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REVIEW

Pathogen evolution, prevention/control strategy and clinical features of COVID-19: experiences from China

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Abstract **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported at the end of 2019 as a worldwide health concern causing a pandemic of unusual viral pneumonia and many other organ damages, which was defined by the World Health Organization as coronavirus disease 2019 (COVID-19). The pandemic is considered a significant threat to global public health till now. In this review, we have summarized the lessons learnt during the emergence and spread of SARS-CoV-2, including its prototype and variants. The overall clinical features of variants of concern (VOC), heterogeneity in the clinical manifestations, radiology and pathology of COVID-19 patients are also discussed, along with advances in therapeutic agents.**

Keywords coronavirus disease 2019; SARS-CoV-2; epidemiology; clinical features

Introduction

In recent 20 years, two highly pathogenic coronaviruses of zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory illnesses, highlighting the emergence of coronaviruses as a new public health concern [1]. In late 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported, causing an outbreak of unusual viral pneumonia, also known as coronavirus disease 2019 (COVID-19) [2,3]. With its high transmissibility, this novel coronavirus infection rapidly spread worldwide, surpassing SARS and MERS in both the number of infected individuals and the geographic extent of the epidemic [4]. The COVID-19 pandemic has resulted in over 765 million cases and 6.9 million deaths globally as of May 10, 2023 [5], which presents a major threat to global public health.

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Pathogen evolution—emergence and spread: from prototype to Omicron variants

In late December of 2019, several health facilities reported clusters of patients with pneumonia of unknown cause in the city of Wuhan [6]. According to a retrospective study, the onset of the first known case in Wuhan dated back to December 8, 2019. On January 30, 2020, the World Health Organization (WHO) declared the novel coronavirus outbreak a public health emergency of international concern. On February 11, 2020, the International Committee on Taxonomy of Viruses named the novel coronavirus "SARS-CoV-2," and the WHO named the disease "COVID-19." In general, we named this original SARS-CoV-2 strain as "wild-type (WT)" or prototype. On March 11, 2020, the WHO officially declared the COVID-19 outbreak as a pandemic. Within a duration of 210 days (30 weeks), this WT SARS-CoV-2 strain had caused 21 294 845 laboratory-confirmed cases and over 761 779 deaths throughout the world and the fatalities continue to increase as of August 16, 2020 [5,7]. The basic reproduction number (R0) of an infectious disease can be estimated by observation of infection chains, clusters of infection or by spread in a population. The consensus estimate for R0 for SARS-CoV-2 WT

strain stands at between 2.2 to 3.77 (range, 1.7–14.8) at that time [8,9]. According to the COVID-19 dashboard of the Center for System Science and Engineering at Johns Hopkins University, as of August 11, 2020, over 20 million COVID-19 cases have been reported in 216 countries and regions across all six continents, with over 733 000 patients losing their lives. High mortality was observed especially when healthcare resources were overwhelmed [10–12].

In September 2020, a new lineage of SARS-CoV-2, classified as VOC Alpha (Pango lineage B.1.1.7) by the WHO, was found to be rapidly spreading in areas of the UK [13]. This lineage carried 10 amino acid mutations in the spike region of the SARS-CoV-2. Researchers estimated the epidemic growth rates of Alpha in England. Phylodynamic modeling of the effective population sizes for both the Alpha and non-VOC Alpha lineages, and suggested a weekly growth rate difference of 0.33 (95% confidence interval (CI), 0.09–0.62). As a result, they estimated that the Alpha lineage reached a 50% frequency within 2.5 to 3 months after its initial emergence in England [13,14]. As of January 7, 2021, 45 countries had reported the presence of Alpha [15,16].

Followed by Alpha, two more rapidly growing lineages were identified in South Africa and Brazil: VOCs Beta (Pango lineage B.1.351) [17] and Gamma (Pango lineage P.1) [18], respectively. These lineages featured a high number of genetic differences compared to the background viruses and some displayed enhanced transmissibility and immune escape properties. There are 18 amino acid mutations in the Beta variant, 7 of which are in the Spike protein. Similarly, the Gamma variant has 21 amino acid mutations, 12 of which are found in the Spike protein.

The Delta lineage (Pango lineage B.1.617.2), identified as a VOC in May 2021 but circulating in India for months prior, caused a significant surge in cases worldwide [18]. The Delta variant has accumulated nine amino acid mutations (T19R, G142D, FR156-157del, R158G, L452R, T478K, D614G, P681R, D950N) in the spike protein [19]. Between May 20 and June 9, 2021, the total number of confirmed cases of Delta infection in the UK rose from 3424 to 42 323 [20]. These findings indicate that the Delta variant was rapidly becoming the dominant strain of the epidemic in numerous countries globally. Previous studies have shown that the Delta variant possesses greater transmissibility and immune evasion than the original virus strain and other VOCs. As of September 2021, over 33 sublineages (AY.1–AY.33) of the Delta VOC had been reported worldwide [21].

