response Secondary (0–28 day): mortality, duration of mechanical ventilation if applicable, proportion of patients in each category of the 7-point scale (7, 14, and 28 days after randomization), proportion of patients with normalized inflammation factors (7 and 14 days after randomization), clinical improvement based on the 7-point scale if applicable, lower Murray	NCT04299724/ Recruiting, Feb15-Dec31 2020–2024

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							lung injury score if applicable (7 days after randomization)	
Safety related factors of endotracheal intubation in patients with severe Covid-19 pneumonia	Severe covid-19 pneumonia with ET	COVID-19 endotracheal intubation	120, all, 18–90	Observational	Intervention details: other: severe covid-19 pneumonia with ET, severe covid-19 pneumonia undergoing endotracheal intubation	–	Primary: Success rate of intubation (the time span between 1 hr before intubation and 24 hr after intubation), infection rate of anesthesiologist (the time span between 1 hr before intubation and 14 days after intubation) Secondary: Extubation time (the time span between 1 hr before intubation and 30 days after intubation)	NCT04298814/Not yet recruiting, Mar7-Jul30 2020
Immunity and safety of Covid-19 synthetic minigene vaccine	Biological: injection and infusion of LV-SMENP-DC vaccine and antigen-specific CTLs	China/COVID-19	100, all, 6 months to 80 years	Treatment	Experimental: pathogen-specific DC and CTLs patients will receive approximately 5×10^6 LV-DC vaccine and 1×10^8 CTLs via subcutaneous injections and iv infusions, respectively	I II	Primary: Clinical improvement based on the 7-point scale (28 days after randomization), lower Murray lung injury score (7 days after randomization) Secondary (0–28 day): 28-day mortality, duration of mechanical ventilation, duration of hospitalization, proportion of patients with negative RT-PCR results (7 and 14 days after randomization), proportion of patients in each category of the 7-point scale (7, 14, and 28 days after randomization), proportion of patients with normalized inflammation factors (7 and 14 days after randomization), frequency of vaccine/CTL events, frequency of serious vaccine/CTL events	NCT04276896/ Recruiting, Mar24-Dec31 2020–2024
Phase I clinical trial in healthy adult	Biological: recombinant novel coronavirus vaccine (adenovirus type 5 vector)	–	108, all, 18–60	Prevention	Experimental: low-dose group subjects received one dose of 5E10 vp Ad5-nCoV at 18–60 years old Experimental: middle-dose group Subjects received one dose of 1E11 vp Ad5-nCoV at 18–60 years old Experimental: high-dose group Subjects received one dose of 1.5E11vp Ad5-nCoV at 18–60 years old	I	Primary (0–7 days postvaccination): safety indexes of adverse reactions Secondary (Day 14, 28, Month 3, 6 postvaccination): Safety indexes of adverse events (0–28 days postvaccination), safety indexes of SAE (0–28 days, within 6 mouths postvaccination), safety indexes of lab measures (pre-vaccination, Day 7 postvaccination), immunogencity indexes of GMT (ELISA) (Day 14, 28, Month 3, 6	NCT04313127/Not yet recruiting, Mar1Dec20 2020–2022

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							postvaccination), immunogencity indexes of GMT (pseudoviral neutralization test method), immunogencity indexes of seropositivity rates, immunogencity indexes of seropositivity rates (pseudoviral neutralization test method, immunogencity indexes of GMI (ELISA), immunogencity indexes of GMI (pseudoviral neutralization test method), immunogencity indexes of GMC (Ad5 vector), immunogencity indexes of GMI (Ad5 vector), immunogencity indexes of cellular immune Other (day、14,28, Month3,6 postvaccination): Consistency analysis(ELISA and pseudoviral neutralization test method), Dose-response relationship (Humoral immunity), Persistence analysis of anti-S protein antibodies, Time-dose-response relationship (Humoral immunity), Dose-response relationship (cellular immunity), Persistence analysis of cellular immuse, Time-dose-response relationship (cellular immunity)	
Development and verification of a new coronavirus multiplex nucleic acid detection system	Diagnostic test: new QIAstat-Dx fully automatic multiple PCR detection platform	China/COVID-19	100, all, 16 years to 100 years	Diagnostic	Diagnostic test: new QIAstat-Dx fully automatic multiple PCR detection platform We use the new QIAstat-Dx fully automatic multiple PCR detection platform to test the enrolled patients	–	Primary: Sensitivity, spectivity turnaround time of the New QIAstat-Dx fully automatic multiple PCR detection platform (3 months)	NCT04311398/Not yet recruiting, Mar14-Dec1, 2020
Hydroxychloroquine treatment for severe COVID-19 pulmonary infection (HYDRA Trial)	Drug: hydroxychloroquine, drug: placebo oral tablet	COVID-19 severe acute respiratory syndrome	500, all, 18–0	Treatment	Active comparator: treatment Hydroxychloroquine tablet 200 mg every 12 hr for 10 days Placebo comparator: placebo identical placebo, one tablet every 12 hr for 10 days	III	Primary (up to120 days): All-cause hospital mortality Secondary (up to120 days): Length of hospital stay, Need of mechanical ventilation, ventilator free days, Grade 3–4 adverse reaction	NCT04315896/Not yet recruiting, Mar23-Mar22 2020–2012
	Drug: tocilizumab Injection			Treatment	Experimental: Tocilizumab Injection	II	Primary (up to 1 month):	

