Coronavirus disease-2019 (Review)

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Abstract. From the end of 2019, an ongoing outbreak of a new type of unexplained pneumonia caused by a novel coronavirus, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China. Since then, it has spread to most parts of China and worldwide, thus affecting the health of individuals worldwide. Until August 2020, >25 million cases of SARS-CoV-2 infection had been confirmed worldwide, causing >800,000 deaths. This disease was named by the World Health Organization as coronavirus disease 2019 (COVID-19). Similar to SARS and Middle East Respiratory Syndrome, which are also caused by coronavirus infections, COVID-19 mainly causes severe respiratory system damage; however, it also causes damage to multiple organs, including the gastrointestinal tract, the cardiovascular system and the nervous system. The main aim of the present review article was to summarize the current knowledge of COVID-19, such as the transmission process, diagnostic methods, pathological characteristics, potential pathogenic mechanisms and treatment measures.

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1. Introduction

A large-scale novel type of pneumonia, caused by coronavirus disease 2019 (COVID-19), began in Wuhan, China at the end of 2019, and it has affected numerous countries and regions worldwide as of early June, 2020. The outbreak of COVID-19 was caused by a coronavirus infection, similar to the prior infectious disease outbreaks Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (1,2). According to the current epidemiological analysis, COVID-19 may be far more infectious compared with SARS-CoV, while it has been reported that this virus is transmitted by humans, albeit with weaker pathogenicity than SARS-CoV (3,4). To this end, governments worldwide have adopted strict measures for the isolation and control of the disease in order to prevent its further large-scale spread, including the lockdown of cities, the isolation of suspected populations and the establishment of new COVID-19 treatment hospitals (5). However, this virus still poses a serious threat to human health. Currently, in addition to numerous epidemiological studies gradually revealing the possible origin, transmission routes and characteristics of COVID-19, several preliminary studies have investigated the histopathological changes, potential pathogenesis and treatment approaches for COVID-19. The results of these studies may provide an important theoretical basis for the understanding and prevention of COVID-19 infection. Furthermore, an in-depth study of COVID-19 by scientists of different specialties worldwide may gradually lead to the elucidation of the pathophysiology of the disease.

2. Transmission and origin

The World Health Organization (WHO) officially named the novel coronavirus pneumonia as COVID-19 (6). On December 30, 2019, the Wuhan Health Commission of China issued an emergency notice stating that patients with pneumonia of unknown origin were admitted to various hospitals in the country, which immediately attracted the attention of the Chinese government, which in turn appointed relevant experts to investigate and analyze this newly identified type of pneumonia. It was finally confirmed that this type of pneumonia was caused by a virus. Based on information obtained from patients, it was initially considered that this virus could have originated from the Wuhan HuaNan Seafood Market. Chinese scholars gradually realized that the virus was rapidly spreading among humans (3). The number of infected individuals significantly increased within a short period of time, and pneumonia cases were first reported outside China in mid-January, 2020. At the end of January, 2020, the Chinese government imposed stricter measures in order to prevent the epidemic from spreading further, and organized the country's

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resources in the fight against this novel coronavirus-associated pneumonia. In mid-to-late February, 2020, the number of new pneumonia cases was gradually declining in China, while the number of patients discharged from hospital was gradually increasing. In early March, with the exception of Wuhan, the number of suspicious infections in China stabilized, and the epidemic was considered to be effectively controlled. However, the COVID-19 outbreak is significantly more severe compared with the previous SARS outbreak. By August, 2020, according to the report of the Health Commission (7), the total number of COVID-19 infection cases in China exceeded 90,000, with >4,700 deaths. Although this disease has had a relatively serious negative impact on the Chinese population, this was markedly restricted due to the successful strict measures imposed by the Chinese government.

