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Review Article

REVIEW ON COVID 19: ORIGIN, TRANSMISSION, CASES AND TREATMENTS OF HUMAN CORONA VIRUSES

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ABSTRACT

The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China and spread around the world. Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses, therefore bats could be the possible primary reservoir. The intermediate source of origin and transfer to humans is not known, however, the rapid human to human transfer has been confirmed widely. There is no clinically approved antiviral drug or vaccine available to be used against COVID-19. However, few broad-spectrum antiviral drugs have been evaluated against COVID-19 in clinical trials, resulted in clinical recovery. In the current review, we summarize and comparatively analyze the emergence and pathogenicity of COVID-19 infection and previous human coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV). We also discuss the approaches for developing effective vaccines and therapeutic combinations to cope with this viral outbreak.

KEY WORDS: Corona virus, Covid 19, spreading, Symptoms, cases, treatments.

INTRODUCTION

The pneumonia caused by the 2019 novel coronavirus (SARS-CoV-2) is a highly infectious disease, the etiological agent of the (Corona Virus Disease 2019) COVID-19, emerged Wuhan, Hubei Province, China in December 2019. (1) On 11th March 2020, The World Health Organization (WHO) declared this disease as pandemic. It is reported that the person-to-person transmission in hospital and family settings has been accumulating 2-4. The patients' common clinical manifestations included fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia. (1,2) Chen et al reported that mortality of COVID-19 was 4.3%, and severe cases (treated in the ICU) were older, more likely to have underlying comorbidities, dyspnea and anorexia. Chinese Centre for Disease Control and Prevention showed an increased mortality in people with diabetes (2.3% vs. 7.3%; overall vs. in patients with diabetes respectively (3) People with diabetes and COVID-19 may need special attention and clinical care. As of February 13, 2020, a total of 55748 cases of COVID-19 in China have been confirmed and 1380 patients have died from the disease. (3) However, the clinical characteristics of the dyed patients were still not clearly clarified. In this study, we summarized the clinical characteristics of 25 death cases with COVID-19, the purpose is to identify critically ill patients of COVID-19 early and reduce their mortality. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus. Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus. The severe acute respiratory syndrome coronavirus (SARS-CoV), H5N1 influenza A, H1N1 2009 and Middle East respiratory syndrome coronavirus (MERS-CoV) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. (4,5)

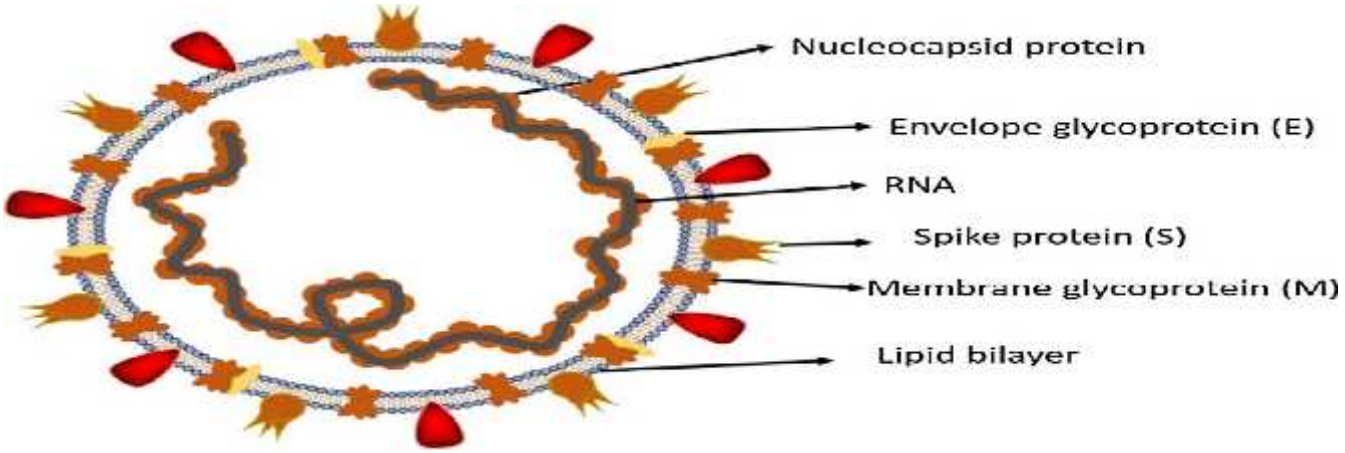


Fig. 1. Structure of respiratory syndrome causing human coronavirus.

