Facing coronavirus disease 2019: What do we know so far? (Review)

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Abstract. Although the World Health Organization declared the outbreak of coronavirus disease 2019 (COVID-19), which originated in China, as a public health emergency of international concern as early as January 30, 2020, the current COVID-19 epidemic is spreading rapidly. As of April 19, 2020, total of 2,392,165 confirmed cases had been reported in 211 countries and regions, with 614,421 (25.68%) cured cases and 164,391 (6.87%) deaths. Scientists and clinicians have made great efforts to learn much about COVID-19 so that it can be controlled as soon as possible. Herein, this review will discuss the epidemiology, pathology, clinical features, diagnosis and treatment of COVID-19 based on the current evidence.

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1. Introduction

At the beginning of December 2019, a cluster of mysterious pneumonia cases was reported in Hubei Province of the People's Republic of China, and a novel coronavirus was identified as the common cause of this unexplained pneumonia (1). The virus and the associated disease were named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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and coronavirus disease 2019 (COVID-19), respectively, by the World Health Organization (2). With the spread of this epidemic, COVID-19 has been identified in other parts of China and around the world. It is urgent to combat this deadly contagious disease with increasing incidence.

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses and include α-coronavirus (α-CoV), β-coronavirus (β-CoV), δ-coronavirus (δ-CoV) and g-coronavirus (γ-CoV) (3). Six coronaviruses were previously identified as human-susceptible viruses, among which HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1 cause mild respiratory illness (4). Two other notorious coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have stronger transmission capacity and high mortality rates (5,6). SARS-CoV-2 is the seventh member of the coronavirus family that infects human beings after SARS-CoV and MERS-CoV were described. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 is also a β-CoV; however, the genome sequence is significantly different from those of SARS-CoV and MERS-CoV (7). Specific recognition mediated by the spike protein and angiotensin-converting enzyme 2 has been revealed to be crucial for SARS-CoV-2 attachment and membrane fusion in host cells (8).

Several reports have described the epidemiology, pathology, clinical manifestations, diagnosis and treatment of COVID-19, and this review provides comprehensive insights on COVID-19 based on the emerging evidence.

2. Epidemiology

Currently, the human-to-human transmission mode of SARS-CoV-2 has been verified, including in both COVID-19-diagnosed and asymptomatically infected patients. The major route of SARS-CoV-2 transmission is through respiratory droplets and close contact (9). Moreover, SARS-CoV-2 can also be propagated by exposure to high-concentration aerosols for a long time in a relatively closed environment. Additionally, SARS-CoV-2 has been isolated from feces and urine; thus, particular attention should be given to the spread of aerosols or contact with environmental pollution containing feces and urine (10). Based on the current epidemiological survey, the incubation period of SARS-CoV-2 ranges from 1 to 14 days, with most cases becoming symptomatic within 3 to 7 days, indicating that individuals with

close contact must undergo 14 days of medical observation or isolation (11). However, some asymptomatic carriers have been reported to have an incubation period of 30 days, which is concerning for the population that is generally susceptible to SARS-CoV-2 (12). This characteristic comprises a persistent challenge for the prevention and control of COVID-19.

3. Pathology

The pathological manifestations of patients with SARS-CoV-2 infection are limited due to the scarcity of biopsies or autopsies. The changes in the lungs are the most noticeable characteristic. Firstly, serous, fibrin exudate and hyaline membranes are found in the alveoli, with the exudate cells mainly including monocytes and macrophages (13). Secondly, type II alveolar epithelial cells filled with inclusion bodies show significant proliferation, and some detach (14). Thirdly, hyperemia, edema, infiltration of monocytes and lymphocytes, and the formation of hyaline thrombi in the alveolar septa occur. Hemorrhagic infarction resulting from focal hemorrhage and necrosis of lung tissue have also been observed (15). Moreover, the spleen shows obvious shrinking, and the histological features include focal involvement of a decreased number of CD4+T and CD8+T cells (16). Degeneration and necrosis can also be seen in cardiomyocytes that are infiltrated by a small number of monocytes, lymphocytes and/or neutrophils (17). Additionally, the liver and gallbladder exhibit a dark red color with an increased volume. Moreover, hepatocyte degeneration and focal necrosis with neutrophil infiltration can be found in the portal area (18). The renal tubular epithelium is denatured and exfoliated with microthrombi and focal fibrosis (19). In summary, the pathological features of COVID-19 greatly resemble those of SARS-CoV and MERS-CoV infection (20,21).