As regards countries other than China, Thailand confirmed the first imported case of COVID-19 as early as January, 2020 (8). By February, 2020, 24 countries globally had reported confirmed cases of COVID-19 (9). Due to the initial lack of awareness regarding the novel coronavirus-mediated pneumonia, the number of cases in several countries rapidly increased. As of August, 2020, the United States of America was the country with the highest total number of confirmed cases (>6 million cases), while Brazil was the country with highest number of confirmed cases per day (>50,000 cases). As regards Asia, India had >3 million individuals diagnosed with COVID-19, while ~1 million cases were confirmed in Russia. In the African continent, a total of 57 countries reported >1 million confirmed cases. At the time of the writing of the present review article, 13 countries in Africa had reported >10,000 confirmed cases of COVID-19, among which South Africa, Egypt and Nigeria were shown to have a markedly increased incidence of the disease (Fig. 1).

The similarity comparison and mutation site analysis of the COVID-19 genome, obtained from the 2019 novel coronavirus resource library released by the National Genomics Scientific Data Center, revealed that the sequence similarity between SARS-CoV-2 (COVID-19) and SARS-CoV, responsible for the 2003 outbreak, was 80%, whereas it was ~50% for MERS-CoV. In addition, SARS-CoV-2 was clustered with SARS-CoVs in the phylogenetic tree of SARS-related coronaviruses (10-12). SARS-CoV-2 belongs to the 'Coronavirus' family, the 'β-coronavirus' genus, and the 'severe acute respiratory syndrome-associated coronavirus' species, which also includes SARS-CoV (13). Based on currently available analyses, the COVID-19 appears to be more infectious than SARS-CoV (3). In addition, it has been reported that COVID-19 exhibits the highest similarity (88%) with the genomic sequence of bat-isolated SARS-like coronavirus (bat-SL-CoVZC45). Bat-SL-CoVZC45 was first isolated from domestic bats in February, 2017 (14,15). Furthermore, SARS-CoV-2 is also closely associated with a type of coronavirus isolated from bats, namely RaGT13-CoV, with a nucleotide identity of 96%, thus indicating that SARS-CoV-2 may have also originated from bats. However, whether SARS-CoV-2 was transmitted directly from bats to humans or through intermediate hosts remains unclear (16). Some studies have suggested that pangolins may also be the host of SARS-CoV-2. Notably, SARS-CoV-2 encompasses a unique peptide (PRRA) insertion; however, this element is lacking from the pangolin-carried coronavirus (17). Therefore, further in-depth research into the identification of the virus hosts may provide the necessary knowledge for preventing these diseases.

3. Diagnosis

In the context of the current SARS-CoV-2 pandemic, accurate and rapid diagnostic tests are crucial for the detection of COVID-19 infection. With the identification of the COVID-19 virus sequence, reverse transcription-quantitative PCR (RT-qPCR) analysis and gene sequencing have been recommended for the diagnosis of COVID-19 (18). However, due to the urgency of the epidemic and since gene sequencing is a time-consuming method, this approach is less frequently adopted. Currently, the most commonly used clinical diagnostic tests for COVID-19 are divided into 3 categories: Molecular testing for the detection of viral RNA (RT-qPCR); serological testing for the detection of anti-SARS-CoV-2 immunoglobulins; and computed tomography (CT). Several manufacturers have developed and produced different diagnostic kits for COVID-19, and have gradually optimized the detection efficiency and detection time. The virus is mainly detected in throat swabs, sputum, alveolar lavage fluid, serum and plasma (19).

RT-qPCR, used to detect viral RNA, is considered as the 'standard diagnostic tool'. A disadvantage of RT-qPCR testing is the risk of false-negative and false-positive results. Emerging evidence has suggested that SARS-CoV-2 is characterized by genetic diversity and rapid evolution. Therefore, the results of RT-qPCR using primers for different genes may be affected by changes in the viral RNA sequence (20,21). Although RT-qPCR assays are designed to be as accurate as possible based on the conserved regions of the viral genome, genome variability may cause mismatches between the primer/probes and the target sequences may lead to decreased accuracy and potential false-negative results (22). The kinetics of the viral load may also lead to false-negative results to a large extent. Currently, rapid and efficient nasal and throat swabs are recommended for sample collection (23). The Coronavirus Standards Working Group (https://jimb.stanford.edu/covid-19-standards) led by the Joint Biometrics Project has developed a set of guidelines to ensure the accuracy of the diagnostic test results (24).