The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19 [3], [4], [5]. In the history, SRAS-CoV (2003) infected 8098 individuals with mortality rate of 9%, across 26 contries in the world, on the other hand, novel corona virus (2019) infected 120,000 induviduals with mortality rate of 2.9%, across 109 countries, till date of this writing. It shows that the transmission rate of SARS-CoV-2 is higher than SRAS-CoV and the reason could be genetic recombination event at S protein in the RBD region of SARS-CoV-2 may have enhanced its transmission ability. In this review article, we discuss the origination of human coronaviruses briefly. We further discuss the associated infectiousness and biological features of SARS and MERS with a special focus on COVID-19. (2,3)

- **Comparative analysis of emergence and spreading of coronaviruses:**

In 2003, the Chinese population was infected with a virus causing Severe Acute Respiratory Syndrome (SARS) in Guangdong province. The virus was confirmed as a member of the Beta-coronavirus subgroup and was named SARS-CoV [6], [7].

The infected patients exhibited pneumonia symptoms with a diffused alveolar injury which lead to acute respiratory distress syndrome (ARDS). SARS initially emerged in Guangdong, China and then spread rapidly around the globe with more than 8000 infected persons and 776 deceases.

A decade later in 2012, a couple of Saudi Arabian nationals were diagnosed to be infected with another coronavirus. The detected virus was confirmed as a member of coronaviruses and named as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

The World health organization reported that MERS-coronavirus infected more than 2428 individuals and 838 deaths [8].

MERS-CoV is a member beta-coronavirus subgroup and phylogenetically diverse from other human-CoV. The infection of MERS-CoV initiates from a mild upper respiratory injury while progression leads to severe respiratory disease. Similar to SARS-coronavirus, patients infected with MERS-coronavirus suffer pneumonia, followed by ARDS and renal failure [9].

Recently, by the end of 2019, WHO was informed by the Chinese government about several cases of pneumonia with unfamiliar etiology. The outbreak was initiated from the Hunan seafood market in Wuhan city of China and rapidly infected more than 50 peoples. The live animals are frequently sold at the Hunan seafood market such as bats, frogs, snakes, birds, marmots and rabbits [10].

On 12 January 2020, the National Health Commission of China released further details about the epidemic, suggested viral pneumonia [10]. From the sequence-based analysis of isolates from the patients, the virus was identified as a novel coronavirus. Moreover, the genetic sequence was also provided for the diagnosis of viral infection.

Initially, it was suggested that the patients infected with Wuhan coronavirus induced pneumonia in China may have visited the seafood market where live animals were sold or may have used infected animals or birds as a source of food. However, further investigations revealed that some individuals contracted the infection even with no record of visiting the seafood market.

These observations indicated a human to the human spreading capability of this virus, which was subsequently reported in more than 100 countries in the world. The human to the human spreading of the virus occurs due to close contact with an infected person, exposed to coughing, sneezing, respiratory droplets or aerosols. These aerosols can penetrate the human body (lungs) via inhalation through the nose or mouth [11], [12], [13],