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
Tocilizumab in COVID-19 pneumonia (TOCIVID-19)		Italy/COVID-19 pneumonia	330, child, adult, older adult, child, adult, older adult		Tocilizumab 8 mg/kg (up to a maximum of 800 mg per dose), with an interval of 12 hr		One-month mortality rate Secondary (up to 1 month): interleukin-6 level, lymphocyte count, C-reactive protein level (cycle 1 and 2 every 12 hr), PaO2 (partial pressure of oxygen)/FiO2 (fraction of inspired oxygen, FiO2) ratio (or P/F ratio) (baseline, during treatment (cycle 1 and 2 every 12 hr), change of the SOFA (sequential organ failure assessment) (baseline, during treatment (cycle 1 and 2 every 12 hr), number of participants with treatment-related side effects as assessed by Common Terminology Criteria for Adverse Event version 5.0, Radiological response, Time Frame: at baseline (optional), after 7 days and if clinically indicated, duration of hospitalization. Time Frame: from baseline up to patient's discharge, Remission of respiratory symptoms	NCT04317092/ Recruiting, Mar19-Dec19 2020–2022
Mesenchymal stem cell NestCell® to treat patients with severe COVID-19 pneumonia	Biological: NestCell®	COVID-19 pneumonia	6, all, 18 years and older	Treatment	Experimental: NestCell®: All patients will receive conventional treatment plus 3 times of 1 × 106 cells/kg body weight intravenously on Day1, Day3, and Day7	I	Primary (28 days): Disappear time of ground-glass shadow in the lungs Secondary: Rate of mortality within 28-days, Improvement of clinical symptoms including duration of fever and respiratory (At Baseline, Day 3, 7, 10, 14, 21, 28), Time of nucleic acid turning negative (28 days), CD4+ and CD8+ T cell count (At Baseline, Day 3, 6, 10, 14, 21, and 28), changes of blood oxygen (At Baseline, Day 3, 6, 10, 14, 21, and Day 28), side effects in the treatment group (28 days)	NCT04315987/Not yet recruiting, Apr-Jun 2020
CD24Fc as a non-antiviral immunomodulator in COVID-19 treatment	Drug: CD24Fc, drug: placebo	United States/severe coronavirus disease (COVID-19)	230, all, 18 years and older	Treatment	Experimental: CD24Fc treatment Single dose at Day 1, CD24Fc, 480 mg, diluted to 100 ml with normal saline, IV infusion in 60 min Placebo comparator: placebo	III	Primary (14 days): Improvement of COVID-19 disease status secondary (14 days): Conversion rate of clinical status at Day 8 (7 days), conversion rate of clinical status at Day 15, hospital discharge time, all cause of death, duration of	NCT04317040/Not yet recruiting,May-May 2020–2022

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					Single dose at Day 1, normal saline solution 100 ml, IV infusion in 60 min		mechanical ventilation, duration of pressors, duration of ECMO, duration of oxygen therapy, length of hospital stay, absolute lymphocyte count	
Acute kidney injury in patients hospitalized with COVID-19	–	China/COVID-19 acute kidney injury-kidney function	287, all, 18 years and older	Observational	Acute kidney injury: COVID-19 patients with acute kidney injury nonacute kidney injury: COVID-19 patients without acute kidney injury	– Rate of death, the length of hospital stay	Primary (up to 60 days): Rate of acute kidney injury Secondary (up to 60 days):	NCT04316299/ Completed, Feb 26-Mar8 2020
Phase I clinical trial in healthy adult	Logical: recombinant novel coronavirus vaccine (adenovirus type 5 vector)	COVID-19	108, all, 18–60	Treatment	(Adenovirus Type 5 Vector) Experimental: low-dose group Subjects received one dose of 5E10 vp Ad5-nCoV at 18–60 years old Experimental: middle-dose group Subjects received one dose of 1E11 vp Ad5-nCoV at 18–60 years old Experimental: high-dose group subjects received one dose of 1.5E11vp Ad5-nCoV at 18–60 years old	I	Primary (0–7 days postvaccination): Safety indexes of adverse reactions Secondary (0–28 days postvaccination, within 6 mouths postvaccination): Safety indexes of adverse events, Safety indexes of SAE, Safety indexes of lab measures, Immunogencity indexes of GMT (ELISA), Immunogencity indexes of GMT (pseudoviral neutralization test method) (Day 14, 28, Month 6 postvaccination), Immunogencity indexes of seropositivity rates (ELISA) (Day 14, 28, Month 3, 6 postvaccination), Immunogencity indexes of seropositivity rates(pseudoviral neutralization test method) (Day 14, 28, Month 6 postvaccination), Immunogencity indexes of GMI (ELISA) (Day 14, 28, Month 3, 6 postvaccination), Immunogencity indexes of GMI (pseudoviral neutralization test method) (Day 14, 28, Month 6 postvaccination), Immunogencity indexes of GMC (Ad5 vector) (Day 14, 28, Month 3, 6 postvaccination), Immunogencity indexes of GMI(Ad5 vector) (Day 14, 28, Month 3, 6 postvaccination), Immunogencity indexes of cellular immune (Day 14, 28, Month 6 postvaccination) Other (Day 14,28, Month 6 postvaccination):	NCT04313127/Not yet recruiting, Mar19-Dec20 2020–2021