Compared with tests using nucleic acid, serological testing requires less technical knowledge and equipment, and is considered as an easy method to perform. The majority of serological assays are based on SARS-CoV-2 nucleocapsid protein (N), transmembrane spike protein (S) or S receptor-binding domain (RBD), due to their high antigenicity (25,26). The spike (S) protein on the surface of the virus mediates the adhesion of the virus to human respiratory cells through its RBD, which, in turn, promotes the fusion of the virus with the cell membrane. A previous study demonstrated that individuals who were not exposed to SARS-CoV-2 had no spike protein at all, and their serum samples showed little or no response in ELISA (27). In another study, the seroconversion of IgM and IgG occurred simultaneously or sequentially, and the median interval for seroconversion for both immunoglobulins was 13 days following the onset of COVID-19, and 19 days report the onset of symptoms (28). Additionally, the IgG seroconversion rate

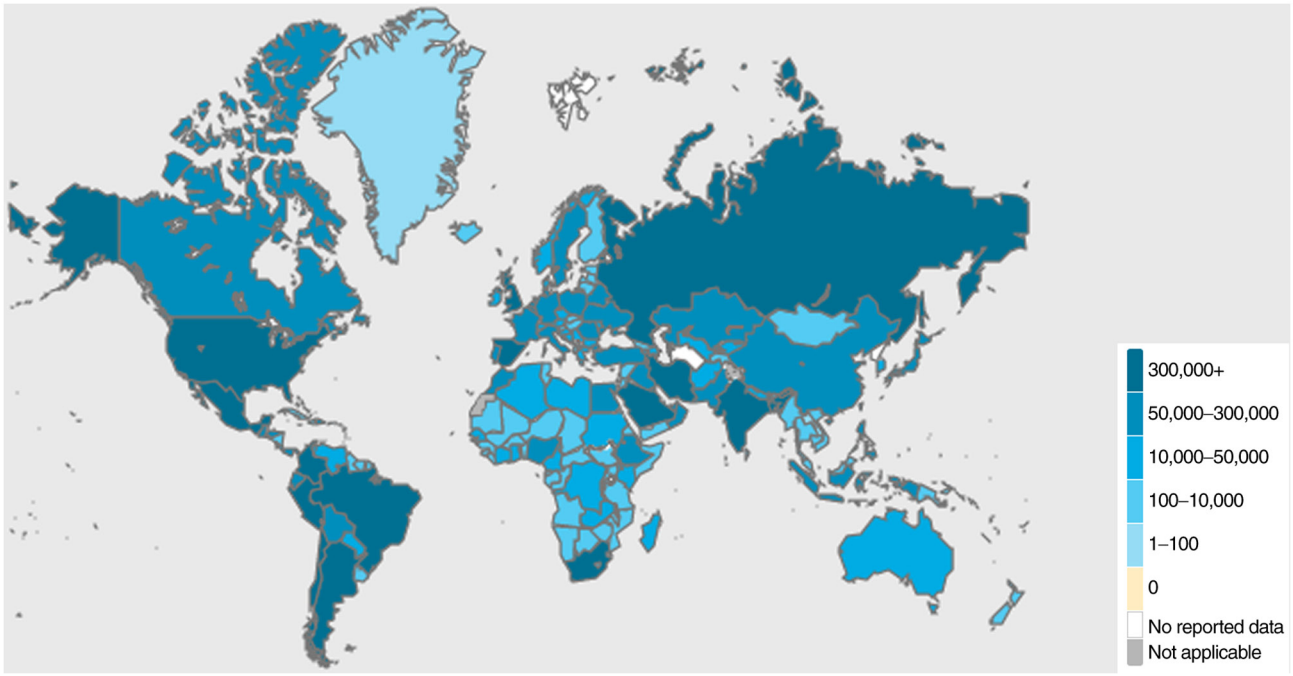

Figure 1. Global number of infections as of August, 2020. Excerpt from the official website of the World Health Organization (https://www.who.int/).

reached 100%, and the sensitivity test range for IgM and IgG was between 72.7 and 100%, while the specificity range was between 98.7 and 100%, respectively. When IgM/IgG ELISA was combined with PCR, the detection rate was significantly improved compared with PCR alone (98.6 vs. 51.9%) (29,30). However, serological tests are affected by several factors, such as specimens, reagents and operations; therefore, false-negative results may occur, affecting the clinical treatment and prevention of the infection.