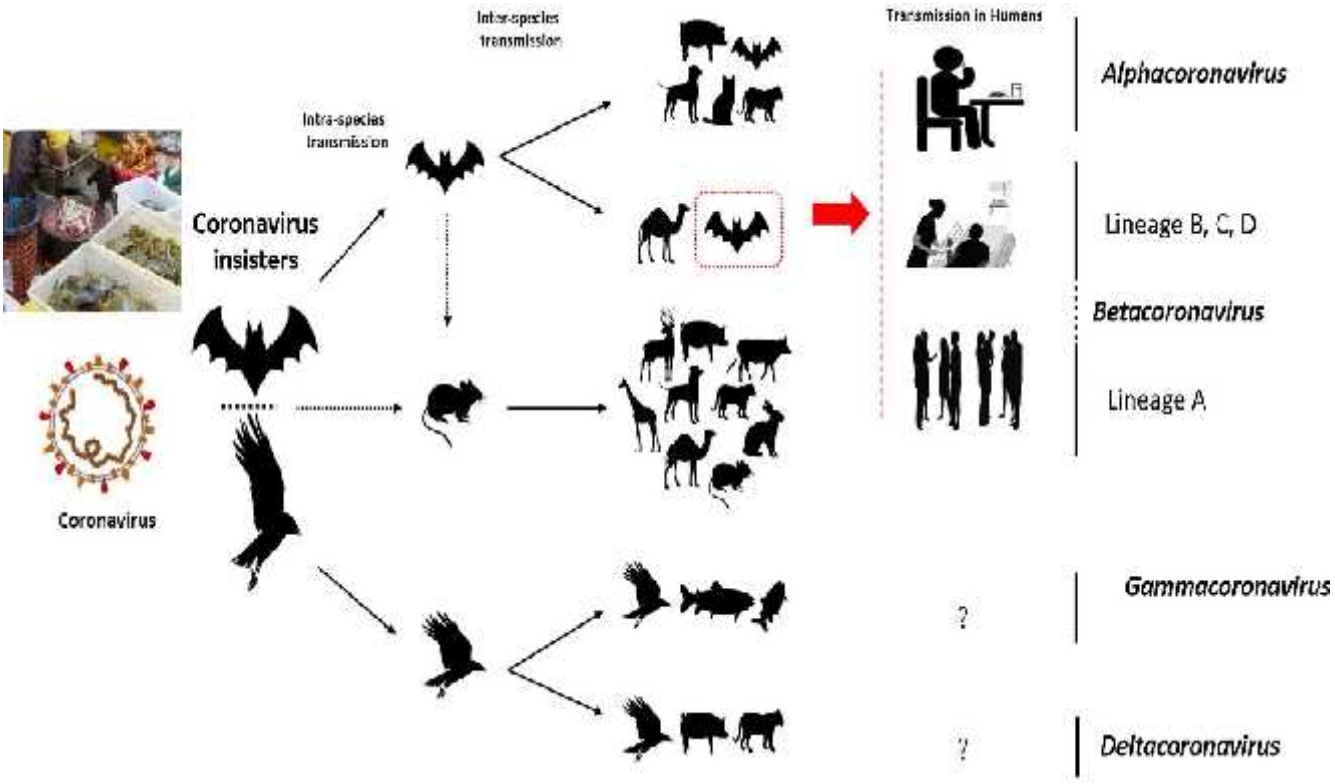


Fig. 2. The key reservoirs and mode of transmission of coronaviruses (suspected reservoirs of SARS-CoV-2 are red encircled); only α and β coronaviruses have the ability to infect humans, the consumption of infected animal as a source of food is the major cause of animal to human transmission of the virus and due to close contact with an infected person, the virus is further transmitted to healthy persons. Dotted black arrow shows the possibility of viral transfer from bat whereas the solid black arrow represents the confirmed transfer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Symptoms

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days [12]. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days [8]. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70-years old compared with those under the age of 70 [8]. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia [5,6,8,13].

Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death [6]. In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs [14] that likely induced both systemic and localized immune response that led to increased inflammation. Regrettably, treatment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities.