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							Consistency analysis (ELISA and pseudoviral neutralization test method), dose-response relationship (humoral immunity) (Day 14, 28, Month 3, 6 postvaccination), Persistence analysis of anti-S protein antibodies (Day 14, 28, Month 3, 6 postvaccination), Time-dose-response relationship (Humoral immunity) (Day 14, 28, Month 3, 6 postvaccination), Dose-response relationship (cellular immunity) (Day 14, 28, Month 6 postvaccination), Persistence analysis of cellular immuse (Day 14, 28, Month 6 postvaccination), Time-dose-response relationship (cellular immunity) (Day 14, 28, Month 6 postvaccination)	
Favipiravir combined with tocilizumab in the treatment of corona virus disease 2019	Drug: favipiravir combined with tocilizumab, drug: favipiravir, drug: tocilizumab	China, COVID-19	150, all, 18–65	Treatment	Experimental: favipiravir combined with tocilizumab group Favipiravir: On the 1st day, 1,600 mg each time, twice a day; from the 2nd to the 7th day, 600 mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 7 days. Tocilizumab: the first dose is 4–8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hr after the first dose and the interval between two medications ≥12 hr. Intravenous infusion. The maximum of cumulative number is two, and the maximum single dose does not exceed 800 mg Active comparator: favipiravir group	Not applicable	Primary (3 months): Clinical cure rate Secondary (14 days after taking medicine): Viral nucleic acid test negative conversion rate and days from positive to negative, duration of fever, lung imaging improvement time, mortality rate because of corona virus disease 2019 (3 months), rate of noninvasive or invasive mechanical ventilation when respiratory failure occurs (3 months), mean in-hospital time (3 months)	NCT04310228/ Recruiting, Mar8-May 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					On the 1st day, 1,600 mg each time, twice a day; from the 2nd to the 7th day, 600 mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 7 days Active comparator: tocilizumab group The first dose is 4–8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hr after the first dose and the interval between two medications ≥12 hr. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800 mg			
Novel coronavirus induced severe pneumonia treated by dental pulp mesenchymal stem cells	Biological: dental pulp mesenchymal stem cells	-COVID-19	24, all, 18–75	Treatment	Experimental: pulp mesenchymal stem cells 1. 3, 7 days to increase the injection of mesenchymal stem cells	Early Phase I	Primary (14 days): Disppear time of ground-glass shadow in the lungs Secondary: Absorption of lung shadow absorption by CT Scan-Chest (7, 14, 28, and 360 days), Changes of blood oxygen (3, 7, and 14 days)	NCT04302519/Not yet Recruiting, Mar5-Jul30 2020–2021
Multicenter clinical study on the efficacy and safety of Xiyanping injection in the treatment of new coronavirus infection pneumonia (general and severe)	Drug: lopinavir/ritonavir tablets combined with Xiyanping injection drug: lopinavir/ritonavir treatment	COVID-19	80, all, 18–100	Treatment	Experimental: experimental group of ordinary COVID-19: Xiyanping injection, 10–20 ml daily, Qd, the maximum daily does not exceed 500 mg (20 ml) + lopinavir tablet or ritonavir tablet + alpha-interferon nebulization, for 7–14 days, Active comparator: control group of ordinary COVID-19: Lopinavir/ritonavir tablets, two times a day, two tablets at a time; alpha-interferon nebulization	Not applicable	Primary: Clinical recovery time (up to Day 28)	NCT04295551/Not yet Recruiting, Mar14-Apr14 2020–2021

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					Experimental: experimental group of severe COVID-19: Xiyanping injection, 10–20 ml daily, Qd, the maximum daily does not exceed 500 mg (20 ml) + lopinavir tablet or ritonavir tablet + alpha-interferon nebulization, for 7–14 days			
Prognostic factors of patients with COVID-19	–	China/SARS-CoV-2 outcome, fatal	201, all, 18 years and older	Prognostic	SARS-CoV-2Outcome, fatal	–	Primary (30 days): all-cause mortality Secondary (15 days): all-cause mortality, Severe state	NCT04292964/ Completed Mar1-Mar13 2020
Chloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting	Drug: chloroquine, drug: placebo	COVID19 coronavirus acute respiratory illnesses	10,000, all, 16 years and older	Prevention	Experimental: chloroquine: a loading dose of 10 mg base/kg followed by 150 mg daily (250 mg chloroquine phosphate salt) will be taken for 3 months Placebo comparator: placebo	Not applicable	Primary (approximately 100 days): Number of symptomatic COVID-19 infections Secondary (approximately 100 days): Symptoms severity of COVID-19, duration of COVID-19, number of asymptomatic cases of COVID-19, number of symptomatic acute respiratory illnesses, genetic loci and levels of biochemical components will be correlated with frequency of COVID-19, ARI, and disease severity Other (approximately 100 days): Drug exposure-protection relationship	NCT04303507/Not yet recruiting, May-May 2020–2022
Yinhu Qingwen decoction for the treatment of mild/common CoVID-19	Drug: YinHu QingWen decoction, drug: YinHu QingWen decoction(low dose), other: Chinese medicine treatment, other: standard western medicine treatment	China/CoVID-19 Chinese medicine	300, all, 18 years and older	Treatment	Experimental: Yin Hu Qing Wen decoction group Based on the standard western medicine treatment, the patients will be given Yinhu Qingwen decoction (granula) for 10 days. Drug: YinHu QingWen decoction YinHu QingWen decoction (granula) consits of 11 Chinese herbal medicine as honeysuckle, *Polygonum cuspidatum*, Schizonepeta, Longspur epimedium, and so forth. The decoction granula will be dissolved into 600 ml	II III	Primary (up to 28 days): Mean clinical recovery time Secondary (up to 28 days): Time to CoVID-19 RT-PCR negative in upper respiratory tract specimen, change (reduction) in CoVID-19 viral load in upper respiratory tract specimen as assessed by area under viral load curve, time to defervescence (in those with fever at enrollment), time to cough reported as mild or absent (in those with cough at enrollment rated severe or moderate), time to dyspnea reported as mild or absent (on a scale of severe, moderate, mild	NCT04278963/ Active, Not Recruiting, Feb27-Jan 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					decoction and divided to three times (once with 200 ml). It will be given a 200 ml per time, three times a day, for 10 days Other: standard western medicine treatment treatment is according to the protocol of treatment of CoVID-19 infection according to guideline appoved by National Health Commission of China Placebo comparator: Yinhu Qingwen decoction low-dose group Based on the standard western medicine treatment, the patients will be given 10% dose of Yinhu Qingwen decoction (granula) for 10 days Drug: YinHu QingWen decoction (low dose) this intervention is given as 10% dose of YinHu QingWen decoction (granula). The granula will be dissolved into 600 ml decoction and divided to three times (once with 200 ml). It will be given a 200 ml per time, three times a day, for 10 days Other: standard western medicine treatment standard western medicine treatment is according to the protocol of treatment of CoVID-19 infection according to guideline appoved by National Health Commission of China Active comparator: integrated Chinese and western medicine group Based on the standard western medicine treatment, the patients will be given Chinese medicine decotion granula according to their symptoms. The daily dose of Chinese medicine decoction granula will		absent, in those with dyspnea at enrollment rated as severe or moderate) Frequency of requirement for supplemental oxygen or noninvasive ventilation, frequency of respiratory progression, severe case incidence, proportion of rehospitalization or admission to ICU, all-cause mortality, frequency of serious adverse events	

