COVID-19 in China: From epidemiology to treatment (Review)

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Abstract. Coronavirus disease 2019 (COVID-19) is a newly emerging infectious disease caused by the novel coronavirus SARS-CoV-2. It first became prevalent in Wuhan, Hubei, China in December 2019. COVID-19 was initially characterized by pneumonia of unknown etiology, accompanied by fever, dry cough and fatigue. Due to its highly infectious nature it rapidly led to widespread human infection, causing 80,924 confirmed cases and 3,140 mortalities in mainland China as of March 9, 2020. The present review highlights the prevalence of COVID-19 in China, the etiology, pathology, clinical presentation, laboratory and chest imaging tests, and treatment of this disease.

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1. Introduction

From December 29, 2019, when cluster cases of pneumonia with unknown etiology (PUE) were first reported in Wuhan, the capital of Hubei, China, the disease spread rapidly across the city (1). On January 3, 2019, researchers at the National Institute for Viral Disease Control and Prevention (Beijing, China) combined the use of Sanger sequencing, Illumina sequencing and nanopore sequencing on bronchoalveolar lavage (BAL) fluid samples from a patient with PUE from Wuhan to analyze the pathogen genome (2). A new β genus coronavirus was identified for the first time and named 2019 novel coronavirus (2019-nCoV) (3). On February 11, 2020, the international committee on taxonomy of viruses designated this novel discovery as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4). On the same day, the World Health Organization (WHO) coined the name 'COVID-19,' meaning coronavirus disease 2019 (5). The present review highlights the epidemiology, etiology, pathobiology, clinical manifestations and treatment of COVID-19.

2. Epidemiology

The initial four cases of PUE, with clinical manifestations resembling viral pneumonia, were reported via the domestic PUE surveillance system (6) on December 29, 2020, in Wuhan, Hubei, China (1). At the end of December 2019, the number of reported cases escalated to ~27 (7). In late December 2019, several patient BAL samples were sent to sequencing companies for next-generation sequencing (NGS) analysis and the results suggested a type of coronavirus. On December 31, 2019, the China National Health Commission (NHC) sent a team of experts to Wuhan to perform the epidemiological investigation (8). The complete genome sequence of the novel coronavirus was determined by researchers from the Wuhan Institute of Virology, Chinese Academy of Sciences, China (3). On January 5, 2020, the virus was isolated, and further phylogenetic analysis of the sequencing data confirmed the novel coronavirus is a new β genus coronavirus (2,8). The first reported mortality from the virus occurred on January 9, 2020 (7). On January 11, 2020, a 69-year-old brain surgery patient who had no respiratory symptoms prior to surgery developed symptoms of fever and was confirmed to have novel

coronavirus pneumonia (NCP) (9). He subsequently infected one doctor and 13 nurses in Wuhan Union hospital, which was the first direct evidence of human-to-human transmission. On the same day, Professor Zhang Yongzhen's team from Fudan University in Shanghai first shared the sequence of the new coronavirus genome on the Virological (https://virological.org) and GenBank (https://www.ncbi.nlm.nih.gov) websites. As the reported number of cases from other provinces besides Hubei continued to rise, on January 23, 2020, Wuhan city was locked down by the local government to prevent the disease from spreading. At the end of January 2020, 11,821 patients were confirmed to be infected with COVID-19 worldwide, and there were 3,215 cases in Wuhan (10). The government renovated and built 86 designated hospitals and 16 mobile cabin hospitals and provided more than 60,000 beds to effectively facilitate the admission and treatment of several confirmed patients as soon as possible in Wuhan (11). In addition, the government focused research on detection reagents, and several nucleic acid detection reagents, such as the BGI Group 2019-nCOV Nucleic Acid Detection Kit, were approved for clinical application, which improved the screening of suspected cases. Since strict joint prevention and control measures were taken by the government, the outbreak of the disease was rapidly restrained. The chronological incidence of confirmed COVID-19 cases and COVID-19-associated mortalities are presented in Fig. 1A-D. As of March 9, 2020, 80,924 cases have been confirmed in mainland China, with 3,140 mortalities (10). A total of 84% of cases were in Hubei and Wuhan was the worst-hit area in Hubei (Fig. 2). The case fatality rate is 3.88% (3,140/80,924) worldwide, with 4.46% (3,024/67,760) in Hubei and 4.81% (2,404/49,965) in Wuhan (10).

3. Etiology

Early virus sequencing analysis of BAL samples from five patients demonstrated that the genomes among these isolates were almost identical, with 99.8-99.9% sequence identity (12). In another study, virus sequencing was performed on BAL and pharyngeal swab samples from nine patients, with 99.98% nucleotide identity (1). Further phylogenetic analysis of the virus indicated that it belonged to the β genus coronavirus (3). Its genome sequence was dissimilar to the middle east respiratory syndrome coronavirus (MERS-CoV), (51.8% identity) and SARS-CoV (79% identity) and was closely associated with the bat SARS-like coronavirus RaTG13 (96.2% identity) obtained from *Rhinolophus affinis* (3). Despite significant differences in genome sequences, the SARS-CoV-2 spike (S)-protein and SARS-CoV S-protein share an almost identical 3D structure in the receptor binding domain (RBD), suggesting that they have the same S-protein-angiotensin-converting enzyme 2 (ACE2) binding pathway (13). In addition, *in vitro* experiments have demonstrated that SARS-CoV-2 infects permissive cells via ACE2 on the cell membrane (3,14-17).