In November 2021, the Omicron lineage (Pango lineages BA.1–BA.5) was identified in South Africa and Botswana, and resulted in new waves of global infection [22]. Omicron variant has critical mutations in the Spike protein that were previously reported in other VOCs (Alpha, Beta, Gamma, and Delta) and Variants of Interest (VOIs) (Kappa, Zeta, Lambda, and Mu), including a number of mutations of spike, namely Δ69–70, P681H, N501Y, and D614G in Alpha, K417N in Beta, H655Y, K417N in Gamma, and T478K mutation in Delta [23]. Although these VOCs arose in different parts of the world, they shared sets of mutations, such as N501Y, E484K, and ΔH69/V70, suggesting convergent evolution. Each of these VOCs showed a markedly higher growth advantage over their predecessors [24]. From November 30 to December 3, 2021, the number of confirmed cases of the Omicron variant in South Africa increased from 4373 to 16 055. As of December 1, 2021, there were a total of 70 confirmed cases of the Omicron variant reported in 13 countries within the European Union and European Economic Area (EU/EEA) [25,26]. However, as of December 19, the number had risen to 4691 confirmed cases in 28 countries within the EU/EEA. This represented a 67-fold increase from the beginning of the month. The average R0 for Omicron is 9.5, with a range from 5.5 to 24 (median, 10; interquartile range (IQR), 7.25–11.88). Meanwhile, the average effective reproduction number (Rt) for Omicron was 3.4, with a range from 0.88 to 9.4 (median, 2.8; IQR, 2.03–3.85) [23,27,28]. Globally, in 2021 and 2022, the Rt of the Omicron outbreaks estimated for South Africa, Denmark, China, England, and India ranged from 2.43 to 5.11, with the pooled estimate being 4.20 (95% CI, 2.05–6.35). Although there were indications that Omicron infections might be less clinically severe than Delta, the sheer number of cases overwhelmed healthcare systems globally, including in the United States and the UK. The Omicron variant experienced constant mutations, with various lineages emerging such as BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5 [29,30]. Four new subvariants (BQ.1, BQ.1.1, XBB, and XBB.1) have been rapidly spreading since July 2022, surpassing the BA.5 variant. BQ.1 and BQ.1.1, which were first detected in Nigeria in early July 2021, and speedily expanding across Europe and North America, representing 67%, 35%, and 47% of cases in France, the UK, and the United States, respectively. To date, Omicron is the most frequently mutated variant among VOCs. As of May 2023, Omicron is classified into five main lineages, BA.1, BA.2, BA.3, BA.4, BA.5 and more than 700 sublineages.

The global COVID-19 waves have repeatedly resurfaced over the last three years. A wide variety of SARS-CoV-2 variants emerged during its persistence, leading to rapid worldwide spread. Generally, the world has experienced three pandemic waves of COVID-19 during the past three years (Fig. 1) [31]: the first wave by WT, Alpha, Beta, and Gamma from January 2020 to March 2021; the second wave by Delta from March 2021

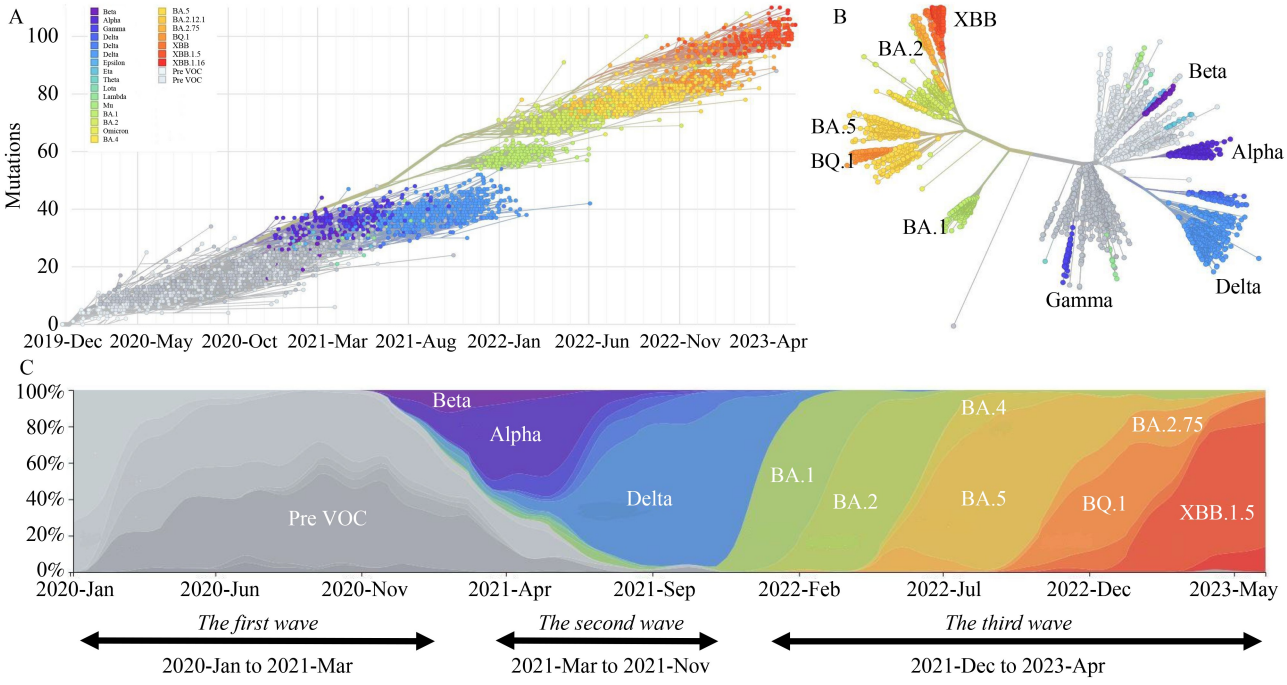

Fig. 1 Trend of COVID-19 epidemics in the world. (A) Accumulation of amino acid mutations in the S1 subunit of SARS-CoV-2 between December 2019 and May 2023, generated by nextstrain.org. (B) Unrooted phylogenetic tree of main SARS-CoV-2 variants, generated by nextstrain.org. (C) Frequency of SARS-CoV-2 lineages over time during the past three years in the world.

to November 2021; and the third wave by Omicron from December 2021 until now [32,33].