4. Clinical characteristics

The spectrum of clinical manifestations of COVID-19 includes a self-reported fever, dry cough and fatigue (22). A small number of patients have been reported to have nasal obstruction, runny nose, sore throat, myalgia and diarrhea (23). Severe cases often involve dyspnea and/or hypoxemia one week after COVID-19 onset, which rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction and multiple organ failure without obvious fever (24). However, the main symptoms in children and newborns with SARS-CoV-2 infection are not typical and include vomiting, diarrhea and gastrointestinal discomfort or only mental confusion and shortness of breath (25).

Patients with COVID-19 can be divided into mild, common, severe and critical types according to the severity of symptoms. Mild or no pneumonia is found on chest computed tomography (CT) images of mild patients. Pneumonia is also commonly presented by patients with a self-reported fever and some respiratory symptoms. Severe patients have overt symptoms, including dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, an arterial oxygen partial pressure to inspired oxygen fraction (FiO_2) ratio of <300, and/or pulmonary infiltration >50% within 24-48 h (26-28). A child with

shortness of breath (<2 months old, respiratory rate ≥60 min; 2-12 months old, respiratory rate ≥50/min; 1-5 years old, respiratory rate ≥40/min; >5 years old, respiratory rate ≥30/min), oxygen saturation ≤93%, assisted respiration (moaning, alar flutter, three concave signs), cyanosis, intermittent apnea, drowsiness, convulsion, refusal to eat or feed, and dehydration signs should be considered as having the severe type (29). Critical patients have worsened medical conditions, such as respiratory failure, septic shock and multiple organ failure, or may even require immediate respiratory support with mechanical ventilation and intensive care unit monitoring and treatment (30).

Clinical laboratory indicators in COVID-19 patients are diverse and can be regarded as discriminatory tools to define patient types.

Serological examination. In almost all patients, the total number of leukocytes in the peripheral blood is normal or decreased, and the lymphocyte count is decreased (31). Half of patients have abnormal liver function, which is manifested as elevation of alanine aminotransferase or aspartate aminotransferase levels. Most patients have an abnormal myocardial zymogram, showing increases in creatine kinase and lactate dehydrogenase (32). The C-reactive protein (CRP) level and erythrocyte sedimentation rate are increased in most patients who show normal serum levels of procalcitonin, D-dimer, inflammatory factors, myoglobin and even troponin, which are often increased in severe and critical patients (33). It should be noted that hyperinflammatory syndrome is characterized by increased interleukin (IL)-2, IL-7, IL-6, granulocyte colony-stimulating factor, interferon (IFN)-γ-inducible protein 10, IL-8, IL-9, IL-10, basic fibroblast growth factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor (TNF)-α (34). Physicians should be alert for the 'inflammatory storm' and end-organ damage caused by the increase in inflammatory factors.

Etiological examination. Real time-polymerase chain reaction (RT-PCR) and/or next-generation sequencing methods can be used to detect the RdRP, N, and E genes of the SARS-CoV-2 genome in nasopharyngeal swabs, blood and feces samples (35). The SARS-CoV-2 genome is more complicated to detect in lower respiratory tract samples (sputum or airway extracts), and indicated samples should be sent for examination as soon as possible after collection (36).

Chest CT imaging. Chest CT imaging results show multiple small-spot shadows and interstitial changes, especially in the extrapulmonary zone, which develop into multiple ground glass opacities and infiltrative shadows in both lungs (37). Lung consolidation and pleural effusion are seldom observed in severe patients.

Suspected COVID-19 cases are classified based on the epidemiological history and clinical manifestations. Patients with a history of travel or residence in a community in which confirmed cases have been reported or individuals with contact with infected persons (positive for nucleic acid detection) within 14 days prior to the onset of the 'COVID-19 manifestations' should be suspected of being infected with

Table I. Details of drugs indicated for treatment of coronavirus disease 2019.

