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An update on the status of COVID-19: a comprehensive review

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Abstract. **The last two decades have witnessed two large-scale pandemics caused by coronaviruses, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). At the end of 2019, another novel coronavirus, designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hit Wuhan, a city in the center of China, and subsequently spread rapidly to the whole world. Latest reports revealed that more than 800 thousand people in over 200 countries are involved in the epidemic disease by SARS-CoV-2. Due to the high mortality rate and the lack of optimum therapeutics, it is crucial to understand the biological characteristics of the virus and its possible pathogenesis to respond to the SARS-CoV-2. Rapid diagnostics and effective therapeutics are also important interventions for the management of infection control. However, the rapid evolution of SARS-CoV-2 exerted tremendous challenges on its diagnostics and therapeutics. Therefore, there is an urgent need to summarize the existing research results to guide decision-making on the prioritization of resources for research and development. In this review, we focus on our current understanding of epidemiology, pathogenesis, diagnostics and therapeutics of coronavirus disease 2019 (COVID-19).**

Key Words:
COVID-19, Epidemiology, Pathogenesis, Diagnostics, Therapeutics.

Introduction

Coronaviruses that infect humans are single positive stranded RNA virus (26–32 kb) and are genetically classified into four major genera: alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus[1,2]. Based on the aggressiveness, six known human coronaviruses were divided into highly and low invasive subgroup. The coronaviruses with low aggressiveness comprise HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1, which mainly caused upper respiratory tract infections and mild respiratory illnesses[3-5]. In comparison, the coronaviruses with high invasion ability, including severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), predominantly infect lower airways and cause life-threatening pneumonia[6,7].

In the late of December 2019, a series of unidentified pneumonia disease outbreaks were found in Wuhan, China[8-10]. The full-length genome sequences of potential pathogens obtained from patients revealed that above 99.9% sequence was shared with each other[11,12], and the analysis based on the phylogenetic tree indicated the pathogen is another novel coronavirus[13] (severe acute respiratory syndrome Coronavirus 2, SARS-CoV-2). Due to the accumulating evidence pointing to continuous person-to-person transmission[14-17], the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a public health emergency of international concern on February 5, 2020. As of March 31, 2020, the pandemic has resulted in 42,412 deaths among over 80 thousand patients in 200 countries, with a case-fatality rate of 4.9%.

Though there are still no specific drugs or vaccine available against SARS-CoV-2, the past three months have witnessed our tremendous progress toward unraveling the epidemiology, pathogenesis, diagnostics and therapeutics of COVID-19. In this review, we timely summarized the existing research results and compared the difference between SARS-CoV-2 and SARS-CoV/MERS-CoV in biological characteristics.

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Epidemiology

Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 is characterized by continuous human-to-human transmission and general susceptibility to human[14-18]. The comparative data on the epidemiology of the three coronaviruses were shown in Table I. Up to March 31, 2020, the outbreak of SARS-CoV-2 has grown substantially to infect 82,631 people in China with 3321 deaths and to infect 778,172 people in 200 other countries with 39,091 deaths. Though the case-fatality rate of 4.9% for SARS-CoV-2 is significantly lower than that 10% for SARS-CoV and 40% for MERS-CoV, it is estimated that the transmissibility of SARS-CoV-2 (R0: 2.2-3.6)[19,20] may exceed both SARS-CoV (R0: 2-4)[21,22] and MERS-CoV (R0: <1)[23]. The majority of cases and deaths occurred in China at early stage of the outbreak, but the number of newly confirmed cases has decreased significantly and fluctuated within 50 cases since March 7, 2020. In comparison, there is a significant increase outside of China, especially in USA, Italy, Spain, Germany, France and Iran after mid-February, 2020.