Distinct stages of prevention/control strategies of COVID-19 in China

The COVID-19 epidemic in China peaked in February 2020, with the National Health Commission reporting a sharp increase in the total number of cases in early February at a rate of over 3000 newly confirmed cases per day. In response, China implemented unprecedentedly strict public health measures to control the spread of the virus. These measures led to a steady decrease in the daily number of new cases in China [34,35]. Although the COVID-19 epidemic in China showed a declining trend, the global transmission rate was accelerated starting from late February, with an increasing number of countries reporting large clusters of infection.

Owing to the strict public health management strategies implemented in China, the COVID-19 epidemics in China during the past three years have differed significantly from those around the world. According to China's experience in epidemic prevention and control, the COVID-19 epidemic in the country can roughly be divided into four stages (Fig. 2): the first stage of "Initial epidemic" from January to April 2020; followed by the stage of "Preventing external importation and internal resurgence of COVID-19 infections with Dynamic Zero policy" after April 2020; the third stage of "Omicron waves" since November 2021 to November 2022; and the fourth stage of "Category B management of COVID-19" after the Chinese government optimized and adjusted the management measures on December 7, 2022.

Stage 1: Initial epidemic

On December 27, 2019, the Wuhan Jianghan Center for Disease Prevention and Control (CDC) received the first report of pneumonia with an unknown cause from Hubei Provincial Hospital of Integrated Chinese and Western Medicine. At the same time, other hospitals in Wuhan also noticed clusters of patients with similar symptoms [36]. Local government and research institutions conducted continuous monitoring and exploration of the uncertain pathogen. On December 30, 2019, bronchoalveolar lavage fluid (BLF) samples from patients hospitalized into Jin Yin Tan Hospital were sent to the Wuhan Institute of Virology, Chinese Academy of Sciences (WIV, CAS) and Wuhan Municipal CDC. By using reverse transcriptase-polymerase chain reaction (RT-PCR) with a generic primer for coronaviruses, both institutions found a sequence of a previously undescribed virus with high homology to the SARS and MERS coronaviruses. On January 5, Prof. Zhengli Shi's group from WIV, CAS isolated the virus in Vero-E6 cell culture and got its whole genome sequence. On January 7, 2020, the Chinese CDC detected the novel coronavirus from a throat swab sample of a hospitalized individual. The first

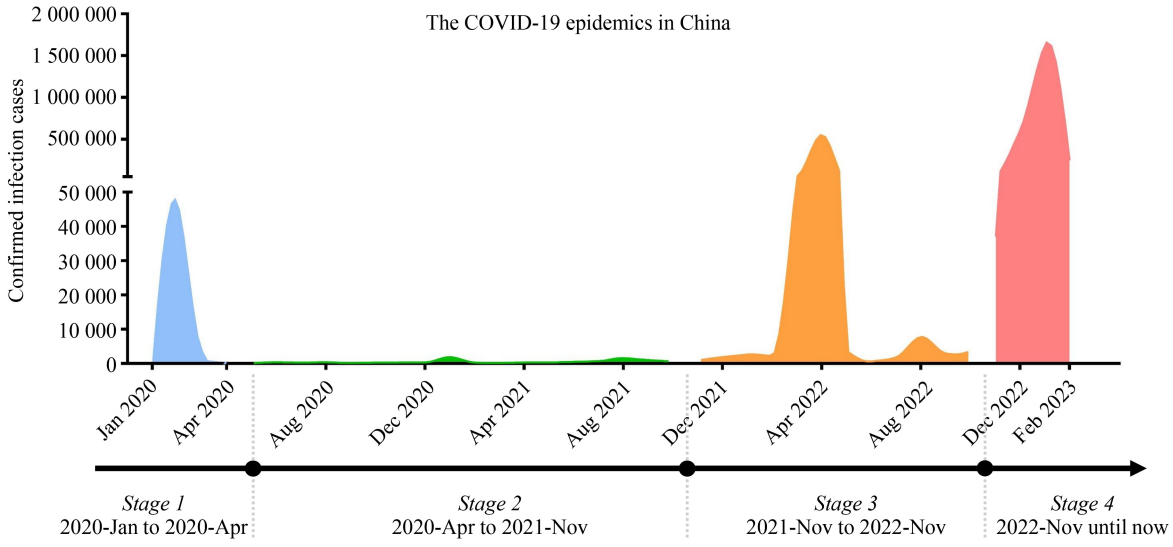

Fig. 2 Four stages of COVID-19 epidemic in China and the dynamic of the confirmed infection cases during past three years. All data were obtained from China's State Council Information (Available at the website of National Health Commission of the People's Republic of China).

death from COVID-19 was reported on January 9, 2020. On January 20, 2020, Wuhan established the Committee for the Prevention and Control of Pneumonia Caused by Novel Coronavirus Infection. On January 22, 131 new cases of COVID-19 were confirmed in China across 25 provinces [37]. Since there were no effective drugs or vaccines for COVID-19 at that time, severe cases rate reached 13.8% of the confirmed infection cases and 6.1% were critical cases. The mortality rate was approximately 5% [38]. To prevent further spread of the virus during the Chinese Spring Festival, on January 23, Wuhan declared a temporary closure of the city's outbound routes and strict traffic control management.