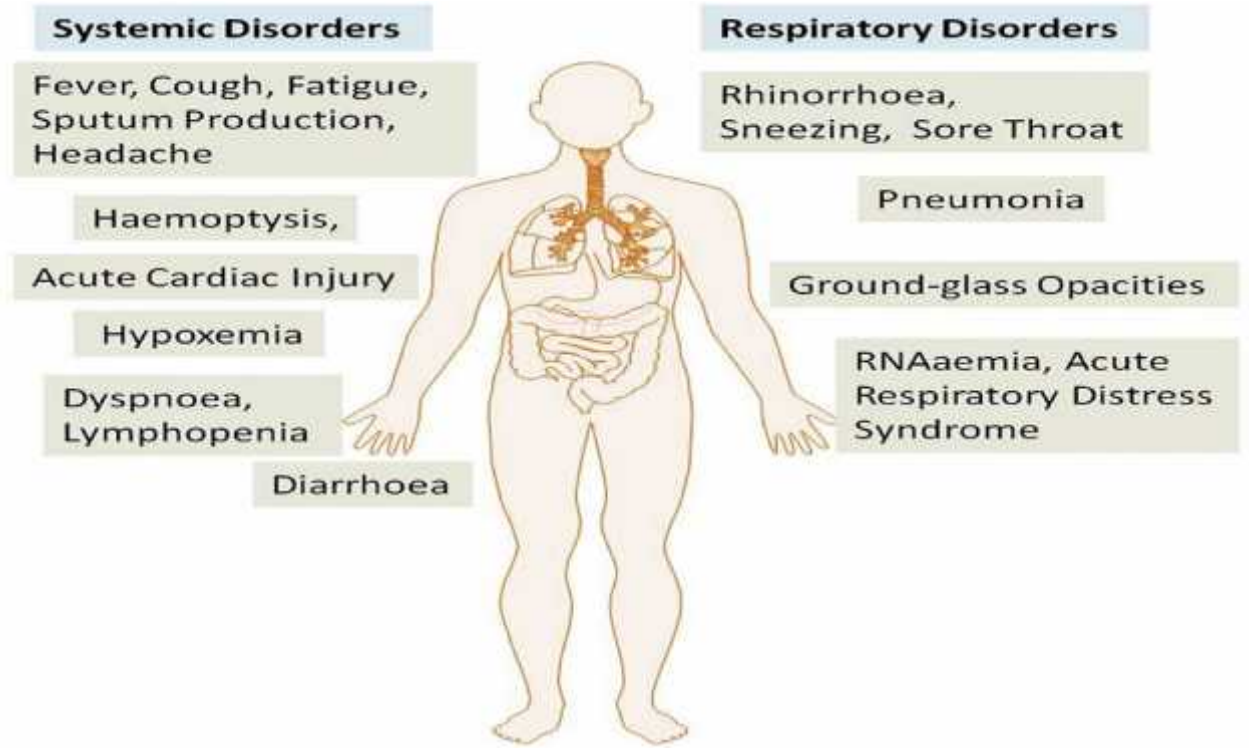


Fig. 3 The systemic and respiratory disorders caused by COVID-19 infection. The incubation period of COVID-19 infection is approximately 5.2 days. There are general similarities in the symptoms between COVID-19 and previous betacoronavirus. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. Additionally, patients infected with COVID-19 developed intestinal symptoms like diarrhoea only a low percentage of MERS-CoV or SARS-CoV patients exhibited diarrhoea.

It is important to note that there are similarities in the symptoms between COVID-19 and earlier betacoronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans [6]. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat [15,16].

In addition, based on results from chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia [17]. Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress.

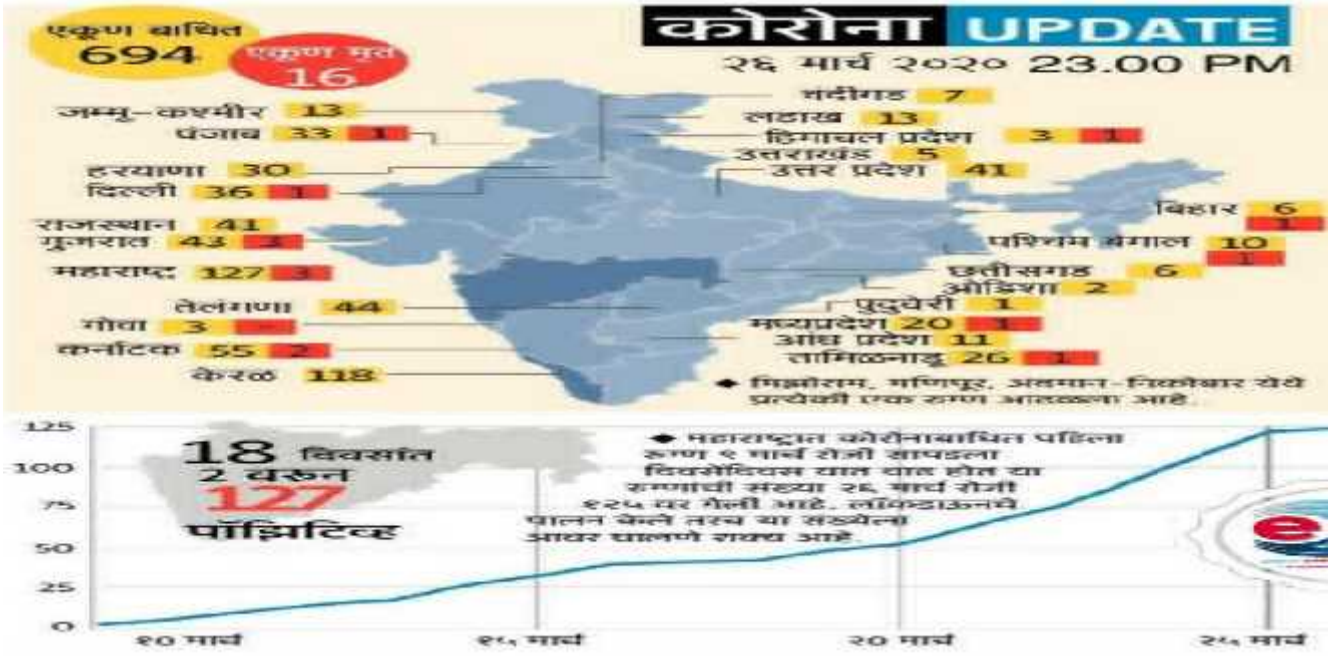
Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc [15,16]. Therefore, development of methods to identify the various modes of transmission such as feacal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease.