The typical and initial clinical symptoms of patients with Coronavirus Disease 2019 (COVID-19) are fever (87.9%) and cough (67.7%), whereas approximately 15% of patients also complained of gastrointestinal disorders, such as diarrhea, nausea and vomiting[8,10,26]. Furthermore, accumulating evidence[29-32] confirmed that stool specimens from confirmed patients with COVID-19 tested positive to SARS-CoV-2. These findings indicated that SARS-CoV-2 not only travels through respiratory tract, but may spread by fecal-oral routes. In addition, there are also some reports about recovered patients with following-up positive RT-PCR test results[33] and transmission from asymptomatic carriers[16,34], which indicated that identifying and managing suspected cases at early stage and following up discharged patients at late stage is another key for disease and outbreak management.

The results of whole-genome sequencing demonstrated that SARS-CoV-2 share 88% sequence identity with SARS-like bat coronavirus bat-SL-CoVZC45 and bat-SL-CoVZXC21, and 96% with bat coronavirus RaTG13[11,12]. Besides, another coronavirus from Malayan pangolins possessed over 90% sequence identity with SARS-CoV-2 at amino acid level, and the receptor-binding domain (RBD) of their S protein has only one amino acid difference[35,36]. Due to the lack of bats on sale in the origin of the epidemic, Huanan Seafood Wholesale Market, it is estimated that bats and pangolins may act as the possible natural reservoirs and intermediary hosts of SARS-CoV-2, respectively. Population genetic analyses of the whole genomes of 103 samples indicated that

Table I. Epidemiology and pathogenesis of SARS-CoV, MERS-CoV, and SARS-CoV-2.

	SARS-CoV	MERS-CoV	SARS-CoV-2
Clinical epidemiology			
Affected countries	29	27	More than 200
Affected people	8098	2254	More than 800 thousand
Mortality	More than 10%	More than 35%	More than 4%
Mean incubation period	4.6 days[24]	5.2 days[25]	3.0 days[26]
Basic reproduction number	2.0-4.0[12]	<1[23]	2.2-3.6[20]
Transmission routes	Droplet transmission; Close contact;	Droplet transmission; Close contact; Potential fecal-oral routes	Droplet transmission; Close contact; Potential fecal-oral routes
Transmission patterns	From animal to human From human to human	From animal to human From human to human	From animal to human From human to human
Possible natural reservoir	Bat	Bat	Bat
Possible intermediary host	Palm civet	Dromedary camel[27]	Malayan pangolin
Predominant receptor	ACE2	DPP4[28]	ACE2
Receptor distribution	Respiratory tract epithelium; monocytes and macrophages; vascular endothelium; arterial smooth muscle; small intestine	Respiratory tract epithelium; kidney; small intestine; liver and prostate; activated leukocytes	Respiratory tract epithelium; gastrointestinal epithelium; renal tubular and testicular cells; pancreatic cells; oral mucosa
Principal affected organs	Lung and immune organ	Lung and kidney	Lung and digestive system

SARS-CoV-2 has evolved into two major types (70% L type and 30% S type). The number of L type with stronger aggressiveness had started to fall after early January, 2020[37]. Though human intervention imposed severe selective pressure on the evolution of SARS-CoV-2, a larger set of data is needed to have a better understanding of its epidemiology.

Pathogenesis

Similar with other coronaviruses, SARS-CoV-2 is a single positive-stranded RNA virus that encodes 27 proteins, including 15 non-structural proteins (NSP, NSP1-10 and NSP12-16), eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b and orf14) and four major structural proteins (spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins) (Figure 1)[11-13]. Among the four structural proteins, spike protein plays a vital functional role in receptor-binding and subsequent viral entry into host cells[38]. The findings of SARS-CoV-2 sharing 79.5% amino acid identity with SARS-CoV indicated that they might have some common pathogenesis (as shown in Table I)[11,12]. The RBD in SARS-CoV-2 that directly interacted with human receptor angiotensin converting enzyme II (ACE2) protein is almost identical to that in SARS-CoV[11]. The latest experiment from Yan et al[39] also revealed that SARS-CoV-2 can enter into cells expressing ACE2, but not into cells without ACE2 or other coronavirus receptors. These results indicated that SARS-CoV-2 enters and replicates in target cells by its spike proteins binding to ACE2, then releases from host cells and infects new target cells. Spike protein of SARS-CoV-2 has a higher affinity with ACE2 than SARS-CoV[40], and SARS-CoV-2 infection can significantly upregulate the expression of ACE2 in host cells[41], which may partly explain the high transmission and aggressiveness of SARS-CoV-2.