Strict traffic control and public venue restriction managements were essential during that critical period, effectively preventing the further spread of COVID19 in China [39]. A study conducted in Wuhan with a sample of 32 583 patients demonstrated that after implementing the traffic control in Hubei and Wuhan, the R0 of SARS-CoV-2 virus decreased from 3.88 to 1.25 [40]. WHO also commented that the Wuhan and Hubei strict restriction on traffic channels reduced the probability of the epidemic spreading and was very appropriate and important. Under the joint efforts of medical and public health strategies, the spread of COVID-19 in China has been effectively suppressed. As of February 20, 2114 of the 55 924 laboratory confirmed cases have died (crude fatality ratio (CFR), 3.8%). The overall CFR varies by location and intensity of transmission (5.8% in Wuhan vs. 0.7% in other areas in China). In China, the overall CFR was higher in the early stages of the outbreak (17.3% for cases with symptom onset from January 1 to 10, 2020) and has reduced over time to 0.7% for patients with symptom onset after February 1 [38].

Stage 2: Preventing external importation and internal resurgence of COVID-19 infections with Dynamic Zero policy

After mid-April 2020, the COVID-19 epidemics in China has been effectively controlled. However, due to the global pandemic of COVID-19, there was a significant risk of imported infection cases for China, including the risk of traffic transmission and contamination of frozen productions. In response to this, China has deployed multilayer nonpharmaceutical intervention (NPI) protocols to contain sporadic COVID-19 outbreaks. China timely adjusted her prevention and control measures since April 2020 to "prevent external importation and internal resurgence." SARS-CoV-2 RT-PCR detection was widely used to monitor the emergence of COVID-19 epidemics and prevent the spread of infection. Through large-scale PCR detection and public health management measures, China has been able to implement a "dynamic zero" policy, a multi-dimensional approach employed to achieve maximum effectiveness with minimal cost [41].

According to the China CDC Weekly reports from May 2020 to November 2021, a total of 11 local clusters of COVID-19 cases occurred, all of the infected cases being exposed to cross-border transportation or the cold chain product trade. On May 21, 2021, the first local infection of the Delta variant was discovered in Guangzhou, China. From May 21 to June 23, 2021, the Delta variant caused epidemics in other cities of Guangdong Province, China [42]. As of June 23, a total of 167 locally transmitted cases related to this outbreak were observed in 4 cities (Guangzhou, Maoming, Foshan, and Zhanjiang) in Guangdong Province. During this epidemic, the Rt

increased from 3.0 to 3.5 between May 27 and May 29, fluctuated near 1 from June 7 to June 15, and subsequently was below 1 after June 16; there were no new infections reported from June 19 to June 23, 2021. To combat this unprecedented threat, Guangdong Province implemented a range of strict intervention measures such as mass testing, active case quarantine, community management, travel restrictions, and affected area lockdown to contain the transmission. The available evidence confirmed that the public health measures implemented by Guangdong Province effectively curtailed the spread of this epidemic [42]. Owing to "dynamic zero" policy in China, the spread of the Delta strain was confined to sporadic cases, which were rapidly brought under control. Overall, during the global pandemic of the Delta variant, China's efforts in preventing and controlling COVID-19 were highly successful.

Stage 3: Omicron waves

In November 2021, the Omicron variant emerged in South Africa and was classified as a new VOC strain. In February 2022, the Omicron variant became the predominant variant in the world instead of the Delta variant. In China, the Omicron variant was first discovered in Chinese Hong Kong on November 27, 2021, and expanded into Chinese mainland on December 9, 2021, triggering a series of local outbreaks. From January to August 2022, the Omicron epidemics had broken out in different provinces such as Tianjin (January 2022), Guangdong (February 2022), Shanghai (March 2022), Jilin (March 2022), Beijing (May 2022) and Hainan (August 2022). From March 1 to April 22 2022, more than 500 000 local Omicron infections were reported in almost all provinces across China, with most (about 93%) cases occurring in Shanghai [43]. SARS-CoV-2 genome sequence data showed that the predominant lineages were BA.2 during this period [44]. Compared to previous outbreaks, the Omicron variant displayed a higher transmissibility, stronger immune escape capability, and reduced pathogenicity [45]. Due to these characteristics of Omicron, each epidemic caused by Omicron in China lasted for several months and resulted in a large number of infections.