Table 1. Comparison of epidemiological characteristics of recent global epidemics as of March 21, 2020

Disease	**Case fatality rate**	**Deaths**	**Cases**
COVID-19 (2019)	4.2	11,299	272,166
Influenza (2017)[a]	N/A	145,000	54,481,000
Ebola (2014)	39.53	11,323	28,646
H1N1 (2009)	0.1	18,449	60,800,000
SARS (2003)	9.56	774	8096

Based on what is known about similar coronaviruses, the longest potential incubation period for COVID-19 is thought to be 14 days from initial exposure [6]. The mean incubation period is 5.2 days (95% CI 4.1–7.0) but can range from 2 to 14 days [4]. Co-infections occur in 22–33% of patients and may be higher in critical patients**.**

- **Recent Corona positive cases in India**



Treatment

1. Anti-inflammation treatment in COVID-19 patients:

No doubt antiviral and supportive treatments are very important in the treatment of patients with COVID-19. As CS is relatively common in severe case and often leads to the exacerbation, anti-inflammation therapy may help in preventing further injury. As we know, there are a variety of anti-inflammatory medications, including non steroidal anti-inflammatory drugs, glucocorticoids, chloroquine/hydroxychloroquine, immunosuppressants, inflammatory cytokines antagonists (such as IL-6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists, janus kinase inhibitor (JAK) inhibitors, et al. Siddiqu and Mehra suggested that

tailored therapy in stage III hinges on the use of immunomodulatory agents to reduce systemic inflammation before it overwhelmingly results in multi-organ dysfunction. In this phase, use of corticosteroids may be justified in concert with the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist). Intravenous immune globulin (IVIG) may also play a role in modulating an immune system that is in a hyperinflammatory state. Overall, the prognosis and recovery from this critical stage of illness is poor, and prompt recognition and application of such therapy may have the greatest yield. However, there is dilemma of anti-inflammatory therapy, balancing the risk and benefit ratio is a critical issue. Should we apply anti-inflammation therapy to COVID-19 patients? Which patient should we treat with anti-inflammation regimen, and when to start? What is the treatment duration? Which medication is the best choice? All the above questions are still under intense debate and do not reach a consensus. The main concern is that anti-inflammatory medications, such as corticosteroid, may delay the elimination of virus and increase the risk of secondary infection, especially in those with impaired immune system. Secondly, biological agents targeting on pro-inflammatory cytokines can only inhibit specific inflammatory factor, and thus may not be very effective in curbing the CS in COVID-19 in which other cytokines maybe of significant importance. Thirdly, some anti-inflammation medication such as JAK inhibitors also block INF-a production, which is important in fighting virus, and theoretically may not be suitable for the treatment of inflammatory CS caused by virus as COVID-19. Finally, the time window of anti-inflammatory treatment is very important. According to reports and our observation, severe patients usually underwent abrupt deterioration in 1–2 weeks after onset, and prompt initiation of the anti-inflammatory therapy at this extremely short time window is likely to achieve a favorable treatment response.