The mechanism of transfer of the virus from its natural hosts to other animals and humans remains unclear. With regards to the search for reservoir hosts, a study proposed that a species of snake may serve as the SARS-CoV-2 reservoir, based on sequence analysis and relative synonymous codon usage bias (18). An additional study suggested that pangolins were the probable animal source of SARS-CoV-2 (19). Although reservoir hosts are yet to be determined, these findings suggest the importance of harmonious coexistence between humans and wildlife. Recently, viral mutations during the epidemic have attracted interest. A study analyzed 103 SARS-CoV-2 genomes and demonstrated that these viruses evolved into two major types (L type and S type) (20). The S type is an ancestral and less aggressive type, which is less prevalent in Wuhan (Wuhan vs. the rest of the world, 3.7% vs. 38.4%) (20). Conversely, the L type has evolved from the S type, has a higher transmission rate compared with the S type and is highly prevalent in Wuhan (Wuhan vs. the rest of the world, 96.3 vs. 61.6%) (20). Analysis suggests that government intervention may have prevented the L type from spreading outwards (20). However, based on existing knowledge of coronaviruses, this new RNA virus may still mutate and recombine in the future, during which the virulence may be enhanced or weakened.

4. Pathogenesis

SARS-CoV-2 acts via ACE-2 on the surface of host cells (14-17). ACE-2 is predominantly expressed on type II alveolar cells in the lungs, and is also expressed in the heart, kidneys, endothelium and intestine (21). Following infection of ACE-2 expressing cells in the respiratory tract, including epithelial, alveolar epithelial and vascular endothelial cells and macrophages in the lungs, macrophages are activated by the pathogen-associated molecular patterns (PAMPs) derived from the virus and damage-associated molecular patterns (DAMPs), including ATP and DNA, which are generated following damage of the infected cells (22). Macrophage activation is generally considered a primary response to viral infection (23). Macrophages secrete interleukin (IL)-6 and IL-1β to recruit neutrophils and T lymphocytes into the lungs (23). In mild or moderate cases, recruited cells clear the infection, the immune response wanes and the patients recover. However, in severe or critical patients, a dysregulated immune response causes hyperinflammatory conditions and a cytokine storm (22).

The major immune characteristics in patients with severe COVID-19 are as follows:

i) hyperinflammatory conditions and cytokine storm. IL-6, secreted by monocytes, macrophages and dendritic cells (DCs) has been reported to be a key driver of inflammatory cytokine storms in patients with SARS-CoV or MERS-CoV (24,25). Elevated IL-6 serum levels have also been exhibited in patients with COVID-19 and are associated with acute respiratory distress syndrome (ARDS), respiratory failure and adverse clinical outcomes, including death (26). IL-6 has notable proinflammatory characteristics. It acts on lymphocytes via cis signaling to promote T helper 17 cell (Th17) and T follicular helper cell (Tfh) differentiation, enhances CD8⁺T cytotoxic activity, and promotes B-cell differentiation and proliferation (26). IL-6 also acts on vascular endothelial cells via trans signaling to induce vascular endothelial growth factor (VEGF) expression and decrease E-cadherin expression on endothelial cells, resulting in increased vascular permeability and leakage (26). It also induces monocyte chemoattractant protein-1 (MCP-1) and IL-8 expression, to recruit monocytes and neutrophils into diseased tissues (26). Granulocyte-macrophage
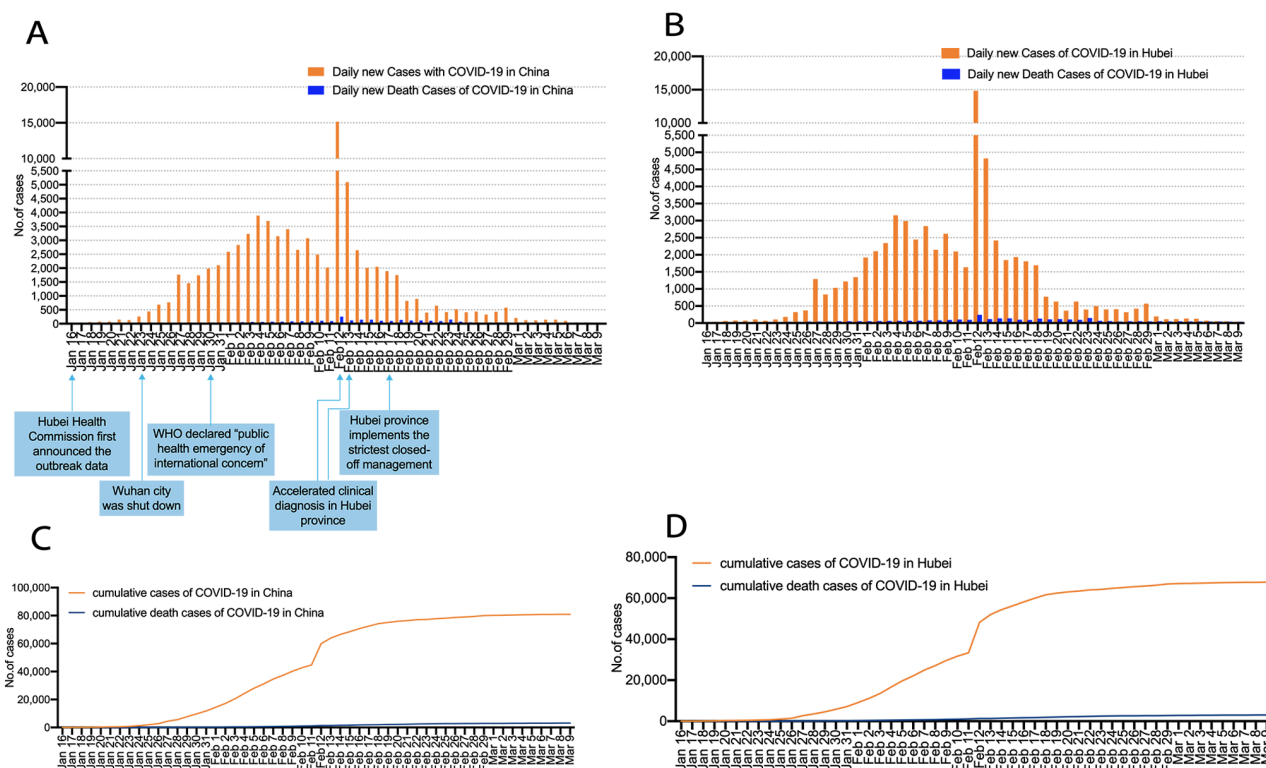
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Figure 1. Chronological incidence of confirmed COVID-19 cases and mortalities in mainland China and Hubei province 2020. Daily new cases and new death cases of COVID-19 in China (A). Daily new cases and new death cases of COVID-19 in Hubei province (B). Cumulative confirmed cases and death cases of COVID-19 by date in China (C). Cumulative confirmed cases and death cases of COVID-19 by date in Hubei province (D). On January 16, 2020, Hubei Health Commission first announced 45 confirmed cases of COVID-19 and 2 mortalities (10). As of March 9, 2020, China had reported 80,924 confirmed cases of COVID-19 and 3,140 mortalities (10).
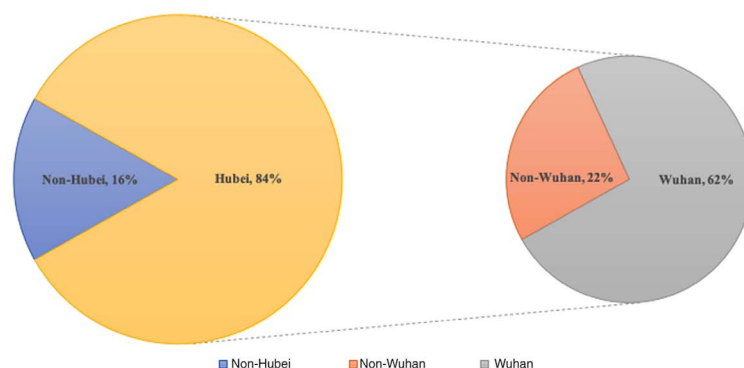