Single cell transcriptome analysis showed that ACE2 was not only highly expressed in the epithelial cells of alveoli, but also in renal tubular and testicular cells, pancreatic cells, oral mucosa and absorptive enterocytes from ileum and colon[42-46]. The autopsy report of COVID-19 cases revealed that SARS-CoV-2 mainly resulted in inflammatory reaction of lower airways and alveolar injury[47,48]. In addition, positive RT-PCR results of anal swabs and the presence of alimentary symptom supported that digestive system may be another target of SARS-CoV-2[30-32]. However, there is still no direct evidence of the damage of SARS-CoV-2 to kidney, testis, pancreas and central nervous system.

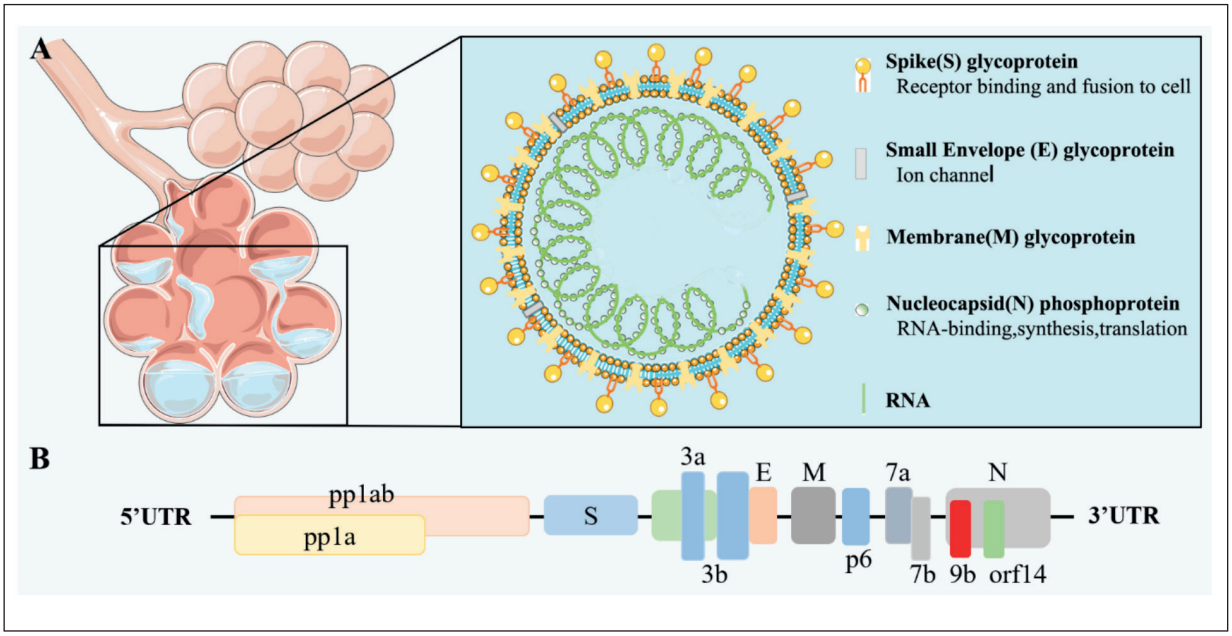

Figure 1. Coronavirus schematic diagram and genome composition. **A,** The schematic diagram of SARS-CoV-2 obtained from bronchoalveolar lavage fluids. **B,** the schematic diagram of the genome.

Table II. The comparison of NGS kits, RT-PCR kits and immunology kits.