As of April 18, 2022, 91.4% of the population aged ⩾ 3 years in Chinese mainland had received the full primary schedule of the COVID-19 vaccination (either inactivated vaccines administered on a two-dose schedule, or recombinant subunit vaccines administered on a three-dose schedule or recombinant adenovirus type-5-vectored vaccines administered as a single dose); 53.7% of those having received a booster shot [43]. However, vaccine-induced population immunity was insufficient to prevent Omicron outbreaks. In a modeling transmission of SARS-CoV-2 Omicron study, when vaccine uptake in the elderly was substantially increased (97%) and 50% or more of symptomatic infections were treated with antiviral therapies, the peak occupancy of intensive care units (ICUs, used for the treatment of critical cases) might not exceed the national capacity and the death toll might be comparable to that of seasonal influenza [46]. In the absence of these two conditions, the most optimistic strategy to prevent overwhelming of the healthcare system and protect people from the high mortality seems to rely on strict NPIs. From this perspective, even though Omicron brought great challenges for China's "Dynamic zero" strategy, the public health managements based on NPIs yielded relatively positive outcomes [47].

Stage 4: Category B infectious disease management of COVID-19

Based on the sequential epidemics caused by the rapid mutations of Omicron, China was facing increasing epidemic prevention pressure and costs over the whole year of 2022. In the fall of 2022, the virulence of Omicron in China was further decreased whereas the Rt was increased to over 20 [48]. In November 2022, the Chinese Joint Prevention and Control Mechanism of the State Council evaluated the then pandemic situation and underscored the importance of optimizing and adjusting COVID-19 prevention and control policies. This was due to the decreased pathogenicity of the Omicron, high vaccination rates among the Chinese population, and effective coordination between pandemic prevention and control efforts and socio-economic development. On December 7, 2022, a "Ten New Measures" announcement was issued by the Central Government to further adjust the prevention and control strategy of COVID-19 from containment to mitigation [49]. Finally, on January 8, 2023, after three years of the pandemic, the COVID-19 was officially downgraded from Category B infectious disease but on Category A management (only two legally notifiable infectious diseases are of Category A in China: plagues and cholera) to exact Category B management.

The adjustment of epidemic prevention strategies inevitably led to an increase in the number of infections in a short period. The confirmed infection cases increased from 28 164 on November 24, 2022 to 1.625 million on January 5, 2023 across 31 provinces in China [50]. The infection cases had reached the peak in early January 2023 and then the number of outpatients and inpatients had declined consistently. A rough estimation was that 80% of Chinese population was infected from mid-December 2022 to mid-January 2023. Nevertheless, the pertinent data has not yet been made accessible to the public. The virus spread decreased to a lower level in late January 2023. During the Spring Festival in 2023, the spread of the SARS-CoV-2 virus did not rebound

significantly [51]. The Rt of this Omicron outbreaks in China were estimated as 4.74 (95% CI, 4.41–5.07) [52]. According to the SARS-CoV-2 genome sequences from September 26, 2022 to January 23, 2023, the predominant lineages are BA.5.2 (70.8%) and BF.7 (23.4%) and no new mutant strains of SARS-CoV-2 have been identified [51]. During this phase, China accelerated the progress of vaccination, conducted comprehensive investigations and categorized registration of individuals aged 65 years and above, and promoted hierarchical treatment for high-risk populations. The new wave of the Omicron epidemic in early 2023 in China ended in February 2023.

Clinical features

Overall clinical outcome of VOC

Since the wild-type strain first emerged, the SARS-CoV-2 virus has experienced numerous changes, some of which have altered its transmissibility and severity. In detail, though the VOCs have evolved increased transmissibility, the Delta variant causes relatively severe disease phenotype, whereas the Omicron variant is much milder clinically. A retrospective study showed that the Delta variant yielded a shorter incubation period, higher viral load, and a longer duration of viral shedding than the wild-type [53]. Meanwhile, a meta-analysis including 8112 patients revealed that the incubation period of COVID-19 decreased gradually from 5.00 days (the Alpha variant) to 3.42 days (the Omicron variant) [54].

The Omicron variant is distinct in clinical features compared to previous variants with some known underlying mechanisms. This now globally dominant VOC is highly contagious and develops advanced immune evasion ability owing to its several mutations in receptor binding domain (RBD), the transmission rate of which is about 3.2 times that of Delta, and breakthrough infection by which in vaccinated people is reported [55]. It was demonstrated that the Omicron variant significantly escaped from the neutralization of convalescent sera from early strain- or Delta-infected patients [56]. Continuous investigation delineated the underlying antibody-evasion mechanism of the Omicron and its sub-lineages XBB and CH.1.1 enabling their escape from the majority of existing neutralizing antibodies [45,57,58].

However, the spike protein of Omicron has a higher affinity for ACE2 compared with Delta and the less efficient spike cleavage of Omicron at S1/S2 is associated with a shift in cellular tropism away from transmembrane serine protease (TMPRSS2)-expressing cells [59]. Mutations in the Omicron non-RBD domain which are unique from previous variants also alter its cellular tropism from lung cells with high TMPRSS2 expression to upper airway cells with low TMPRSS2 expression [60]. Therefore, Omicron demonstrated lower replication in lung cells and usually presents milder manifestations. Lacking TMPRSS2-mediated endocytosis, the Omicron variant is also less capable of forming syncytia than the previous variants, which may be another reason for its relatively lower pathogenicity. In contrast to the Delta variant, the *in situ* architecture of the most virulent SARS-CoV-2 variant was recently found by Li *et al*. capturing the virus–virus fusion events [61].