Figure 2. Geographical distribution of COVID-19 cases in mainland China. In mainland China, most cases were concentrated in Hubei province and Wuhan was the worst-hit city in Hubei (10).

colony-stimulating factor (GM-CSF) is another important cytokine in COVID-19 (27-29). CD4^{+}T lymphocytes activated by SARS-COV-2 become pathogenic T helper (Th) 1 cells and serve as a source of GM-CSF (27). GM-CSF activates mature myeloid cells to a proinflammatory phenotype, with enhanced cytokine and chemokine secretory capacity (28). Thus, GM-CSF is considered a primary communication conduit between inflammatory lymphocytes and myeloid cells (28). Patients with COVID-19 have been reported to have increased plasma concentrations of GM-CSF and increased percentages of GM-CSF-expressing leukocytes (29). Based on this, blocking the IL-6 or GM-CSF pathway is expected to decrease the severity of the cytokine storm in the lungs.

ii) Delayed and lowered type I interferon (IFN) response. Unlike the immune process of other respiratory viral infections, SARS-CoV-2 infection elicits delayed and lowered IFN-I and IFN-III responses, while inducing elevated chemokine expression (30,31). This delayed IFN secretion is not conducive to early disease control, and instead induces more chemokines and promotes systemic inflammation and lung injury (23). This suggests that different timing of IFN administration may lead to completely different clinical effects.

iii) T cell depletion and exhaustion. Lymphopenia is common in patients with COVID-19 (32). There is a significant decrease in CD4^{+}T cells in patients with COVID-19; however, the proportion of GM-CSF^{+} and IL-6^{+}T cells is

higher in these patients (27). CD8⁺T cells, B cells and natural killer (NK) cells are also drastically decreased in patients with severe cases of COVID-19 (33). In addition, exhaustion markers on CD8⁺T cells, such as TIM-3, PD-1 and NKG2A are upregulated in patients with COVID-19 (23,27,33), and lymphodepletion progresses in accordance with patient deterioration (22). Notably, an increase in lymphocytes tends to precede clinical recovery (34).