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					also be dissolved to 600 ml decoction and divided into three times (once with 200 ml). The Chinese medicine decoction will be given 200 ml per time, three times a day for 10 days Other: Chinese medicine treatment This intervention will be given with Chinese medicine decoction granula based on the symptoms differentiation of the patients for 10 days Other: standard western medicine treatment Standard western medicine treatment is according to the protocol of treatment of CoVID-19 infection according to guideline appoved by National Health Commission of China			
Prognositc factors in COVID-19 patients complicated with hypertension	–	China, COVID-19	0, all, 18–100	Prognostic	ACEI treatment hypertension patients with ACEI treatment when suffered with novel coronavirus infection in China Control hypertension patients without ACEI treatment when suffered with novel coronavirus infection in China	–	Primary (up to 28 days): Occupancy rate in the intensive care unit, mechanical ventilation, death Secondary (up to 28 days): All cause mortality, time from onset of symptoms to main outcome and its components, time to clinical recovery	NCT04272710/ Withdrawn, Jan25-Apr30 2020
Evaluating the efficacy and safety of bromhexine hydrochloride tablets combined with standard treatment/standard treatment in patients with suspected and mild novel coronavirus pneumonia (COVID-19)	Drug: bromhexine hydrochloride tablets, drug: arbidol hydrochloride granules, drug: recombinant human interferon α2b spray, drug: favipiravir tablets	China, novel coronavirus pneumonia 2019-nCoV	60, all, 18–80	Treatment	Experimental: group A treatment group: Bromhexine hydrochloride tablets, arbidol hydrochloride granules: Standard treatment refers to the latest edition of pneumonia diagnosis and treatment scheme for novel coronavirus infection. Arbidol hydrochloride granules is recommended but not enforced to use Recombinant human interferon α2b spray:	Not applicable	Primary (within 14 days from the start of medication): Time to clinical recovery after treatment Secondary (within 14 days from the start of medication): Rate of aggravation, clinical remission rate, dynamic changes of oxygenation index, time to cure, rate to cure, time to defervescence, time to cough remission,days of supplemental oxygenation, rate of patients with requring supplemental oxygen, rate of patients with mechanical ventilation, time of	NCT04273763/ Enrolling by invitation, Feb16-Apr30 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					Standard treatment refers to the latest edition of pneumonia diagnosis and treatment scheme for novel coronavirus infection Favipiravir tablets Active comparator; group B control group: Drug: arbidol hydrochloride granules Standard treatment refers to the latest edition of pneumonia diagnosis and treatment scheme for novel coronavirus infection. arbidol hydrochloride granules is recommended but not enforced to use Drug: recombinant human interferon α2b spray Standard treatment refers to the latest edition of pneumonia diagnosis and treatment scheme for novel coronavirus infection		negative COVID-19 nucleic acid results, rate of negative COVID-19 nucleic acid results, rate of ICU admission, 28-day mortality (From the first day of screening to the day of follow-up (28 days))	
Various combination of protease inhibitors, oseltamivir, favipiravir, and chloroquin for treatment of covid19: a randomized control trial	Drug: oral	Thailand, coronavirus infections COVID19	80, all, 16–100	Treatment	Experimental: oseltamivir plus chloroquin in mild COVID19 Oseltamivir 300 mg per day plus chloroquin 1,000 mg per Day In mild COVID19 Experimental: lopinavir and ritonavir plus favipiravir Lopinavir 10 mg/kg and ritonavir 2.5 mg/kg plus favipiravir 2,400 mg, 2,400 mg, and 1,200 mg every 8 hr on Day 1, and a maintenance dose of 1,200 mg twice a day in Mild COVID19 Experimental: lopinavir and ritonavir plus oseltamivir in mild COVID19 Lopipinavir 10 mg/kg and ritonavir 2.5 mg/kg plus oseltamivir 4–6 mg/kg In mild COVID19	III	Primary (Up to 24 weeks): SARS-CoV-2 eradication time Secondary (up to 24 weeks): Number of patient with death, number of patient with recovery adjusted by initial severity in each arm, number of day with ventilator dependent adjusted by initial severity in each arm,number of patient developed acute respiratory distress syndrome after treatment Other (up to 24 weeks): Number of patient with acute respiratory distress syndrome recovery	NCT04303299/Not yet recruiting, Mar15-Nov30 2020

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					Experimental: lopinavir and ritonavir oseltamivir moderate to severe COVID19 Lopipinavir 10 mg/kg and ritonavir 2.5 mg/kg plus oseltamivir 4–6 mg/kg in moderate to critically ill COVID19 Experimental: favipiravir lopinavir/ritonavir for mod. To severe favipiravir 2,400 mg, 2,400 mg, and 1,200 mg every 8 hr on Day 1, and a maintenance dose of 1,200 mg twice a day plus lopipinavir 10 mg/kg and ritonavir 2.5 mg/kg in moderate to critically ill COVID19 Experimental: darunavir/ritonavir oseltamivir chloroquine mod-severe Combination of Darunavir 400 mg every 8 hr ritonavir Ritonavir 2.5 mg/kg plus Oseltamivir 4–6 mg/kg plus Chloroquine 500 mg per Day In moderate to critically ill COVID19 Experimental: darunavir/ritonavir favipiravir chloroquine mod-severe Favipiravir 2,400 mg, 2,400 mg, and 1,200 mg every 8 hr on Day 1, and a maintenance dose of 1,200 mg twice a day plus darunavir 400 mg every 8 hr ritonavir ritonavir 2.5 mg/kg plus chloroquine 500 mg per Day In moderate to critically ill COVID19 No intervention: conventional qurantine Patient who unwilling to treatment and willing to quarantine in mild COVID19			