CT examination is also an important method (31,32), which may help clarify the false-negative results in the detection of COVID-19 obtained by PCR and serological examinations. During or outside the COVID-19 incubation period, a CT scan of infected patients may reveal some characteristic lesions in their lungs that are indicative of infection. The most common chest CT manifestation is bilateral ground-glass opacity (GGO) (33). This is defined as a hazy area in the lung that exhibits a slight increase in density, without blurring of the edges of the bronchi and blood vessels, which is caused by the partial displacement of air promoted by the partial filling of the alveolar cavity or the thickening of the gap (34). The presence of GGO usually indicates pulmonary edema or hyaline membrane formation (33). In addition, the lung CT examination of patients with COVID-19 may also reveal a reticular pattern, crazy paving pattern and the air bubble sign (35-37). The pathological fluid covers the edges of the underlying blood vessels and airway walls and increases the density of the lung parenchyma, which is referred to as consolidation (38). In patients with COVID-19, consolidation may be associated with cellulose and mucus exudates in alveolar cells (39). It was recently reported that consolidation is considered a sign of disease progression, while GGO in a lung CT scan is considered as an early finding of SARS-CoV-2 infection (40). GGO may evolve into consolidation after 1-3 weeks (33). In patients with severe COVID-19 infection, multifocal or large-area sheet consolidation may appear in the lungs, which is characterized by large white areas on lung CT images, also referred to as 'white lungs' (41). All the aforementioned detection techniques are associated with shortcomings; therefore, in order to improve the detection rate of COVID-19, clinicians may opt to use a combination of these methods. Patients with 'white lungs' are usually infected within their familiar environment and, although they may not have been tested or tested negative for COVID-19 by RT-qPCR analysis, some researchers refer to such patients as 'clinical diagnostic cases'. Although these patients are not really confirmed cases, they are recorded as confirmed or suspected cases, requiring high caution and immediate isolation (42).

4. Pathology and mechanisms

Understanding the pathological changes of the disease is a prerequisite for its treatment. A pathological examination of the lungs of patients with COVID-19 revealed that the lung tissue was grossly affected by diffuse congestion and partial necrosis, while the bronchi were lined with a large amount of mucus and exudate (43-47). Microscopic analysis also revealed extensive hemorrhage, infarction, pulmonary interstitial fibrosis, extensive type I alveolar epithelial cell damage and atypical proliferation of type II alveolar cells, hyaline membrane formation, exudation, pulmonary edema and consolidation. Additionally, a large number of inflammatory cells, including lymphocytes and plasma cells, infiltrated the lung tissue, while increased vascular proliferation was also observed. Several studies have also reported other characteristics of the lungs of patients with COVID-19, such as the loss and squamous metaplasia of alveolar epithelial cells and a large amount of cellulose-like exudate in the alveoli. Other pathological analyses demonstrated that patients with COVID-19 exhibited structural damage to the lung tissue and

a large amount of mucus and exudate blocking the airway lumen and alveoli, thus leading to severe respiratory failure and insufficient spontaneous breathing. Therefore, for patients with severe COVID-19, even the use of extracorporeal assisted ventilation is ineffective. The primary function of the lungs is to rely on normal physiological movements to maintain the body's normal oxygen supply based on the inhalation and discharge of oxygen or carbon dioxide (43-47). Varga *et al* reported for the first time that patients with COVID-19 exhibited endothelial cell damage in multiple organs, including the heart, kidney, lung and small intestine, thus indicating that SARS-CoV-2 infection may facilitate the induction of endotheliitis, apoptosis and pyroptosis in several organs, as a direct consequence of the host's inflammatory response (48). Necrotic lymphocyte infiltration, interstitial edema and fibrosis have also been found in the gastrointestinal tract (49), kidneys (50) and liver (51) of patients, while axonal damage has been observed in brain nerve cells (52). Furthermore, in several patients, COVID-19 has been found to be accompanied by viral rashes and vascular endodermatitis of the skin and blood vessels, respectively (48,53). The aforementioned reports indicate that lung injury is the most common lesion of COVID-19; however, the damage is not limited to the lungs, suggesting that COVID-19 is a systemic disease characterized by multiorgan injury.