Heterogeneity in the clinical manifestations of patients with COVID-19

During the three-year pandemic, SARS-CoV-2 is constantly evolving and emerging several VOCs. As the dominant strains changed, the incubation period was different, and the clinical manifestations of COVID-19 patients were not entirely consistent, with symptoms ranging from asymptomatic or mild to severe [62]. At the early stage of the pandemic, for most symptomatic patients affected with WT, Alpha, Beta, and Gamma, symptoms start from 2 to 14 days after viral exposure. Healthy individuals may recover from the viral infection within 2–4 weeks of therapy. For the Delta variant, the average incubation time was shortened to 4.4 days. Regarding the third wave caused by Omicron, the incubation period was shortened to 2–4 days, and patients' symptoms were always milder than that in the first and second waves. The National Health Commission of China set the clinical classifications for all symptomatic patients according to their severity to better reflect the clinical characteristics of symptomatic patients. As the prominent strains change over time, patients with the same clinical classification also have slightly different clinical presentations.

Asymptomatic patients and underlying immunological features

Asymptomatic patients have tested positive for SARS-CoV-2 in seemingly healthy individuals during the so-called silent SARS-CoV-2 infection phase. Asymptomatic infections are generally divided into persistent asymptomatic and incubated asymptomatic patients, depending on the subsequent development of the disease. Approximately three-quarters of asymptomatic patients were real asymptomatic cases; the remainder were presymptomatic cases that would progress into the acute phase [63]. The former manifested neither COVID-19-related symptoms nor CT-confirmed pneumonia until the SARS-CoV-2 test turned negative. As virus biology and the host factors modulate the human immune response against SARS-CoV-2, many studies have revealed that asymptomatic and symptomatic individuals exhibit

different viral loads and immunological alterations, determining the disease progression in asymptomatic patients. Peng *et al*. compared viral loads and antibody indicators in asymptomatic and persistently symptomatic patients. They found that asymptomatic patients had significantly lower viral load and shorter duration of antibody presence [64]. Tam *et al*. longitudinally compared the T cell profiles of asymptomatic and symptomatic patients. They found that the distribution of T cells between the two groups was similar. Still, the levels of IFN-γ and IL-2 were higher in the asymptomatic infection group, which was related to the proportional secretion of inflammatory factors IL-10 and pro-inflammatory factors IL-6, TNF-α, and IL-1β when asymptomatic infection occurred, while the proportion of factors secreted by T cells in symptomatic patients was imbalanced. This suggests that asymptomatic individuals produce a more effective virus-specific cellular immune response [65]. In addition, the different clinical presentation of persistent asymptomatic and latent asymptomatic infections in asymptomatic infections may also be due to underlying immune differences. Compared to asymptomatic patients, presymptomatic immune signatures mainly manifest as monocytic overactivation and differentiation blockage, a likely lymphocyte exhaustion and immunosuppression [66].

Mild and moderate patients

According to the Guidelines on the Diagnosis and Treatment of COVID-19 issued, symptoms of COVID-9 vary in different stages and individuals. The classic symptoms in patients with mild or moderate COVID-19 were respiratory symptoms, including fever, chills, headache, myalgia, fatigue, and dry cough [67]. The less commonly reported symptoms are gastrointestinal symptoms such as tastelessness, vomiting, nausea, and diarrhea. The research conducted by Zhou *et al*. at the early stage of the pandemic showed that the most prominent symptom was fever, followed by cough and shortness of breath [3]. Cao *et al*. also found respiratory symptoms like fever and cough were prominent in waves caused by WT and Delta [68]. Except for those respiratory symptoms, other neurological symptoms including gustatory and olfactory dysfunctions, taste and smell impairment, and myalgia were observed in a considerable number of patients [69]. However, in the Omicron phase, more mild and moderate patients presented with a runny nose, headache, fatigue, sneezing, and sore throat [55].

Mild and moderate patients presented different lesions on chest imaging. According to the Guidelines on the Diagnosis and Treatment of COVID-19 issued (5th edition), mild patients always present with no abnormal radiological change, while moderate patients always present with multiple mottling and ground-glass opacity in chest imaging.

Severe and critical patients and related risk factors

Severe and critical cases were first defined in the Chinese Guidelines on the Diagnosis and Treatment of COVID-19 (2nd edition) and were slightly modified in subsequent editions. In the last edition (10th edition), patients were considered severe if they exhibited: dyspnoea with RR $\geqslant$ 30 beats/min; oxygen saturation at rest $\leqslant$ 93%; arterial partial pressure of oxygen (PaO_2)/inhaled oxygen concentration (FiO_2) $\leqslant$ 300 mmHg (1 mmHg = 0.133 kPa); progressive clinical symptoms with the significant progression of > 50% of the lesion within 24–48 h on lung imaging. Patients are considered critical if they present with: respiratory failure requiring mechanical ventilation; shock, comorbid other organ failure requiring ICU care. Shang *et al*. published the first retrospective study of the clinical characteristics of critically ill patients and found that respiratory manifestations were usually fever, cough, and dyspnoea [70]. Most critically ill patients also have impaired function of organs other than the lungs. For example, COVID-19 is often complicated by cardiac diseases such as acute coronary syndrome, myocarditis, stress cardiomyopathy, and arrhythmias [71]. Renal involvement in COVID-19 may manifest as pathological tubular, proteinuria, and reduced glomerular filtration rate [72]. Patients with COVID-19 are also at increased risk of thrombotic events such as venous thromboembolism (VTE) [73]. Patients with severe COVID-19 may also present with gastrointestinal symptoms [74]. Severe COVID-19 patients have a high incidence of abnormal liver function and elevated serum amylase, lipase, and glucose levels. Neurological disorders can severely complicate it, including stroke, cerebral hemorrhage, encephalitis, and meningitis.