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
Yinhu Qingwen Granula for the treatment of severe CoVID-19	Drug: Yinhu Qingwen granula, drug: Yin Hu Qing Wen granula (low does), other: standard medical treatment	China, COVID-19 severe pneumonia Chinese medicine	116, all, 18 years and older	Treatment	Experimental: Yinhu Qingwen granula group: Drug: Yinhu Qingwen Granula Yinhu Qingwen granula is a kind of herbal granula made from "Yinhu Qingwen Decoction," which consits of 11 Chinese herbal medicine as honeysuckle, *Polygonum cuspidatum*, schizonepeta, *Longspur epimedium*, etc. The granula will be dissolved into 600 ml decoction and divided to three times (once with 200 ml). It will be given a 200 ml per time, three times a day, for 10 days. Other: standard medical treatment Standard medical treatment is adhered to the protocol of the treatment for the severe CoVID-19 according to the guideline approved by National Health Commission of China. Placebo comparator: Yinhu Qingwen granula low-dose group: Drug: Yin Hu Qing Wen granula (low does). This intervention is given as 10% dose of YinHu QingWen Granula.The granula will be dissolved into 600 ml decoction and divided to three times (once with 200 ml). Other: standard medical treatment Standard medical treatment is adhered to the protocol of the treatment for the severe CoVID-19 according to the guideline approved by National Health Commission of China.	II	Primary (Day 10): changes in the ratio of PaO2 to FiO2 from baseline Secondary (up to 30 days): PaO2, blood oxygen saturation (SpO2), clinical status rating on the 7-point ordinal scale, time to clinical improvement, duration (hours) of noninvasive mechanical ventilation or high-flow nasal catheter oxygen inhalation use, duration (hours) of invasive mechanical ventilation use, duration (hours) of extracorporeal membrane oxygenation (ECMO) use, duration (days) of oxygen use, The proportion of the patients reporting 2019-nCoV RT-PCR negativity at Day 10 after treatment, the counts/percentage of lymphocyte, time to hospital discharge with clinical recovery from the randomization, the incidence of critical status conversion in 30 days, all-cause mortality within 30 days, frequency of severe adverse drug events	NCT04310865/Not yet recruiting, Mar20-Jun30 2020–2021
Clinical characteristics and long-term prognosis of 2019-nCoV infection in children	–	China, 2019-nCoV	500, all, up to 18 years	Prognosis	2019-nCoV infection group Children hospitalized with direct laboratory confirmed of novel coronavirus with or without	–	Primary (6 months): The cure rate of 2019-nCoV, the improvement rate of 2019-nCoV, the incidence of long-term adverse outcomes	NCT04270383/Not yet recruiting, Feb15-Dec30 2020

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
					pneumonia are classified as the 2019-nCoV infection group Control group Children hospitalized with pneumonia other than the novel coronavirus pneumonia during the same hospitalization period as 2019-nCoV infection group are classified as the control group		Secondary (2 weeks): Duration of fever, duration of respiratory symptoms, duration of hospitalization, number of participant(s) need intensive care, number of participant(s) with acute respiratory distress syndrome, number of participant(s) with extra-pulmonary complications, including shock, renal failure, multiple organ failure, hemophagocytosis syndrome, et al., number of participant(s) who died during the trial (10 months)	
The effect of T89 on improving oxygen saturation and clinical symptoms in patients with COVID-19	Drug: T89	Coronavirus disease 2019 novel coronavirus pneumonia	120, all, 18–85	Treatment	Experimental: The T89 treatment group Besides a standard background treatment (antiviral drug + antibacterial + oxygen therapy + Traditional Chinese Medicine decoction), all subjects in the T89 treatment group will receive 30 pills of T89 each time, orally, BID (every morning and evening), for 10 days (depending on clinical need and practicability, the use can be extended for up to 14 days) No intervention: the blank control group All subjects in the blank control group will only receive a standard background treatment (antiviral drug + antibacterial + oxygen therapy + Traditional Chinese Medicine decoction), for 10 days.	Not applicable	Primary (Day −1 to 10): the time to oxygen saturation recovery to normal level (≥97%), the proportion of patients with normal level of oxygen saturation(≥97%) Secondary (Day −1 to 10): The degree of remission of symptoms of patients, including: fatigue, nausea, vomiting, chest tightness, shortness of breath, and so forth, the time to the myocardial enzyme spectrum recovery to normal after treatment, the proportion of the patients with normal myocardial enzyme spectrum after treatment, the time to the electrocardiogram recovery to normal level after treatment, the proportion of the patients with normal electrocardiogram after treatment, the time to the hemodynamics recovery to normal after treatment, the proportion of the patients with normal hemodynamics after treatment, the time to exacerbation or remission of the disease after treatment, the proportion of the patients with exacerbation or remission of disease after treatment, the proportion of patients who need other treatment (e.g., heparin, anticoagulants) due to microcirculation disorders, the all-	NCT04285190/Not yet recruiting, Feb26-Sep15 2020

(Continues)

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms	Phase	Measure outcome/time frame	Code/status/date
							cause mortality rate, the proportion of patients with acidosis, the total duration of the patients in-hospital, the total duration of oxygen inhalation during treatment, the oxygen flow rate during treatment, the oxygen concentration during treatment	
Immunoregulatory therapy for 2019-nCoV	Drug: PD-1 blocking antibody + standard treatment, drug: Thymosin + standard treatment, other: standard treatment	-2019 nCoV, PD-1	120, all, 18 years and older	Treatment	Experimental: PD-1 group Anti-PD-1 antibody, 200 mg, IV, one time Experimental: thymosin group Thymosin, 1.6 mg sc qd, last for 5 days Placebo comparator: control group stand treatment	II	Primary (7 days): lung injury score Secondary: Absolute lymphocyte counts (7, 14 and 28 days), serum level of CRP, PCT and IL-6 (3, 7 and 14 days), SOFA score (7 days), all cause mortality rate (28 days), ventilation free days (28 days), ICU free days (up to 28 days)	NCT04268537/Not yet recruiting, Feb10-Oct31 2020
Tocilizumab vs CRRT in management of cytokine release syndrome (CRS) in COVID-19	Drug: tocilizumab, other: standard of care, procedure: continuous renal replacement therapy	China, Covid-19 SARS cytokine storm (and 2 more…)	120, all, 18–80	Observational	Tocilizumab Subjects received 8 mg/kg (body weight) Tocilizumab once in 100 ml 0.9% saline solution and administered intravenously within no <60 min. Tocilizumab was administered according—continuous renal replacement therapy Femoral vein catheterization was performed to complete continuous renal replacement therapy for consecutive three times or more. to the local label Standard care Standard of care therapy per local written policies or guidelines	–	Primary (up to 14 days): Proportion of participants with normalization of fever and oxygen saturation Secondary: Duration of hospitalization (Up to 28 days), proportion of participants with normalization of fever (up to 14 days), change from baseline in white blood cell and differential count (up to 28 days), time to first negative in 2019 novel corona virus RT-PCR test (Up to 28 days), all-cause mortality (up to 12 weeks), change from baseline in hsCRP (Up to 28 days), change from baseline in cytokines IL-1β, IL-10, sIL-2R, IL-6, IL-8 and TNF-α (Up to 28 days), change from baseline in proportion of CD4 + CD3/CD8 + CD3 T cells (Up to 28 days)	NCT04306705/ Recruiting, Feb20-Jun20 2020
Sars-CoV2 seroconversion among front line medical and paramedical staff in emergency, intensive care units and infectious disease departments during the 2020 Epidemic	Other: blood sample	France, Sars-CoV2	1,000, all, child, adult, older adult	Other	Caregiver caregivers from emergency, ICU, virology and infectious disease services: Two blood samples at T0 and 3 months	Not applicable	Primary (3 months): Quantify the proportion of patients with documented Sars-CoV2 infection among medical and paramedical staff Secondary (3 months):	NCT04304690/ Recruiting, Mar16-Oct16 2020