It has been reported that the cytokine storm (54) and angiotensin-converting enzyme 2 (ACE-2) may be the potential mechanisms underlying the aforementioned pathological changes (5,55). The overactive immune responses of the host against the SARS-CoV-2-infection may lead to excessive and aggressive inflammatory responses, eventually leading to the release of a large amount of pro-inflammatory cytokines, a process referred to as cytokine storm (56). As regards the innate immune responses following virus infection, the pattern recognition receptor (PRR) recognizes the conserved molecular structures of the invading virus, namely the pathogen-associated molecular pattern (PAMP). The combination of PAMP and PRR triggers the activation of a variety of signaling pathways and transcription factors, which in turn induce the expression of several genes associated with the immune responses against viral infections, such as pro-inflammatory cytokines (56,57). Macrophages, dendritic cells, endothelial cells, natural killer cells and T and B lymphocytes are the main immune cell subtypes responsible for the secretion of cytokines. In addition, interleukin (IL)-1, IL-6, chemokines and tumor necrosis factor-α (TNF-α) are mainly involved in the inflammatory responses (58). The normal and adequate release of cytokines is necessary for the human body to be able to resist against various pathogens. In patients with COVID-19, the balance of the secreted cytokines is disrupted. Therefore, the increased secretion of cytokines within a short period of time may cause damage to tissue endothelial cells, blood vessels and alveoli and, may eventually, lead to organ failure (15,56).

ACE-2 is expressed on bronchial and alveolar epithelial cells, and it is also widely distributed in the gastrointestinal tract, brain, heart and other organs (59). Recent studies have demonstrated that both SARS-CoV-2 and SARS-CoV have ACE-2 cell invasion receptors (5,11); therefore, it is likely to cause acute lung injury by binding to the ACE-2 like SARS-CoV. The S-protein of the coronavirus contains two functional units, namely S1 and S2. S1 contains the RBD, which directly binds to the coronavirus host receptor ACE-2. S2 is responsible for the fusion of the virus with the host cell membrane. When S1 binds to the host ACE-2 receptor, the cleavage site of S2 is exposed, producing lytic host protease (60). The expression of ACE-2 is downregulated in SARS-CoV-2-infected cells (59). ACE-2 is a known peptidase that regulates the renin-angiotensin-aldosterone system, thereby controlling blood pressure. It has been reported that hypertension and cardiovascular diseases are the most common complications of COVID-19 (61).

5. Clinical symptoms and treatment

According to the current epidemiological data, SARS-CoV-2 is mainly transmitted through respiratory droplets and close human contact. Increased amounts of aerosols and human excreta are also considered as potential routes of transmission. The incubation period of COVID-19 is estimated to be 1-14 days, with an average of 3-7 days (15). Furthermore, infected patients are primarily characterized by symptoms of the upper respiratory tract, such as fever (highest incidence), cough and runny nose. In addition, diarrhea and nervous system abnormalities are often observed (62,63). Therefore, individuals with the aforementioned symptoms residing in areas with a high incidence of viral pneumonia are considered as high-risk individuals. The majority of adults or children infected with SARS-CoV-2 develop mild flu-like symptoms, while a small number of patients, particularly those with cardiovascular diseases and diabetes, are prone to rapid acute respiratory distress syndrome, respiratory failure, multiple organ failure, or even death (64).