5. Pathology

On February 17, 2020, Dr Xu's team were the first to publish the lung pathology of biopsy specimens obtained from an elderly patient who had died of NCP (35). Subsequently, lung pathology from two patients with NCP who underwent lobectomy for lung tumors was also reported (36), which represented early lung pathology. The first lung autopsy pathology of a patient who had died of severe NCP was reported on February 27, 2020 (37). Combined with the pathological description in the COVID-19 guidelines in China (38), the pathological changes can be summarized as follows:

i) Lungs. On gross examination, the lungs exhibited diffuse congestion and hemorrhage, accompanied by partial hemorrhagic necrosis (37). On the cut surface, the bronchi were covered with mucus (38). Hemorrhage and necrosis were most common at the margin zone of the lungs (37).

Histopathological findings included pulmonary interstitial fibrosis, focal pulmonary hemorrhage and hemorrhagic infarction (37). Serous or fibromyxoid exudates and hyaline membranes were observed in the alveolar cavity, and the exudated cells were predominantly monocytes and macrophages (38-40). Prominent hyperplasia of type II pneumocytes was observed, and some type II pneumocytes desquamated (39,40). Inclusion bodies were also observed in type II pneumocytes and macrophages. Monocyte and lymphocyte infiltration were present in the alveolar septa and the alveolar capillaries were congested, accompanied by the formation of hyaline thrombus (38,39). Inflammatory cell infiltrations, including lymphocytes, plasma cells and monocytes, were exhibited in the pulmonary interstitium (39). Some of the epithelial cells in the bronchial mucosa were desquamated, and mucus plugs were observed in the lumen (38). Some alveoli were overinflated, and alveolar septa were ruptured or accompanied by cystic cavity formation. Coronavirus particles were seen in the cytoplasm of bronchial epithelial cells and type II pneumocytes under electron microscopy (10^5x magnification) (38,40). Immunohistochemical staining demonstrated that some alveolar epithelium cells and macrophages were positive for the novel coronavirus antigen (38,40).

ii) Spleen, lymph nodes and bone marrow. There was significant atrophy in the spleen (38). In the spleen, the number of lymphocytes decreased significantly, focal hemorrhage and necrosis were observed, along with macrophage proliferation and phagocytosis. In the lymph nodes, low levels of lymphocytes and necrosis were observed. Immunohistochemical staining demonstrated a decrease in CD4⁺T and CD8⁺T cells in the spleen and lymph nodes. Furthermore, the number of red blood cells, white blood cells and platelets decreased in the bone marrow.

iii) Heart and blood vessels. Degeneration and necrosis of the cardiomyocytes was present (38). Several monocytes, lymphocytes and neutrophils were observed in the stroma (38,40). Some vascular endothelial cells were desquamated, inflammation of the vascular intima was present and thrombosis was observed (37,38).

iv) Liver and gallbladder. The liver was enlarged and dark red (38). Hepatocyte degeneration and focal necrosis with neutrophil infiltration was observed (38,40). Hepatic sinus hyperemia, infiltration of lymphocytes and monocytes into the portal area, and microthrombi were present (38). The gallbladder was enlarged (38).

v) Kidneys. Proteinaceous exudate was observed in the urinary space (38). The tubular epithelial cells demonstrated degeneration and loss, and the tubular lumen contained hyaline casts. Interstitial hyperemia was exhibited, with microthrombi and focal fibrosis (38).

vi) Other organs. Focal necrosis was observed in the adrenal gland (38). The brain tissue exhibited hyperemia and edema (38). In addition, the epithelial cells of the esophagus, stomach and intestine exhibited degeneration, necrosis and desquamation at varying degrees (38).

6. Clinical characteristics

The incubation period was 1-14 days, most commonly 2-7 days (32). The most common symptoms included fever and coughing, and other symptoms included fatigue and sputum production (38,41). Several patients had symptoms that were accompanied by headache, sore throat, shortness of breath, myalgia, arthralgia and chills. In severe cases, dyspnea and/or hypoxemia usually occurred one week after onset of the disease, and in critical cases, acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulation dysfunction and multiple organ failure progressed rapidly (42). Notably, some severe and critical patients developed a low-grade fever or no obvious fever in the development of the disease (38). Younger patients (≤14 years old) may have atypical symptoms, such as vomiting, diarrhea and other gastrointestinal symptoms, or only presented a decreased mental state and shortness of breath (38). Patients with mild symptoms exhibited low-grade fever, slight fatigue and no pneumonia (38). According to the data from the Chinese Center for Disease Control and Prevention (CDC) (43), most patients had a good prognosis, whereas elderly patients with chronic underlying diseases had a poor prognosis. The clinical course of NCP in pregnant and parturient women was similar to that of other patients of the same age (38). In children, the disease was relatively mild (38).