Advantages	Disadvantages	
NGS kits	1) high sensitivity and specificity; 2) Monitoring virus evolution	1) high cost; 2) long testing cycle (2-3 days); 3) unavailable facilities in most healthcare institutions
RT-PCR kits	1) shorter turnaround time (2-3 hours); 2) lower cost; 3) high specificity	1) high false negative rates; 2) medical staff have a high risk of exposure to SARS-CoV-2 when taking swab samples
Immunology Kits	1) generate results within only 15 minutes 2) high sensitivity and specificity	1) there may be cross-reactivity with SARS-CoV; 2) need to collect paired serum samples to eliminate potential cross-reactivity from non-specific antibodies

Diagnosis

Highly sensitive and specific laboratory diagnostics for COVID-19 are essential for case identification and infection control. Currently, there are three broad categories of commercially available laboratory detection kits, including next-generation genome sequencing (NGS), reverse transcription-polymerase chain reaction (RT-PCR) and immunology kits (as shown in Table II). As the rapid development of NGS technology, it is possible for patients with low viral load to be diagnosed at early stage[12,49]. However, the use of NGS for establishing rapid diagnosis is not practical due to high cost, long testing cycle and unavailable facilities in most healthcare institutions. The results of whole-genome sequencing exerted considerable influence on the development of specific primers targeting RNA-dependent RNA polymerase, envelope and nucleocapsid genes[12,50,51]. Therefore, due to its shorter turnaround time and lower cost, RT-PCR test for specific gene has become the standard diagnostic method for patients infected COVID-19. Nevertheless, RT-PCR kits also have their own limitation. First, many factors in the process of sample collection and analysis could result in high false negative rates of the kits, such as non-standard sampling and RNA extraction, delayed sample delivering, and low viral load[52]. Second, it will take about 2-3 hours to generate results, which could not meet the requirements for rapid screening of suspected populations[53]. Third, medical staff have a high risk of exposure to SARS-CoV-2 when taking swab samples. To remedy the limitations of RT-PCR kits, another kind of testing kits for detection of IgM and IgG against SARS-CoV-2 within 15 minutes, with high sensitivity (88.66%) and specificity (90.63%), has been developed and is being validated in Chinese Centers for Disease Control (CDC) agencies[54]. However, the key limitations of serological testing are required to collect paired serum samples in the acute and convalescent phases to eliminate potential cross-reactivity from non-specific antibodies from past exposure or infection by other coronaviruses.

In addition, Clinical diagnostic criteria of COVID-19 based on clinical manifestation, laboratory findings and chest imaging examination, and response to antibiotics treatment, was recommended in hyper-infection areas, especially when laboratory testing kits are in short supply. These criteria were adopted to ensure timely treatment and isolation measures. It was reported that computed tomography (CT) positive changes have been observed in asymptomatic patients and some patients with initial negative RT-PCR results[55-58]. Therefore, repeated swab in combination with other findings (such as body temperature rising, lymphocytes and white blood cells decreasing, and CT changes) may play an important role in differentiating the patients from those with high clinical suspicion but negative RT-PCR screening.

Therapeutics

The treatment of COVID-19 is a major challenge for medical staff because there is no consensus on the optimal therapy. The evidence-based supportive care supplemented by diverse combinations of drugs is the mainstay for the management of COVID-19. In this section, we mainly summarized the clinical application of non-steroid anti-inflammatory drugs (such as corticosteroids) and antiviral agents.

Corticosteroids were widely used in confirmed patients at the initial stage of SARS-CoV-2 outbreak, but current guidance from WHO advises against the use of corticosteroids for COVID-19[59]. Russell et al[60] explained that corticosteroids might

not only prevent pulmonary progressive fibrosis and inhibit inflammatory storm, but also inhibit immune responses and subsequent pathogen clearance. Besides, lessons from managing SARS-CoV and MERS-CoV prevalence revealed that corticosteroids application is significantly correlated with adverse outcomes, including higher plasma viral load, psychosis and viremia[61,62]. However, some randomized clinical trials demonstrated that corticosteroids at low-to-moderate dose were found to reduce the duration of exiting from ICU and mechanical ventilation for critically ill patients[63]. Therefore, the guidance from Peking Union Medical College Hospital recommended systematic corticosteroids treatment (methylprednisolone, <1-2 mg/kg.d, 3-5 days) as adjuvant therapy for individuals with rapid progression of pneumonia[64]. However, the use of corticosteroids for COVID-19 remains controversial at present, prospective randomized controlled studies are required to validate its clinical effects on COVID-19.