Compared to the original strain, the Omicron variant has milder intrapulmonary symptoms and a slightly lower incidence of cardiovascular-related complications and pulmonary embolism. Several real-world studies have indicated that the Omicron variant may be milder than earlier variants. An early retrospective observational study in the Gauteng Province of South Africa showed that the hospitalization rate during the fourth wave (Omicron-dominated) was 8.3%, which was markedly below the rate in waves dominated by Beta or Delta variant, and the probability of severe illness was reduced by 73% in the Omicron-dominated wave [75]. Similarly, the risk of severe hospitalization or death was reduced by 25% in the Western Cape Province of South Africa [76,77]. Several analyses in the UK, Canada, France, and Norway showed that the risk of hospitalization with Omicron was approximately one-third of that with Delta [78,79]. The percentage of hospitalization, intensive care

unit (ICU) admission, receipt of invasive mechanical ventilation (IMV), and in-hospital death were reported lower during the Omicron pandemic than during the Delta pandemic, and the mean length of hospital stay was considerably shorter in the United States [80,81]. In China, studies show that the proportion of severe COVID-19 caused by the Omicron variant BA.1 was 0.5% in Tianjin from January to February 2022 and severe disease rate was 0.27% and case fatality rate was 0.09% for BA.2 in Shanghai from February to June 2022 [81,82].

Regardless of which strains, the early warning indicators of severe disease should be always focused on. Regarding risk factors for severe and critical cases, Ning *et al*. found that immunological markers such as $CD4^+$ T cell count and IFN-γ production were associated with the severity of COVID-19 pneumonia [83]. IL-6 > 50 pg/mL and LDH > 400 U/L on admission were reported independently associated with the severity of COVID-19 pneumonia [84]. Regarding risk factors for death, Feng *et al*. found that organ dysfunction, impaired immune function, multilobar infiltration, and pleural effusion occurred in a higher proportion of critically ill patients, and advanced age was a risk factor for death [85]. Chinese Guidelines on the Diagnosis and Treatment of COVID-19 (7th edition) added high-risk clinical indicators: people aged ⩾ 65 years, without being vaccinated; underlying cardiovascular disease (including hypertension), chronic lung disease, diabetes, chronic liver and kidney disease, tumors and patients on maintenance dialysis; immunodeficiencies (e.g. AIDS, immunocompromised due to long-term use of corticosteroids or other immunosuppressive drugs); obesity (body mass index ⩾ 30); in late pregnancy and perinatal period; heavy smokers, all at high risk of severe/critical illness. Hypoxaemia or progressive dyspnoea; worsening oxygenation parameters (e.g. oxygen saturation, oxygenation index) or progressive elevation of lactate; progressive decrease in peripheral blood lymphocyte count or progressive elevation of inflammatory factors such as interleukin-6 (IL-6); CRP, ferritin; significant elevation of coagulation-related parameters such as D-dimer; significant progression of pulmonary lesions on chest imaging are early warning signs and should be monitored for deterioration.

In severe and critical patients, X-rays or CT shows diffuse lesions in both lungs, with a few showing "white lung." Cao *et al*. found ground-glass opacity will change to the consolidation lesions with the aggravation of severity [68]. The lesions in severe and critical patients are predominantly solid, combining ground glass density, air bronchial signs, and multiple wind cords. The extent of the lesion may increase by up to 50% within 48 h.

Pathological characteristics

The lungs are the most affected organ by SARS-CoV-2, showing diffuse alveolar damage, exudation, interstitial fibrosis, and extensive infiltration of immune cells [86,87].

Pathological features of COVID-19 in the pulmonary tissues of mild, severe or recovering patients are not identical. A postmortem study in an aged patient with mild COVID-19 pneumonia found that the lung was predominated with diffuse alveolar damages, including disruption of alveolar septa, proliferation and desquamation of type II AE, exudation of fibrin, monocytes and macrophages, and formation of the hyaline membrane. Positive SARS-CoV-2 virus nucleic acid was only in the lung but not in the liver, heart, intestine, and skin [88]. For critically ill status of COVID-19 cases, pulmonary pathologies showed three phases of diffuse alveolar damage (DAD): exudation, proliferation, and fibrosis. The SARS-CoV-2 viral RNA distributed in postmortem organs, including those in the respiratory and other systems. DAD-fibrosis was found as early as 15 days after the symptom onset and increased with disease progression [89]. Mucous plugs were found in all respiratory tracts, terminal bronchioles, and pulmonary alveoli in two COVID-19 patients with acute respiratory distress syndrome (ARDS), which was not described in SARS [90].