TABLE 4 (Continued)

Study title	Interventions	Location/condition	Subjects, sex, age	Primary purpose	Arms		Phase	Measure outcome/time frame	Code/status/date
								Identification of risk factors for seroconversion, quantify the proportion of asymptomatic infections among staff who have seroconverted, describe symptomatic infections for personnel developing acute clinical (respiratory or digestive) viral syndrome	

erythematosus. Recently, an investigation in China reported that remdesivir and chloroquine phosphate were effective experimental agents for controlling SARS-CoV-2 infection in the lab (Chen et al., 2013). Initial findings reported by a recent study on effectiveness of therapeutic agents in management of SARS-CoV-2 infection, and suggested successful application of chloroquine phosphate in treatment of patients with COVID-19-associated pneumonia. Following the promising results, scientists recommended chloroquine phosphate to be included in treatment regimen of COVID-19 patients with severe involvement of the lungs (Yu et al., 2013). On February 15, 2020, participants from different organizations, including medical experts and authorities, made an agreement on potency of Chloroquine phosphate against SARS-CoV-2 infection (https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/).

So far, close monitoring of over 100 patients, who were under treatment of chloroquine phosphate, has provided further evidence regarding the effectiveness of this long-known medicine. Investigations indicated that chloroquine phosphate prevented exacerbation of pneumonia in these patients, improved their chest CT findings, and shortened the otherwise long natural course of the disease. Importantly, there have been no records of severe reaction or hypersensitivity to this therapeutic agent. It has been suggested that the broad-spectrum antiviral activity of chloroquine phosphate lies within the complicated pharmacodynamics of the drug that results in a basic shift in the endosomal pH required for successful fusion of virus onto the host cell. chloroquine phosphate also seems to have disruptive effects on glycosylation of cellular receptors of SARS-CoV (Yin & Wunderink, 2018; Zumla et al., 2020), rendering them nonfunctional. It also interferes with activation of p38 mitogen-activated protein kinase, a signaling event involved in replication of HCoV-229E (Kono et al., 2008).

7.2 | Lopinavir/ritonavir, leronlimab, galidesivir

Lopinavir/Ritonavir, commonly used for treatment of HIV infection, has been indicated for treatment of COVID-19 in a number of reports (Kim et al., 2020). Previous studies suggested that when combined together, Lopinavir and Ritonavir act in concert to hinder further replication of SARS-CoV, and improve the clinical status of patients with SARS (Chu et al., 2004). This might also mean that the well-known antiretroviral duo can also prove beneficial in treatment of COVID-19.

Other candidates for possible management of SARS-CoV-2 include Leronlimab and Galidesivir, both of which have been of clinical value in treatment of several fatal viral infections, and were shown to improve the survival of patients. Leronlimab is a humanized monoclonal antibody (CCR5 antagonist). Galidesivir, on the other hand, belongs to the family of nucleoside RNA polymerase inhibitors (https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/). In the absence of any specific therapeutic agents to quell SARs-CoV-2, it might be a salutary strategy to repurpose the already

TABLE 5 Therapeutic options that are available for the treatment of novel coronaviruses (cell line, animal, and human studies)

General treatment	Nutritional interventions, targets or function	Vit A	Measles virus, measles-related pneumonia, HIV, avian CoV, IBV		Upregulating the elements of the innate immune, Making the cells refractory to infection
		B vit	MERS-CoV		Enhancing immune system, Inhibiting the of neutrophil infiltration into the lungs, Anti-inflammatory effects during ventilator-induced lung injury
		Vit C	Avian CoV		Supporting immune functions, protecting against CoV infection, preventing of the lower respiratory tract infections
		Vit D	Bovine CoV		Triggering the maturation of immune cells
		Vit E	Coxsackievirus, bovine CoV		Antioxidant function
		Omega-3 PUFA	Influenza virus, HIV		Attenuating the replication of influenza virus
		Selenium	Influenza virus, avian CoV		Antioxidant function, inducing immune response
		Zinc	Influenza virus, avian CoV, SARS-CoV		Maintenance/development of innate and adaptive immune systems simultaneously
		Iron	Viral mutations		Enhancing the immune system
	Immunoenhancers	IFNs	SARS-CoV, MERS-CoV		Acting as apart of the innate immune response, Inhibiting the replication of CoVs in animal and human
		IVIg	SARS-CoV		Increasing the viscosity in hypercoagulable states
		Ta1	SARS-CoV		Restoring the homeostasis of the immune system, Increasint the resistance glucocorticoid-induced death of thymocyte
		TP5, munox	Restore antibody production		Restoring antibody production, Enhancing the antibody response, As adjuvant treatment
		Levamisole	Immunostimulant/ immunosuppressive agent		Increasing the functions of cellular immunity, Act as immunostimulant agent or immunosuppressive agent through dose- and time-dependent manner, reversing the depressed helper/inducer lymphocytes
		Cyclosporine A	SARS-CoV, avian infectious bronchitis virus		Both facilitating or inhibiting virus replication, blocking the all genera replication of CoV
		CTM	Glycyrrhizin, Baicalin, Ginseng	SARS-CoV, avian infectious bronchitis virus	Enhancing host immunity, Inhibiting the replication of SARS-associated virus and SARS-CoV, Enhancing the specific-antibody responses
Specific treatments	Protease inhibitors	3C-like inhibitors	Cinanserin,	SARS-CoV	Act as serotonin receptor antagonist, Inhibiting the replication
			Flavonoids	MERS-CoV	Act as antioxidant and antiviral compound, blocking the enzymatic activity of MERS-CoV/3CLpro
		PLP inhibitors	SARS-CoV	Inhibit PLP of SARS-CoV	
	S protein-ACE2 blockers	Human mAb	SARS-CoV		Neutralizing SARS-CoV, inhibiting syncytia formation between cells expressing the S protein and the SARS-CoV receptor ACE2
		Chloroquine	SARS-CoV		Possess antiviral effect, inhibiting of SARS-CoV infection via interfering with ACE2
		Emodin	SARS-CoV		Blocking the interaction between the S protein of virus and ACE2
		Promazine	SARS-CoV		Inhibiting the replication of virus, inhibiting the binding of S protein to ACE2
		Nicotianamine			Inhibiting the ACE2