Drugs	Status	Recommended dosage	Refs.
Lopinavir/ritonavir tables	Approved	2 tablets, bid	(46)
Oseltamivir	Approved	75 mg, bid for prevention	(47)
		75 mg, qd for treatment	
Ribavirin	Approved	500 mg, bid or tid for ivgtt	(48)
Ganciclovir	Investigational	Controversial	(49)
Remdesivir	Experimental	Controversial	(51)
α-Interferon	Recommended in China	5 million U, bid for nebulization	(52)
Chloroquine	Controversial	For those weighing >50 kg: 500 mg, bid for 7 days; for those weighing <50 kg: 500 mg, bid for the first and second days, followed by 500 mg, qd from the third to the seventh days	(53)
Arbidol	Recommended in China	200 mg, tid for no more than 10 days	(54)
Lianhua Qingwen capsule	Recommended in China	1.4 mg, tid	(34)
Shuanghuanglian oral liquid	Recommended in China	20 ml, tid	(34)
Methylprednisolone	Controversial	1-2 mg/kg, qd	(55)
Topiramab	Approved	4-8 mg/kg, qd	(34)

bid, twice a day; qd, one time a day; tid, three times a day; ivgtt, intravenous drip.

SARS-CoV-2 (38). COVID-19 manifestations include fever and/or respiratory symptoms, chest CT imaging features, and normal or decreased numbers of white blood cells and lymphocytes (39).

COVID-19 cases are further identified in suspected infected patients based on pathogenic or serological evidence. Particularly, confirmed cases include suspected infected patients in whom nucleotide fragments for the SARS-CoV-2 genome are successfully detected by RT-PCR or in whom the genes of the causative virus are highly homologous to those of the known coronavirus as determined by genomic typing and sequence analysis (40). Furthermore, confirmed patients are positive for SARS-CoV-2-specific IgM and IgG antibodies, and the accumulated levels are four times higher than the levels in the acute phase (34).

RT-PCR is regarded as a convincing method for the identification of pathogenic viruses in respiratory secretions (41). However, some patients in Wuhan were diagnosed as confirmed cases according to typical symptoms, exposure history and chest CT manifestations without nucleic acid testing due to the shortage of RT-PCR testing kits (42). In the early stage of COVID-19, the positive rate of RT-PCR was ~60% for throat swabs (43). In addition, a study was carried out to compare the diagnostic value of chest CT imaging and RT-PCR in patients suspected with SARS-CoV-2. The results showed that the sensitivities of chest CT based on positive and negative RT-PCR results were 97 and 75%, respectively (44). Therefore, chest CT imaging and RT-PCR are both powerful tools for diagnosing COVID-19 and are complementary to each other.

5. Effective treatment

Patients with suspected and confirmed COVID-19 should be treated in single rooms of a designated hospital with effective isolation and protective conditions as much as possible. The treatment of patients with COVID-19 is as follows.

General supportive care. It is necessary to instruct the patient to lie in bed and ensure a sufficient temperature. The oxygen saturation, fluid and electrolyte balance, the complete blood count, CRP, and liver, coagulation and kidney functions should also be closely monitored (45). The administration of high-flow oxygen and even an admixture of hydrogen and oxygen (H_2/O_2: 66.65/33.39%) should be performed in a timely manner (34).

Drug treatment. Currently, no specific drug has been approved for therapy, but some indicated medications can be used on a trial basis.

The development of antiviral drugs has received continuous attention since the outbreak of COVID-19. Antiviral-drug candidates including lopinavir/ritonavir, oseltamivir, ribavirin and ganciclovir have been used to optimally decrease viral shedding and subsequent transmission (46-49). However, the results of an urgent randomized clinical trial performed by Cao *et al* (50) were disappointing, indicating that lopinavir/ritonavir are not effective in patients with COVID-19 (50). Remdesivir was also reported to be effective, but only in the treatment of a patient with COVID-19 in the United States (51). Thus, rapidly initiated, high-quality, randomized clinical trials need to be performed to verify the efficacy of these antiviral drugs for COVID-19. In addition, IFN-α, chloroquine phosphate and Arbidol, which have been shown to be effective in decreasing the SARS-CoV load in cell culture, were also empirically used in Wuhan (52-54). The use of three or more antiviral drugs at the same time is not recommended, and indicated drugs should be stopped if intolerable side effects occur. Blind or inappropriate use of broad-spectrum antibiotics