According to a statistical analysis of 44,672 confirmed patients in mainland China by the Chinese CDC epidemiology team (43), 80.95% of the patients had mild disease symptoms, 13.81% were severe cases and 4.67% were critical (Fig. 3A). The age group with highest prevalence was 40-69 years (Fig. 3B). Statistical analysis demonstrated that fatality rate increased with age (Fig. 4). In addition, the case fatality rate was 0.9% in patients with no underlying disease, 6.0% in patients with hypertension, 7.3% in patients with diabetes, 10.5% in patients with other cardiovascular diseases, such as coronary heart disease, 6.3% in patients with underlying
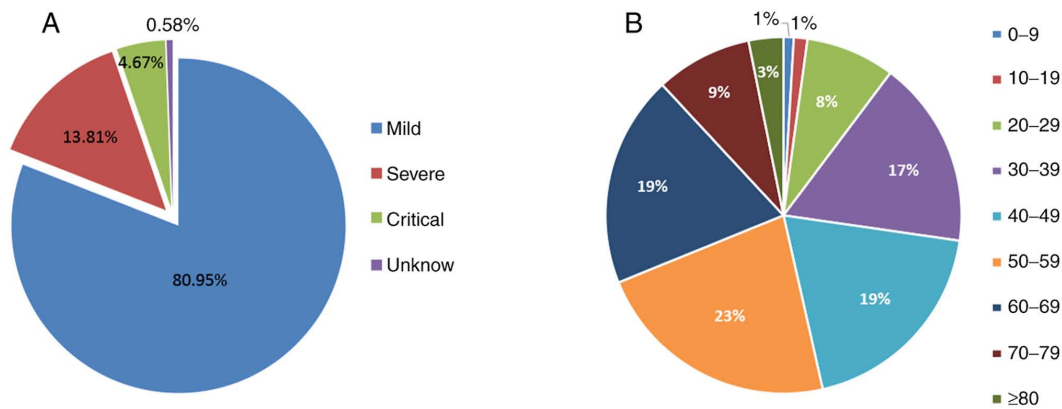
Figure 3. Diagnostic classification and age distribution of patients with COVID-19. (A) Disease diagnostic classification of 44,415 confirmed patients and (B) age distribution of 44,672 confirmed patients. Mild: The clinical symptoms are relatively mild, with no or mild manifestations of pneumonia on imaging. Severe: Any of the following; i) Respiratory distress, RR>20 times/min; ii) at rest, SPO2<93% and iii) the PaO_2/FiO_2<300 mmHg. Critical: Meeting one of the following conditions: i) Respiratory failure, requiring mechanical ventilation; ii) shock and iii) complications of other organ failure requiring ICU care. [Data source: ref. (10)].
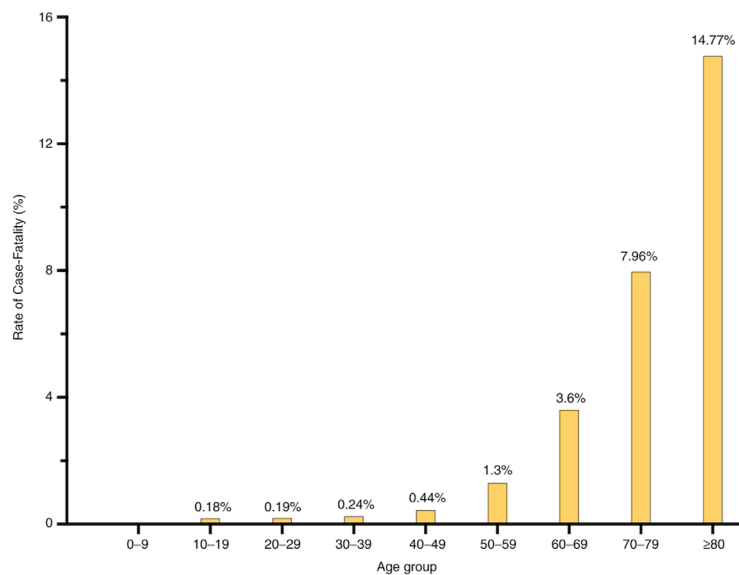

Figure 4. Case fatality rates of 44,672 confirmed cases by age group in mainland China [Data source: ref. (10)].

respiratory infections and 5.6% in patients with cancer (43). Analysis of this large sample data indicated that the case fatality rate was closely associated with patient age and whether there was any underlying disease.

7. Laboratory and chest imaging tests

According to the COVID-19 guidelines in China, reverse-transcription polymerase chain reaction (RT-PCR) detection and chest imaging examinations are considered the most important methods for screening and diagnosing patients with NCP (38). Pathogen related tests include qualitative detection of SARS-CoV-2 nucleic acids and screening of serum antiviral antibodies. By March 16, 2020, the China National Medical Products Administration had approved 11 SARS-CoV-2 nucleic acid detection reagents and eight antibody detection reagents (44). The methods used for PCR detection of SARS-CoV-2 nucleic acids included nucleic acid fluorescence

PCR and nucleic acid sequencing (44). Currently, approved reagents detect the novel gene segments of the coronavirus, including the open reading frame 1ab (ORF1ab), envelope protein (E) and nucleocapsid protein (N) coding region, and are classified as the single-target detection (ORF1ab), double-target detection (ORF1ab, N protein) and triple-target detection (ORF1ab, N protein and E protein). Viral nucleic acids can be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood and feces via PCR or sequencing analyses. Serum antibody screening can detect antiviral antibodies IgM and IgG. The techniques used by these kits include the immune colloidal gold technique, the magnetic particle-based chemiluminescence enzyme immunoassay and the chemiluminescent microparticle immunoassay (44). The IgM antibodies against SARS-CoV-2 in serum usually appear positive 3-5 days after the onset, which indicates a recent infection, whereas IgG antibodies indicate convalescence or a past infection (38).

The most common CT findings are ground-glass opacification (GGO) and bilateral consolidative opacities (45). In the early stage of the disease, the lung is characterized by single or multiple focal GGO and local patchy shadows with a peripheral distribution (46). In the progressive stage, multiple GGO, consolidative opacities, air bronchograms and interstitial abnormalities are observed in both lungs (46). In severe and critical cases, extensive consolidative opacities of both lungs are present (46). Pleural and pericardial effusion are less common. Although several cases of pulmonary inflammatory lesions begin in peripheral areas, these CT findings alone cannot easily distinguish them from other viral pneumonias (47).