2. Antiviral treatment in covid 19 patients:

These is no specific antiviral treatment which has been proven to be effective for COVID-19. Combinations of over three antivirals are not suggested. Current treatment options are mainly based on previous experience showing clinical benefits in treating influenza, Ebola, MERS, SARS, and other viral infections. It is reported that most of COVID-19 patients received antiviral therapy in China [5,21,25], and here we will introduce some commonly used drugs. Ribavirin is representative of nucleoside analogs. The combination of ribavirin and recombinant interferon, a broad spectrum antiviral agent, showed augmentation effect in inhibiting MERS-CoV replication and reduced doses of both ribavirin and interferon [26]. However, most of clinical experiences in MERS patients come from limited case reports and observational studies, making the quality of evidence for ribavirin and interferon treatment efficacy very low [22]. It is recommended to administer ribavirin by intravenous infusion in combination with inhaled interferon-α or oral lopinavir/ritonavir in the 5th version guideline on COVID-19 diagnosis and treatment issued by Chinese National Health Commission [20]. Notably, ribavirin is not suggested by military medical team coming to Hubei [18] and interferon-α inhalation is worried to increase the risk of virus-containing aerosol production and airway stimulation. Lopinavir/ritonavir is a combination of a protease inhibitor and a booster used for the treatment of human immunodeficiency virus (HIV) infection. Currently, randomized controlled trials for the efficacy of a combination of lopinavir/ritonavir with interferon-α in mild to moderate patients (ChiCTR2000029387) and severe to critical patients with COVID-19 (ChiCTR2000029308) are in progress. Remdesivir, a novel nucleotide analog RNA polymerase inhibitor, is considered as the most promising antiviral drug for the treatment of COVID-19. It showed broad spectrum antiviral activities, from inhibition of human and zoonotic coronavirus (including SARS-CoV-2 [41] as well Ebola virus) in vitro, to prophylactic and therapeutic effects in animal model of MERS-CoV and SARS-CoV infection [15,17]. The first COVID-19 patient identified in the United States was given remdesivir without obvious adverse reactions. Two trials on efficacy of remdesivir have been launched in China among mild to moderate patients (NCT04252664) and severe to critical patients (NCT04257656) infected with SARS-CoV-2. Neuraminidase inhibitors (NAIs), such as oral oseltamivir and intravenous peramivir, showed substantial clinical improvement in treating influenza patients [13,21,23]. Oseltamivir was widely used for suspected and confirmed COVID19 patients in China [26], however, there is no exact evidence that supports its application. A research team from Zhejiang University reported that abidolhasthepotentialtoinhibitSARS-CoV-2,whichwas previously used for influenza. There is a multicenter, randomized, and controlled trial (ChiCTR2000029573) to

evaluate the efficacy of abidol and lopinavir/litonavir, either alone or in combination with a new type of interferon, Novaferon.

3.Corticosteroids:

According to current WHO interim guidance on COVID19 management [27], corticosteroids were not recommended as routine therapy unless indicated for another reason, because possible harms and higher risk of mortality attributed to corticosteroids therapy have been identified by studies on other coronaviruses and influenza. An epidemiological study conducted in Wuhan observed a larger percentage of patients receiving corticosteroids in ICU groups when compared with non-ICU groups (6 (46%) vs. 3 (11%); P = 0.013), while we still cannot determine the effects of corticosteroids due to the limited sample size [25]. According to the latest guidelines issued by National Health Commission of China (version 7) [20] and the interim guidance of WHO [27], when SARS-CoV2 infection is suspected, corticosteroids should be recommended to use with caution. New Coronavirus Infection Diagnosis and Treatment Scheme (Trial Version) published by Military Support Hubei Medical Team also put forward that for mild to moderate COVID-19 patients, corticosteroids should not be given principally and highdose corticosteroid pulse therapy was not recommended. Only patients presenting ongoing deterioration in oxygenation index, or rapid progression of radiological findings, or excessive activation of immune responses, will be considered to use short-term corticosteroid therapy within 10 days of illness onset. Seven designated hospitals in Zhejiang Province gave patients corticosteroids when they showed increased resting respiratory rate (> 30 breaths/ minute), drop in oxygen saturation (< 93%) on room air, or multi-lobular progression (> 50%) on imaging within 48 h [21]. Timely and appropriate use of corticosteroids combined with ventilator support should be considered for severe patients to prevent progression to ARDS [30]. The pharmacologic use of corticosteroids in COVID-19 treatment should vary with severity [20,40]. For severe cases, it is suggested to start at a dose of 40 to 80 mg/day methylprednisolone and slowly taper over 7 to 10 days, and some suggested for a shorter period of 3 to 5 days. For critically ill cases, a starting dose of 80 to 160 mg/day methylprednisolone, following a slow withdrawal within 7 to 10 days is considered.