Antiviral treatments	Ribavirin	SARS-CoV	Inhibiting the the replication of SARS-associated CoV
	LPV/RTV (Kaletra)	HIV, SARS-CoV, MERS-CoV	protease inhibitor
	RDV	SARS-CoV, MERS-CoV	Improving the pulmonary function, reducing the lung viral loads and severe lung pathology
	Nelfinavir	HIV, SARS-CoV	Act as selective inhibitor of HIV protease, Inhibiting the replication virus
	ARB	influenza A/B, hepatitis C virus	Blocking viral fusion, entry and replication
	Nitric oxide	SARS	Antiviral effects
Other compounds	ALA	human CoV-229E, HIV	Act as antioxidant, inhibiting the replication of HIV-1
	Estradiol and phytoestrogen	SARS-CoV, MERS, influenza A	Reducing virus replication in primary human nasal epithelial cells
	Mucroporin-M1	influenza H5N1 viruses, and SARS-CoV	Virucidal activity against viruses

Abbreviations: 3 CLpro, 3C-like protease; Ab, antibody; ACE2, angiotensin converting enzyme 2; ALA, α-lipoic acid; ARB, arbidol; CoV, coronavirus; CTM, Chinese traditional medicine; HIV, human immunodeficiency virus; IBV, bronchitis virus; IFN, interferons; IVIg, intravenous gammaglobulin; LPV/RTV, lopinavir/ritonavir; mAb, monoclonal antibody; PLpro, papain-like protease; PUFA, polyunsaturated fatty acids; RDV, remdesivir; S, spike; Ta1, thymosin α-1; TP5, thymopentin; Vit, vitamin.

available medicine, and include them in treatment of COVID-19 (Tian et al., 2020).

Several clinical trials can be viewed at ClinicalTrials.gov, that are currently in progress. These trials have specially focused on potency of Remdesivir, immunoglobulins, and combinational therapies, for example, Arbidol hydrochloride with interferon atomization, ASC09F and oseltamivir, ritonavir and oseltamivir, and lopinavir combined with ritonavir (https://clinicaltrials.gov/ct2/results?cond=&2019nCoV&term=&cntry=&state=&city=&dist=).

7.3 | RAAS inhibitors

ACE2 is a prominent regulatory arm in the RAAS axis, thus, a disruption in ACE-Angiotensin II-Angiotensin Type 1 Receptor (AT1R), and ACE2/Angiotensin-(1-7)/Mas Receptor axes can result in multisystem inflammation. Increased levels of ACE and Angiotensin II in plasma are considered poor prognostic factors in severe pneumonia. Several studies on animal models have reported effectiveness of RAAS inhibitors in alleviation of severe pneumonia and acute respiratory failure. In the aftermath of SARS-CoV-2 and ACE2 binding, the enzyme is eventually degraded, hence, the inhibition of ACE2/Angiotensin-(1-7)/Mas Receptor pathway. Accordingly, it is assumed that ACE and AT1R inhibitors might be game-changing agents that can especially be administered for COVID-19 patients who have serious impairments in their homeostasis. Maintenance of homeostasis may ultimately result in suppression of the inflammatory response, mostly in the pulmonary tissue (Sun, Yang, Sun, & Su, 2020).

7.4 | Combination therapy

Combination therapy is a more extensive and rigorous approach mainly aimed at correction of life-threatening events such as shock, hypoxemia, secondary or super infection, and maintenance of homeostasis, that is, electrolyte, acid and base balance. As a palliative practice, antiviral treatment in the early stages of COVID-19 might lessen the severity and prevent further progression of the disease. Trials on combination therapy with lopinavir/ritonavir and arbidol (umifenovir) have reported satisfactory results in treatment of COVID-19. Alongside a proper antiviral treatment, patients may also benefit from an artificial liver blood purification system, which is capable of rapidly removing the inflammatory factors from blood, thus, halting the disastrous cytokine release syndrome. This system can also facilitate the sustenance of critically ill patients by preserving the balance of bodily fluid. Administration of glucocorticoids in moderate doses is another intervention that has recently been indicated for patients with severe COVID-19-associated pneumonia. However, secondary fungal infection should be considered. Patients with an oxygenation index of less than 200 mmHg might benefit more from oxygen therapy than noninvasive ventilation. A rational prescription of antimicrobial medicines has been cautioned only for patients with remittent fever and elevated antimicrobial prophylaxis

should be prescribed rationally and was not recommended except for patients with long course of disease, repeated fever, and elevated PCT levels. Ultimately, to maintain the balance of intestinal microbiota, oral intake of prebiotics or probiotics has been suggested. This can reduce the risk of secondary infections as a result of microbial translocation; however, effectiveness of such interventions on post-infection clearance pattern of SARS-CoV-2 has not been studied (Xu et al., 2020).