The characteristics of other laboratory tests are summarized as follows (32): Blood routine examination indicates that the white cell count is normal or decreased, and lymphocytopenia ($<1,500/mm^3$) is present in most patients. The majority of patients have elevated levels of C-reactive protein (>10 mg/l) and procalcitonin (≥ 0.5 ng/ml), whereas aminotransferase and creatine kinase are less often observed (26). Plasma concentrations of inflammatory mediators and cytokines, such as IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α and VEGF are increased (29).

8. Treatment

Antiviral therapy
IFN-α. Effective antivirals and antiviral regimens are important for combating COVID-19. IFN-α has been extensively used in the treatment of viral infectious diseases (48). IFN, as an antiviral drug with an exact curative effect, is limited to the treatment of hepatitis B virus (HBV), hepatitis C virus (HCV), human herpes virus type 8 (HHV-8) and human papillomavirus infection (49). It is also used to treat other common viral infectious diseases, including the common cold (50), influenza (50), and mumps (51); however, the curative effects have not yet been proven in these diseases (50,52,53). As early as the SARS epidemic, two studies reported the therapeutic effect of IFN combined with glucocorticoids and/or ribavirin in patients with SARS (54,55). However, a subsequent systematic evaluation study revealed that there is no benefit from IIFN treatment due to the complexity of clinical intervention measures and lack of a suitable control group in the two studies (56). Although inhalation therapy with IFN-α is recommended by the NHC guidelines (57), and several patients with COVID-19 underwent treatment with IFN-α during hospitalization in China, the exact efficacy of interferon remains to be verified.

Lopinavir/ritonavir. Lopinavir/ritonavir (LPV/r), an anti-HIV drug was hypothesized to have effects on SARS and MERS (58), and was used in the treatment of patients with COVID-19 (57,59). However, a randomized, controlled, open label study from China demonstrated that LPV/r treatment of patients with severe COVID-19 did not significantly change the clinical outcome, including the mortality and oropharyngeal virus persistence time (60).

Remdesivir. Remdesivir is a broad-spectrum antiviral that has been reported to inhibit the replication of SARS-CoV and MERS-CoV *in vitro* (8,61-64), and has been successfully used to treat a US patient with NCP (65). A report of 53 patients with severe COVID-19 who were treated with compassionate-use remdesivir demonstrated improvement in the oxygen-support status of 36 patients (68%) (66). However, the results were limited by the lack of a control group and the small sample size. In China, a double-blind, randomized, placebo-controlled trial enrolling 237 patients with severe COVID-19 demonstrated no clinical improvement in patients treated with remdesivir (67). The trial was originally scheduled to include 453 patients with COVID-19 but failed to complete full enrollment due to the end of the outbreak in China. Recently, another double-blind, randomized, placebo-controlled study of remdesivir (Adaptive COVID-19 Treatment Trial 1, ACTT-1) in 1,059 hospitalized patients with COVID-19 suggested that a 10-day course of remdesivir was superior compared with placebo in shortening the time of recovery (median days, 11 vs. 15; $P<0.001$) (68). However, given the high mortality in both groups, the report indicated that monotherapy with an antiviral drug is not likely to be sufficient. Thus, combined therapeutic approaches are urgently required to further improve patient outcomes.

Favipiravir. Favipiravir is a nucleoside analogue against the RNA-dependent RNA polymerase of some viruses, including influenza A and B (69). It has also been used as post exposure prophylaxis and was evaluated in clinical trials for Ebola virus (70-72). An open-label control study from China assessed the efficacy and safety of favipiravir on 80 patients with mild or moderate COVID-19, whereby 35 patients were assigned to favipiravir and 45 were assigned to LPV/r. The results demonstrated that patients treated with favipiravir had a shorter viral clearance time ($P<0.001$) and better radiographic improvement ($P<0.01$) compared with patients treated with LPV/r (73). Furthermore, a lower rate of adverse events, such as nausea, was observed in the favipiravir group ($P<0.05$). These preliminary clinical findings require further research.

Chloroquine and hydroxychloroquine. Chloroquine is an antimalarial drug. Hydroxychloroquine is a superior analogue of chloroquine, which possesses a more tolerable safety profile (74). Both exert anti-inflammatory effects and are extensively used in the treatment of rheumatic diseases (74). Previous *in vitro* experiments have demonstrated that chloroquine inhibits the replication of SARS-CoV by interfering with the binding of SARS-CoV to the ACE2 receptor of the Vero E6 cell line (75). Recent *in vitro* studies further supported the efficacy of chloroquine and hydroxychloroquine in inhibiting MERS-CoV-2 (76-78). Based on its antiviral effect *in vitro* and previous wide clinical usage in patients with a safety track record, chloroquine has been recommended for the treatment of patients with COVID-19 in China (79). However, recent clinical data seem to less promising for both chloroquine and hydroxychloroquine in COVID-19 (80). An open label, randomized controlled trial from China (148 patients with mild to moderate COVID-19 and two patients with severe COVID-19) demonstrated that the probability of negative conversion of SARS-CoV-2 in the hydroxychloroquine group was 85.4% by 28 days, which was similar to 81.3% in the standard treatment group (81). There was also no significant difference between the two groups in the time to negative