4.Antimicrobial therapy:

It is widely recognized that many patients, especially critically ill patients were susceptible to secondary infections. Patients receiving corticosteroids had increased risks of developing HAP due to the immunosuppression effects, and those who received mechanical ventilation were susceptible to VAP. The latest guidelines issued by National Health Commission of China for the diagnosis and treatment of COVID-19 infection (version 7) [20] advise against inappropriate and unnecessary use of antimicrobial therapy, especially combination of broadspectrum antibiotics. If the sputum or blood specimens showed a clear evidence of etiology or the PCT levels increased, administration of antimicrobial agents should be considered. As shown in a study of 99 patients with COVID-19, Acinetobacter baumannii, Klebsiella pneumoniae, and Aspergillus flavus were simultaneously cultured in one patient. Meanwhile, one case of fungal infection was attributed to Candida glabrata and three cases of fungal infection were caused by Candida albicans [5]. When selecting antimicrobial agents for initial empiric treatment, in addition to the local epidemiological data of HAP/VAP pathogens, imaging features of pulmonary lesions should also be taken into account [25]. As for fungal infections, voriconazole is recommended for the treatment of Aspergillus infections, while fluconazole is more suitable for Candida spp. infections. When patients are suspected with Pneumocystis pneumonia, sulfamethoxazole and caspofungin should be promptly administrated [24].

5.Anticoagulant:

In clinical practice, nearly20% ofpatientswithCOVID-19 are found to have abnormal coagulation function, and almost all severely and critically ill patients presented coagulation disorders [5,25,26]. In view of no relevant experience for reference, anticoagulation should be given with great caution in patients with DIC though microthrombosis was observed in lung, liver, and other organs by autopsy. When patients exhibit a bleeding tendency or when surgical treatment is needed, platelet transfusion or administration of fresh-frozen plasma is recommended to correct coagulopathies analogs [27]. Low molecular weight heparin(LMWH)can be used for drug prevention. As for subjects with clinical manifestations, clinicians need to be alert to the occurrence of PTE, initiate the diagnostic procedures, and develop corresponding treatment strategies based on risk strati

fication. Considering the risk of disease transmission and the false positive results caused by the presence of lung lesions, the diagnosis of PTE by pulmonary ventilation-perfusion imaging is not recommended. If the critically ill patients cannot take examination due tospecificconditionsandtheinfectivityofCOVID-19, itis recommended to perform anticoagulant therapy for patients without contraindications. If the condition is life threatening and bedside echocardiography indicates new onset of right ventricular volume overload or pulmonary hypertension, thrombolytic therapy or other cardiopulmonary support treatments, such as extracorporeal membrane oxygenation (ECMO) can be initiated with the patient's full informed consent.

6.Oxygen therapy:

For mild to moderate patients with hypoxemia, nasal catheters and masks and even high-flow nasal cannula oxygen therapy (HFNC) are advised. While for severe and critical patients with respiratory distress, HFNC, non-invasive mechanical ventilation(NIV)or invasive mechanical ventilation, and even ECMO should be considered.

a. HFNC (high-flow nasal cannula oxygen therapy)

HFNC can provide accurate oxygen concentration and a certain positive airway pressure to promote alveolar expansion to improve oxygenation and respiratory distress [28]. However, according to expert consensus on the use of HFNC for COVID-19, patients with cardiac arrest, weak spontaneous breathing, PaO2/FiO2 < 100 mmHg, PaCO2 > 45 mmHg and pH < 7.25 and upper airway obstruction are contraindicated.

b. NIV or invasive mechanical ventilation

For severe patients with respiratory distress or hypoxemia that cannot be alleviated after standard oxygen therapy, NIV can also be considered with close surveillance [24,26]. Dangers et al. considered that changes in dyspnea could be used as a variable to predict the failure of noninvasive ventilation [29]. If the patient continuously deteriorates or the respiratory rate cannot be improved after a short time (about 1–2 h), timely tracheal intubation and invasive ventilation are required [49]. Notably, patients with hemodynamic instability, multiple organ failure or abnormal mental status should not receive noninvasive ventilation. Lung protection ventilation strategies (small tidal volume, limited plateau pressure, and permissive hypercapnia) are suggested to be adoptedin invasive mechanical ventilation to reduce ventilator-related lung injury [9]. Compared with NIV, invasive mechanical ventilation can more effectively improve the pulmonary ventilation function and respiratory mechanics of patients with acute respiratory failure. It can effectively increase the SaO2 level and ismore conducive to lower the plasmaBNP level [11]. However, invasive mechanical ventilation requires tracheotomy, or oral/nasal tracheal intubation to establish an artificial airway, which is very likely to cause damage to patients, such as mediastinal emphysema, ventilator related lung injury, and other related complications, such as reduced swallowing function, gastresophageal reflux, infections, etc. What's more, invasive mechanical ventilation also increases the risk of secondary infections transmitted by aerosol particles [11,12].