Specific agents of proven efficacy against SARS-CoV-2 are still being developed. Currently, there are three broad categories of antiviral agents, including immunoenhancer, spike protein-ACE2 blocker, and broad-spectrum antiviral drugs. Interferon (IFN) has been approved to have significant effects on antivirus and immunoregulation. IFN-α and IFN-β could inhibit the replication of animal and human coronaviruses[65,66], but IFN-γ did not possess antiviral activity[67]. Furthermore, IFN-α in combination with corticosteroids was reported to improve oxygenation and faster resolution of chest radiograph abnormalities[68]. Since ACE2 is the sole receptor for spike protein of SARS-CoV-2, blocking spike protein binding to ACE2 is a key target for antivirals. Human monoclonal antibodies elicited by active or passive immunization using vaccines or convalescent plasma, is a promising blocker[69]. Though convalescent plasma is significantly associated with improved mortality, the bulk of factors limited its wide use, including the potential contamination of plasma and limited eligible donors[70,71]. Vaccines may play an important role in protecting against infection when exposed to the specific pathogen of interest, whereas there are still no commercial vaccines available against SARS-CoV-2[72]. Chloroquine as a known antimalarial drug was also found to be a potent inhibitor of SARS-CoV through interfering with ACE2[73]. A latest trial also demonstrated that chloroquine at low-micromolar concentration could block SARS-CoV-2 infection and was significantly correlated with improved clinical outcomes and shorten hospital stay[74]. As a known inhibitor of HIV cytochrome P450, the combination of lopinavir with ritonavir was found to be associated with better outcomes of COVID-19[75,76]. Moreover, the triple combination therapy of LPV/RTV, ribavirin and IFNα was recommended as an option at early stage of the disease[77].

In addition, the limited but emerging evidence regarding expanded umbilical cord mesenchymal stem cells in managing COVID-19 suggested that it might be considered for compassionate use in critically ill patients to reduce morbidity and mortality in the United States[78]. Hypertension is one of the most frequent complications in patients with COVID-19[26,79,80]. Anti-hypertensive drugs (such as ACE2 inhibitors and angiotensin II receptor blockers) could increase the expression of ACE2 in some cells (particularly alveoli)[81,82], which may raise the risk of infection with SARS-CoV-2. However, scientific foundation of this theory is very weak to date[83]. Besides, the abrupt drop-out of anti-hypertensive treatment could be associated with serious risks such as acute myocardial infarction and death from cardiovascular causes[84]. Therefore, the correlation between COVID-19 and hypertension need to be investigated further.

Conclusions

Understanding the epidemiology, potential pathogenesis, rapid diagnostics and effective therapeutics is crucial to SARS-CoV-2 surveillance and control. Although tremendous progress has been achieved, the continuous evolution of this RNA virus may exert new challenges on the diagnosis and treatment of COVID-19. Therefore, a larger set of prospective randomized controlled trials and basic researches is required to have a better understanding of COVID-19.

Due to the rapidly evolving situation of the SARS-CoV-2, this study's limitations deserve commentary. First, there might be some bias and errors in epidemiological data as a result of many social and personal factors. Second, a proportion of evidence in our review from preprints in medRxiv and bioRxiv have not been peer reviewed. As a result, the reliability of the content in these studies needs to be further validated. Third, quality assessment and meta-analysis is not feasible due to the limited data and heterogeneous style of the recruited studies. However, our comprehensive review may provide references for follow-up studies.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Availability of Data and Material

The raw data containing epidemiological data were obtained from WHO website (https://www.who.int/zh/emergencies/diseases/novel-coronavirus-2019).

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Authors' contributions

ZN, ZZL, and SXG conceived and designed the study. ZN, WL, ZXD, HSB, SY and BHJ consulted literature and collected data. ZN wrote the paper. ZZL and SXG reviewed and edited the manuscript. All authors read and approved the manuscript.

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Conflict of Interests

The authors declared that they have no conflict of interests.

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