RT-PCR test of SARS-CoV-2. A large observational study involving 1,376 patients with COVID-19, hospitalized in a medical center in New York, also demonstrated that hydroxychloroquine administration did not result in a significantly lowered or an increased risk of intubation or mortality (82). Another retrospective study analyzed the in-hospital mortality among 1,438 hospitalized patients with COVID-19 in New York who were treated with hydroxychloroquine, azithromycin, combined hydroxychloroquine and azithromycin, or neither drug. The results demonstrated that treatment with hydroxychloroquine, azithromycin, or both, did not show a significant difference in in-hospital mortality compared with neither treatment (83). In addition, hydroxychloroquine used as post exposure prophylaxis for COVID-19 did not seem to offer much hope either (84).

Anti-inflammatory drugs. Since SARS-CoV-2 can trigger hyper-inflammatory syndrome in the body (22), resulting in damage to multiple target organs, it is speculated that anti-inflammatory treatments may benefit critically ill patients. Anti-inflammatory drugs include glucocorticoids (GCS), such as dexamethasone and methylprednisolone, and non-steroidal anti-inflammatory drugs (NSAID), such as acetaminophen and ibuprofen. The use of GCS in COVID-19 pneumonia remains controversial (85-92). Early case analysis from China demonstrated that the rate of systemic GCS use was up to 18.6% in the total number of admitted patients with COVID-19, and was 44.5% in severe patients (32). Despite lack of evidence that the use of GCS in critically ill patients with COVID-19 does more good than harm, experience in dealing with SARS (93) and H1N1 (2009) (94) outbreaks has demonstrated that rational use of GCS in critically ill patients can decrease mortality and shorten hospital stays (86). Furthermore, a recent multicenter randomized controlled trial reported that dexamethasone treatment can decrease mechanical ventilation duration and overall mortality in patients with moderate-to-severe ARDS (95). Thus, the use of GCS in patients with COVID-19 cannot be generalized. The indiscriminate use of GCS will lead to secondary infection, prolonged virus shedding and disease progression (86). Thus, the Chinese expert group (86,96) recommended the following: i) The advantages and disadvantages of GCS should be fully assessed prior to the prudent use of GCS in critically ill patients with pneumonia; ii) the dosage should be low to medium (≤0.5-1 mg/kg per day methylprednisolone or equivalent) and iii) the duration of treatment should not exceed 7 days. Celecoxib and carprofen are NSAID drugs that were screened by computer-aided analysis, and were demonstrated to potentially exert anti-coronavirus effects (97). However, their exact efficacy requires verification via *in vivo* and *in vitro* experiments.

GM-CSF pathway inhibitors. Mavrilimumab is a humanized monoclonal antibody (mAb) (Ig4) targeting GM-CSF receptor α, which has demonstrated efficacy and safety in phase I and phase II clinical trials in rheumatoid arthritis (RA) (98). GM-CSF is secreted by fibroblasts, macrophages, dendritic cells, T cells, neutrophils, eosinophils and tumor cells (99). Analysis of serum cytokine levels in 41 patients with COVID-19 demonstrated that these patients had higher GM-CSF levels compared with healthy controls (29). De Luca *et al* (99) recently performed a prospective study on mavrilimumab in non-mechanically ventilated patients with COVID-19 pneumonia and systemic hyperinflammation. The results demonstrated that all 13 patients in the mavrilimumab treatment group exhibited clinical improvement compared with 17/26 patients (65%) in the control group, who received standard care (P=0.030), and treatment of mavrilimumab was well tolerated.

Lenzilumab is a recombinant humanized anti-GM-CSF mAb (100). The GM-CSF signaling to myeloid progenitor cells is blocked by lenzilumab through neutralization of GM-CSF, which prevents GM-CSF binding to the receptor (101). Lenzilumab has been implemented in clinical trials for patients with eosinophilic asthma, RA, chronic myelomonocytic leukemia and cytokine release syndrome associated with chimeric antigen receptor T (CAR-T) cell therapy (28). The clinical use of lenzilumab in 12 patients with severe or critical COVID-19 pneumonia demonstrated that lenzilumab may improve oxygenation and decrease serum levels of cytokines, such as IL-6, G-CSF, IL-1a and IL-12p70 (102). Gimsilumab, developed by Roivant Sciences, is another recombinant human anti-GM-CSF mAb (28). The phase I study on gimsilumab for ARDS in COVID-19 has been completed (results unpublished) and the phase II clinical trial is underway. Results from these clinical trials verified the association between GM-CSF and the overactivated immune response in severe and critical COVID-19 pneumonia (27). Thus, blocking the GM-CSF pathway is a potential treatment for severe COVID-19.

IL-6 inhibitors. Tocilizumab is a recombinant mAb against the IL-6 receptor (IL-6R) and has been approved for the treatment of RA and giant cell arteritis (103). IL-6 is the main inducer of the acute phase response (104) and is classified as an important infection-related marker (105-107). Due to high levels of IL-6 observed in severely ill patients, tocilizumab treatment in these patients may decrease lung damage (27). In a recent report, 21 patients with severe or critical COVID-19 were treated with tocilizumab and the clinical symptoms notably improved, with no significant adverse events observed (108). However, the study's credibility was limited by the lack of a control group. In China, tocilizumab has been recommended for the treatment of severe COVID-19 pneumonia with high IL-6 levels (38). As of September 11, 2020, there are currently 38 clinical trials involving tocilizumab for the treatment of COVID-19 registered at clinicaltrials.gov. Sarilumab is another humanized anti-IL-6R mAb approved for the treatment of RA (103). According to clinicaltrials.gov, eight clinical trials are underway to assess the safety and efficacy of sarilumab in the treatment of COVID-19.