c. Continuous renal replacement therapy (CRRT)

For critical patients, CRRT can support organ function, reduce cytokine storms and maintain internal environment stability [13]. Three clinical studies showed that the incidence of AKI in patients with COVID-19 was 3% to 7%, and 7% to 9.0% were treated with CRRT. In ICU, the rate of CRRT application was 5.6% to 23.0% and reached as high as 66.7% to 100% in patients with AKI [5,26,8]. CRRT is recommended for patients who exhibit AKI indications (hyperkalemia, acidosis, pulmonary edema, severe sodium ion disorders) or patients with CKD who have not undergone hemodialysis. During septic shock, CRRT can effectively remove inflammatory mediators and significantly improve hemodynamics. When ARDS appears in combination with multiple organ dysfunction syndrome (MODS), early CRRT is recommended [15]. CRRT combined with the treatment of ECMO may remove cytokines, reduce the activity of macrophages and monocytes, and better preserve lung parenchyma.

7.Convalescent plasma therapy for COVID-19:

Some studies reported that early convalescent plasma treatment for influenza and SARS-CoV infection is associated with decreased viral load and reduction in mortality [16], however, the studies were heterogeneous and of low quality. The WHO deemed convalescent plasma transfusion as the most promising therapy for MERS-CoV infection, while the efficacy remained inconclusive, with a lack of adequate clinical trials [16–18]. Since the virological and clinical characteristics among SARS, MERS, and COVID-19 were comparable [19],

convalescent plasma could have immunotherapeutic potential in COVID-19 treatment and further investigations are needed to prove its safety and efficacy. One possible explanation for the efficacy of convalescent plasma therapy is that the neutralizing antibodies from convalescent plasma might suppress viremia [20], so understanding the antibody response during the course of SARS-CoV-2 infection could provide strong empirical support for the application of convalescent plasma therapy. A study reported that on day 5 after treatment, an increase of viral antibodies can be seen in nearly all patients, IgM positive rate increased to 81%, whereas IgG positive rate increased to 100%, which was considered as a transition from earlier to later period of infection [9]. Preliminary study has showed that patients who have recovered from COVID-19 with a high neutralizing antibody titer and could provide a valuable source of the convalescent plasma. Plasma transfusion may cause adverse effects; so convalescent plasma therapy is recommended as a last resort to improve the survival rate of severe patients with COVID-19. The optimal dose and treatment time point, as well as the therapeutic indications of convalescent blood products in COVID-19 remain uncertain, which need to be further investigated in randomized clinical studies.

- **Tocilizumab:**

Tocilizumab is a humanized IgG1k monoclonal antibody whichcanspecificallybindsolubleormembrane-typeIL-6 receptors (Sil-6RandMil-6R), and has been widely used in the treatment of autoimmune diseases such as rheumatoid arthritis [17], adult-onset Still's disease [22], and large vessel vasculitis [63]. For COVID-19 infection, clinical studies have shown that serum levels of inflammatory mediators in severe patients are significantly higher than those in common patients [25].

Excessive immune responses can trigger cytokine storms and cause damage to multiple target organs. Recent guidelines also point that a progressive rise in IL-6 may be a clinical warning indicator for the deterioration of COVID-19. A domestic research team found that tocilizumab can block the signaling pathways of two key inflammatory factors, IL6 and GM-CSF, and reduce the inflammatory response. A multicenter, randomized, controlled clinical study has been coducted to evaluate the efficacy and safety of tocilizumab in the treatment of moderate patients at high risk to develop into severe and critical patients (registration number: ChiCTR2000029765). For patients with elevated IL-6 levels, the efficacy of tocilizumab can be expected.

Table 2. COVID-19 therapies under study.

Medication	**Dosing**
Remdesivir	200 mg for 1 day, then 100 mg IV every day for 9 days
Lopinavir/Ritonavir	400–100 mg PO BID for 14 days
Chloroquine	500 mg PO BID for 10 days
Hydroxychloroquine	400 mg PO BID for 1 day, then 200 mg PO BID for 4 days
Tocilizumab	8 mg/kg in 100 mL of 0.9% NS IV over 60 min
Favipiravir	1600 mg PO BID for one day, then 600 mg PO BID for 6 days

Abbreviations: mg – milligrams, IV -intravenous, BID – twice per day, PO – per os, NS – normal saline, mL – milliliters, kg – kilogram.

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