7.5 | Other future possible options

7.5.1 | Convalescent blood therapy

A conspicuously conventional method, transfusion of human convalescent plasma, might be viewed as a beneficial strategy for prevention and even treatment of COVID-19. The method is as facile as its age since it only requires an adequate number of recovered patients who are willing to donate their immunoglobulin-containing serum. Although one still might argue the possibility of SARS-CoV-2 infection via convalescent blood transfusion, no such incident with SARS-CoV was reported by WHO amidst the outbreak of the disease in 2003. The heft of past experience should come to mind once it is noted that the majority of approaches and therapeutic strategies that are currently being tested for COVID-19 are derived from clinical experience in treatment of SARS, MERS, and other correspondents viral epidemics (Casadevall & Pirofski, 2020; Cunningham, Goh, & Koh, 2020).

7.5.2 | Mesenchymal stem cell (MSC) therapy

A new therapeutic for treating immune-mediated diseases, MSC therapy might have the capability to terminate the inappropriate release of cytokines in COVID-19. Through its anti-inflammatory effects, MSC therapy has been reported to improve respiratory function in murine models with acute lung injury. Evidence suggests that MSCs might be doing so by repressing the aberrant release of inflammatory factors (Hu & Li, 2018; Wang, Yao, Lv, Ling, & Li, 2017; Xiang et al., 2017). In particular, a study by Chinese scientists concluded that transplantation of MSCs could be considered as a novel approach in treatment of viral pneumonia, noting promissory implications of this method in management of H7N9-induced ARDS. Since H7N9 and SARS-CoV-2 can result in similar complications, for example, ARDS and respiratory failure, MSC-based therapy might lead to a new path in treatment of COVID-19-associated pneumonia (Chen, Hu, et al., 2020).

7.5.3 | Nano drug delivery systems

It has long been known that the traditional circulation-based delivery of therapeutic agents is not as effect, prompting pharmaceutical industries to develop novel platforms for delivery of molecules to hard-to-reach tissues in human body. Conjugation of antiviral agents, particularly nucleoside analogs, with specific nanoparticles has proved to be effectual in treatment of resistant HIV infection (Agarwal, Chhikara, Doncel, & Parang, 2017; Agarwal, Chhikara, Quiterio, Doncel, & Parang, 2012). Today, an appreciable number of drug delivery platforms based on nanotechnology are available that can be experimentally used with custom therapeutic formulations for treatment of COVID-19 (Chhikara & Varma, 2019) in hopes of shortening the course of the disease (Chhikara et al., 2020).

7.5.4 | Psychological interventions

Progression of COVID-19, similar to any other disease, can result in suffering of the patients, prompting psychological symptoms, which will require special interventions. It has been well-established today that individuals who fall victim to public health emergencies, for example, disease outbreaks, develop variable degrees of stress disorders. The problem persists even after the individual has recovered and discharged from the hospital (Cheng, Wong, Tsang, & Wong, 2004; Fan, Long, Zhou, Zheng, & Liu, 2015). With that in mind, one should consider several factors for classification of patients who will most probably benefit from psychological interventions; that is overall course of the disease, severity, and quality of hospitalization (e.g., home, ordinary wards, ICU, etc.) (Duan & Zhu, 2020).

In large-scale outbreaks such as COVID-19 epidemic, healthcare workers become the frontline at providing psychological cares for patients who battle against the disease. Primary medical and mental care should be provided for those individuals who are recognized as "suspected case" and duly quarantined at home. (Duan & Zhu, 2020).

Interventions should be discreetly formulated following a thorough evaluation of risk factors involved in emerging of these psychological issues, including a history of impaired mental health, bereavement after a deceased family member, panic, separation from loved ones, and a low income (Kun, Han, Chen, Yao, & Anxiety, 2009).

8 | PATIENTS RECOVERED FROM COVID-19

The following criteria must be met in order for a patient to be discharged from hospital or released from quarantine: (a) having been afebrile for at least 3 consecutive days, (b) remission of respiratory distress, (c) regression of infiltrations/consolidations on chest CT images, and two consecutive negative reports of RT-PCR test performed at least 1 day apart (d). Despite these thoroughly formulated criteria, one study reported positive RT-PCR test results 5–13 days after hospital discharge for four patients with COVID-19, who met all of the criteria above before they were discharged. These findings are important in that they imply the slight possibility that even a fully recovered patient might still be a silent carrier of the virus. In this

scenario, however, no family members were reported to be infected, since all of the four patients with bizarrely late positive tests were medical professional, and followed all of the guidelines while they were at home quarantine. With due attention to this incident, the current criteria for hospital discharge may need to be reconsidered (Lan et al., 2020).

9 | CONCLUSIONS AND FUTURE PERSPECTIVES

Deemed a global health emergency, COVID-19 outbreak has continued to be the headline of the news. The number of confirmed cases is on the rise, and the seamless spread of the virus has become a plight for general population, and the entire medical community. In spite of the extreme preventive measures while near a patient, clinicians are still at great risk for contracting the disease from the visitors. Else, it is vividly known that quarantine alone is not the optimal choice for containing of the virus. On the other hand, the devastating potential impact of the outbreak is a much feared topic around the world. Science has always been the ultimate arsenal of weaponry when it comes to battling obstinate pathogens; however, time is needed for conduction of proper investigations on human-to-human and animal-to-human transmission of SARS-CoV-2.

With no access to requisite information on the structure and life cycle of the novel Coronavirus, research and development programs on therapeutic agents become a far-fetched milestone, rendering the tried-and-true primary prevention measures the only proper means to confront SARS-CoV-2. As of today, few existing drugs have been considered for treatment of COVID-19, with scant reports on benevolence of the results. As our meager knowledge of SARS-CoV-2 is advancing, one may speculate the advent of an effectual vaccine, alongside treatment options that might include antiviral agents, and even monoclonal antibodies. At the time of writing this manuscript, no definitive treatment option has been known for COVID-19; however, the unabating flow of investigations and clinical trials may soon lead us to the optimal therapy for COVID-19-associated pneumonia.

Needless to say, the fascinatingly high transmissibility of COVID-19 demands meticulous monitoring of the transmission routes and patterns to a reach a firm theory on adaptive mechanisms wielded by SARs-CoV-2, thus, making an accurate prediction about the future outcomes regarding pathogenicity, transmissibility, and evolution of the virus. These efforts will hopefully result in better prognosis and fewer mortalities.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to different parts of the study.

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