Janus kinase (JAK) pathway inhibitors. Baricitinib, an approved drug for the treatment of RA, is a reversible inhibitor of the intracellular signaling molecule, JAK (109). Baricitinib inhibits the production of multiple cytokines by suppressing the JAK-signal transducer and activator of transcription (STAT) signaling pathway, thus producing anti-inflammatory effects (110). Another advantage of baricitinib is its *in vitro* anti-coronavirus activity (111-113), which is mediated by

suppressing endocytosis-associated enzymes adaptor-associated kinase-1 (AAK1) and cyclin G-associated kinase (GAK) (111). A recent open-label pilot study demonstrated that baricitinib may significantly improve clinical and laboratory parameters, including fever, SPO_2, Horowitz Index and CRP, in patients with moderate COVID-19 pneumonia (114). The ACTT-2 led by the US National Institute of Allergy and Infectious Diseases is recruiting to assess the effectiveness and safety of remdesivir and baricitinib in treating COVID-19 (115). The trial is based on ACTT-1 to determine whether JAK inhibitors can provide extra benefits to patients, including decreasing mortality (116).

Convalescent plasma therapy. Convalescent plasma is collected from patients who have recovered from COVID-19. In China, the time of blood donation should be at least 3 weeks after the onset of COVID-19 symptoms. Convalescent plasma contains virus-specific neutralizing antibodies, which can directly bind the virus and eliminate it via cellular cytotoxicity and phagocytosis (117). For those with coagulation disorders, plasma transfusion can also replenish coagulation factors (118). Thus, convalescent plasma transfusion may be beneficial to patients with severe COVID-19. Convalescent plasma has been used for treatment of viral infectious diseases, such as SARS, H5N1 avian influenza, Ebola hemorrhagic fever and MERS (119). It has also been used in patients with severe COVID-19. Some COVID-19 cases exhibited a clinical benefit, including improvement in oxygenation, the sequential organ failure assessment (SOFA) scores and other clinic status (120-123). However, a recent open-label randomized clinical trial of 103 patients with severe COVID-19 given convalescent plasma did not result in a significant improvement in time to clinical improvement within 28 days compared with standard treatment alone (124). There are currently more than 70 ongoing registered clinical trials globally assessing the efficacy of convalescence plasma in the treatment of COVID-19.

Vaccine. Given the persistence of the COVID-19 epidemic and the inaccessibility of specific drugs, vaccine research is of great significance for preventing further development and potential future epidemic peaks. An optimal vaccine for SARS-CoV-2 would elicit long-lasting antibody protective effects, an effective T-cell response, simultaneously avoid generating antibody-dependent enhancement (ADE) and a skewed Th2 immune response (125).

Currently, there are over 100 COVID-19 vaccines under development worldwide. According to the design strategy, these vaccines can be classified into four categories (126), as follows: i) virus vaccines; ii) nucleic-acid vaccines; iii) viral-vector vaccines; and iv) protein-based vaccines. The most common vaccines for SARS-COV-2 are protein-based and adenovirus vectored vaccines, and most of these vaccine trials are pre-clinical (126). The PiCoVacc and BBIBP-CorV inactivated virus vaccine candidates have exhibited effective protection against SARS-CoV-2 in animal experiments (127,128). Currently, there are eight registered clinical phase I or II vaccine trials worldwide, including Moderna's and BioNTech's mRNA COVID-19 vaccines, Inovio Pharmaceuticals' DNA vaccine, three inactivated COVID-19 vaccines manufactured by Sinovac (Wuhan and Beijing Institute of Biological Products), University of Oxford's non-replicating chimpanzee adenovirus vectored vaccine (also known as ChAdOx1 nCOV-19) and CanSino's non-replicating adenovirus type 5 vectored vaccine (Ad5-nCoV) (125,128). The phase I study of Ad5-nCoV has been completed, and the results demonstrated that Ad5-nCoV has good safety and can induce specific antibodies against the viral spike proteins and specific T cell responses to SARS-CoV-2 (128); however, it still requires verification in phase II clinical trials.

9. Conclusion

Since the COVID-19 outbreak in Wuhan, the Chinese government and Chinese people have made great efforts to control the development and spread of the epidemic. These controls include: Restricting and decreasing outdoor activities, home isolation, banning gatherings, introducing population screening and education, accelerating the admission and treatment of confirmed patients, accelerating the supply of medical necessities, strengthening the research and development of diagnostic reagents, and mobilizing all citizens to participate in the prevention and control of the epidemic.

Although the severity of the epidemic has greatly decreased, a significant amount of work remains. Future endeavors should aim to identify the origin of the coronavirus, clarify the pathogenesis of COVID-19, hasten the research and development of antiviral drugs and vaccines, and discuss how to establish a global prevention and control system for emerging infectious diseases.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

HC drafted the initial manuscript. SW and XZ revised the manuscript. All authors have read and approved the final 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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