COVID-19 is a severe infectious disease, and active isolation measures are a prerequisite for all types of treatment. Therefore, the interruption of the transmission route, the protection of susceptible individuals and the active isolation of the virus carriers are crucial. At present, numerous countries worldwide, including China as well as countries first affected by the pandemic, are adopting strict quarantine measures, including the imposition of short-term lockdowns. Patients diagnosed with COVID-19 are treated individually or collectively. Patients with COVID-19 are most commonly treated with the timely inhalation of effective hydrogen-oxygen mixture and antiviral therapy (65). Body temperature and oxygen saturation should be recorded regularly. In patients with severe COVID-19 infection, invasive mechanical ventilation or extracorporeal membrane oxygenation may also be applied (66). In addition, treatment with plasma isolated from recovered patients is also considered an effective treatment approach (67). Among conventional drugs, antiviral agents, such as oseltamivir and acyclovir, and systemic glucocorticoids, such as methylprednisolone, have been also used in the treatment of patients with COVID-19. However, their effectiveness is questionable (68). Chloroquine/hydroxychloroquine, two antimalarial agents, can alter the pH of cells and are stored in lysosomes in a protonated form. It has been reported that these compounds weaken the ability of the virus to release its genetic material into the cell and replicate (69,70). Studies have demonstrated that the combination of chloroquine/hydroxychloroquine,

remdesivir and azithromycin has shown great promise in the treatment of COVID-19 (71,72). Another study revealed that the viral load was significantly reduced in patients treated with lopinavir and ritonavir (73). Based on the mechanism through which ACE2 mediates the invasion of the human body by SARS-CoV-2, captopril is considered an inhibitor of ACE2, which acts by attenuating the inflammatory reactions in severely ill patients (72). The immunopathology of COVID-19 is characterized by lymphopenia and lymphocyte dysfunction (74). In response to the immune characteristics of COVID-19, some researchers have proposed several immunotherapeutic strategies, such as enhancing the activity of lymphocytes or inhibiting inflammation. NK cell-based therapies and immunomodulators are used to enhance the activity of lymphocytes. To suppress inflammation, mesenchymal stem cell-based therapies, regulatory T-cell-based therapies and other strategies may be used (75).

The S protein on the surface of the coronavirus binds to the target protein that invades the surface of the receptor, thereby mediating the release of the viral genome into the host cell for replication (60). Therefore, S protein has been used as an immunogen for the development of antibodies (76). Compared with small-molecule drugs, monoclonal antibodies are relatively costly and more difficult to produce. However, they differ from other drugs, since they can engage the host immune system through the binding of their constant domains to the Fc gamma receptors on host immune cells. Antibodies are key components of most vaccines and will likely prove crucial for the development of an effective vaccine against SARS-CoV-2. It has been reported that vaccines that selectively induce the production of antibodies targeting the RBD of SARS-CoV-2 may be particularly effective (25). Currently, >100 vaccines against COVID-19 are under research, including traditional live attenuated viral vaccines, inactivated viral vaccines, vector-based vaccines, as well as a new generation of safer recombinant-protein vaccines (77). Unfortunately, none of these has been approved for large-scale clinical application.

An important feature in the landscape of vaccine research and development for SARS-COV-2 is represented by the varied range of evaluated technological platforms, including nucleic acids (DNA and RNA), virus-like particles, peptides, viral vector (replicative and non-replicative), recombinant proteins, live attenuated viruses and inactivated viruses (78), potential vaccines must also pass the same clinical trial phase. This is especially important when it comes to safety issues, even during a pandemic.

6. Summary

SARS that erupted 17 years ago posed a threat to human health, and the current spread of COVID-19 has again brought feelings of fear. With the continuous research of scholars worldwide, a basic understanding of the transmission mode, pathological characteristics and potential pathogenesis of COVID-19 has now been acquired. Methods have also been developed to rapidly identify the virus, and various treatment measures have been systematically evaluated. This has strengthened the confidence of researchers and has provided hope that COVID-19 will be defeated. At present, some countries, including China, the United States, and the United Kingdom have increased the speed of vaccine research through open green channels, and some vaccines that have undergone clinical trials are beginning to be administered. However, judging by the current global pandemic trend, the threat of SARS-CoV-2 infection may continue for a long time to come.

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JL designed the theme of the present review. YS, XS, HH and YL retrieved the relevant literature. XS wrote and reviewed the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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