should be avoided unless secondary bacterial infection occurs. The treatment practice of COVID-19 in China indicated that intervention with Traditional Chinese medicine (TCM) is an important management strategy to improve the prognosis and prevent the deterioration of patients with COVID-19. TCM prescriptions such as *qingfei paidu* decoction, *gancaoganjiang* decoction, *sheganmahuang* decoction, *qingfei touxie fuzheng* recipe, and Chinese traditional patent medicines including *Lianhua Qingwen* capsule and *Shuanghuanglian* oral liquid were all commonly used (34). Corticosteroids were used for short-term treatment (3-5 days), as appropriate, but high-dose corticosteroids can increase the immunosuppressive effect, thus delaying the SARS-CoV-2 clearance (55). Detailed information for the drugs indicated for COVID-19 treatment is supplied in Table I.

Treatment of severe and critical cases. The treatment of patients with severe and critical cases is rather difficult to manage. For such patients, the principle of treatment is to actively prevent and treat complications and secondary infection, and to rapidly improve the organ function via respiratory and circulatory support.

Patients with severe and critical cases must be given oxygen using nasal catheters or face masks. When respiratory distress and/or hypoxemia cannot be relieved after standard oxygen treatment, high-flow oxygen should be administered, and noninvasive ventilation may be considered (56). If the condition does not improve or even worsens in a short period of time (1-2 h), intubation and invasive mechanical ventilation should be carried out immediately. It is noteworthy that low tidal volume (6-8 ml/kg) and airway platform pressure (≤ 30 cmH$_2$O) are needed to decrease ventilator-associated lung injury (57). Patients with severe ARDS will require salvage treatment as soon as possible. In particular, more than 12 h of prone position ventilation should be performed every day (58). Moreover, extracorporeal membrane oxygenation can be implemented when the FiO$_2$ is >90% and the oxygenation index is <80 mmHg for 3-4 h (59).

Vasoactive drugs are also encouraged to improve microcirculation in patients with severe and critical cases, and changes in blood pressure, heart rate and urine volume, as well as elevations of lactate and alkali levels in the arterial blood must be closely monitored. These patients should also be assessed for septic shock, gastrointestinal hemorrhage and heart failure when a sudden increase in heart rate of >20% or a decrease in blood pressure of >20% of the baseline value occurs, accompanied by poor skin perfusion and decreased urine volume (60).

The cytokine storm seems to induce damage to the lungs or multiple organs and can affect patients with severe conditions (61). During the COVID-19 outbreak in China, blood purification treatments were used to clear inflammatory factors and block the cytokine storm, thus protecting host organs from damage (62). Furthermore, blocking IL-6 with tocilizumab may be an effective measure, and blocking IL-1 and TNF-a may also benefit patients (63). Mesenchymal stromal/stem cells have been shown to exert their anti-inflammatory effects in patients with severe COVID-19 infection (64). However, more solid evidence needs to be accumulated.

Various clinical sites in China have also declared that continuous renal replacement therapy and plasma from convalescent populations are suitable for patients with severe and critical illness (65). However, evidence has yet to be accumulated.

Overall, symptomatic treatment is vital for patients with COVID-19, and many outstanding issues need to be clarified in the process of pursuing effective treatment for COVID-19.

6. Conclusions and prospects

The outbreak of COVID-19 is ravaging many countries that bear a large burden of morbidity and mortality, which has been reported as ~3.41%, compared with 10% for SARS and 35% for MERS in China (66,67). Nevertheless, it is too early to evaluate the total mortality because the current COVID-19 outbreak in the United States and European countries is moving rapidly.

Early diagnosis by rapid and reliable technologies, early isolation in a community or designated hospital, and early treatment with individualized programs have been helpful for managing COVID-19. Staying at home, limiting social contacts, wearing masks in public and using necessary disinfectants are the best strategies to protect healthy individuals from SARS-CoV-2 infection. However, it is possible that humans will coexist with SARS-CoV-2 for a long time until specific drugs and vaccines become available.

Availability of data and materials

Not applicable.

Authors' contributions

HYJ and XLZ contributed to the conception and design of the present study. WX, PFW and KW consulted relevant references and performed the literature data collection. QG wrote the first draft of the manuscript. JL revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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