SARS-CoV-2 infection affected multiple organs to a different extent of acute injuries. Extrapulmonary organs, especially the lymphatic organs such as the spleen and lymph nodes, contained reduced lymphocytes but increased macrophages. SARS-CoV-2 infection may impair the survival of lymphocytes and disrupt lymphocyte-mediated immune reactions [87]. The brains of severe COVID-19 patients showed infiltration of monocytes with extensive microglial activation, swelling endothelial cells and discontinuous perivascular astrocytic end-feet layers with edema [91]. Myocardia displayed cell degeneration, scattered necrosis, interstitial edema, and mild infiltration of monocytes, lymphocytes, and neutrophils. The liver showed hepatocyte degeneration, spotty necrosis, and piecemeal, bridging or massive necroses with neutrophil infiltration [92]. It has been found that SARS-CoV-2 can directly infect human kidney tubules through the ACE2 receptor and initiate hypoxic damage in infected kidney tubules [93]. The mechanisms of the infection course and prevention measures are the subject of further investigation.

Current therapeutic agents and treatments

Antiviral therapy

Antiviral therapy is one of the main treatment measures

for COVID-19. With the continuous evolution of the pandemic strain, the treatment guidelines advocated by WHO [94] and in different countries have also been adjusted accordingly. Antiviral therapy can be broadly classified into small molecule antiviral drugs and neutralizing antibody therapeutics. The latter include monoclonal antibodies such as casirivimab/imdevimab, convalescent plasma therapy, and COVID-19 immunoglobulin.

Small-molecule inhibitors are essential tools for SARS-CoV-2 treatment. Many promising drug targets have been shown to impact the stages of virus attachment, entry, uncoating, transcription, and genome replication based on the structural biology, such as angiotensin-converting enzyme 2 (ACE2), serine protease TMPRSS2, RNA-dependent RNA polymerase (RdRp), 3C-like protease (3CLpro), and papain-like protease (PLpro) [95]. Current guidelines published in China recommend Paxlovid (nirmatrelvir/ritonavir), molnupiravir, and azvudine as early treatments for adults at high risk of severe COVID-19 [96]. Many studies have confirmed that these drugs can effectively shorten the median time to viral clearance among the target population and reduce the rate of hospitalization and mortality [97]. A retrospective cohort study of hospitalised patients with COVID-19 showed that azvudine was associated with a significantly reduced risk of composite disease progression outcome compared with those who did not receive azvudine or other antiviral agents (the rate of composite outcome was 6.94% vs.12.65%) [98]. VV116, developed by Chinese scientists and approved by the National Medical Products Administration (NMPA) of China on January 29, 2023, is an oral analog of remdesivir with wide distribution in the preferred target issues of SARS-CoV-2. The phase 3 trial showed that the median duration of sustained clinical recovery was one day shorter with VV116 (4 days) compared to Paxlovid (5 days), and VV116 experienced fewer adverse events (67.4% vs. 77.3%) among adults with mild-to-moderate COVID-19 [99]. Several promising drugs are currently undergoing preclinical or clinical trials. Peptidomimetic inhibitors of SARS-CoV-2 3CLpro, such as Xiannuoxin (simnotrelvir/ritonavir) and RAY1216, also developed in China, exhibit significant antiviral effects against mutant strains and have been conditionally approved for marketing by NMPA of China [100]. Further investigation of these promising small molecule anti-virals should be made for new variants in the future.

Due to the rapidly evolving VOCs and the resultant immune escape, many monoclonal antibody drugs effective at the early phases of the pandemic have been withdrawn by the regulatory institutions in many countries [101].

IL-6/IL-6R antagonist

The clinical manifestation of COVID-19 can vary from asymptomatic or mild cases to severe and critical cases. Approximately 15% to 30% of patients may develop severe illness [102]. Severe COVID-19 cases may lead to dysregulated immune responses, which trigger the cytokine storm syndrome. This syndrome is marked by early interferonopathy followed by hypercytokinemia, with abundant inflammatory markers and a deficiency of reparative growth factors. Studies revealed that elevated levels of IL-6 or C-reactive protein (CRP) were associated with disease severity in COVID-19 [103]. Tocilizumab, a humanized monoclonal antibody against the IL-6 receptors, is commonly used to treat autoimmune diseases such as rheumatoid arthritis. This drug has been reported for the first time in the therapy for COVID-19 by a Chinese group [104]. A systematic living review including 32 RCTs presented that tocilizumab reduced all-cause mortality at D28 compared to placebo or standard care [105]. The results suggest that anti-cytokine therapeutic is effective and may be suitable for treating different variants with cytokine storm in the future. Tocilizumab has still been listed on the COVID-10 treatment protocol recommended by WHO in January 2023 [94].

Continuous renal replacement therapy (CCRT)

Adult respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) are the most common co-morbidities in patients with severe COVID-19. Since kidneys are the target organs of SARS-CoV-2, the frequency of acute kidney injury (AKI) in the initial stage of COVID-19 reached 8.9% [106]. The severity of AKI tends to increase in patients admitted to the ICU, with an incident rate ranging from 25% to 29% [70,107]. Patients who exhibit indications of AKI, such as hyperkalemia, acidosis, pulmonary edema, or severe sodium ion disorders, are recommended to undergo CRRT. CRRT can effectively support kidney function and help manage these complications to maintain the homeostasis. CRRT with the oXiris hemofilter has been found to significantly decrease proinflammatory cytokine levels, leading to improved hemodynamics and organ function in severe COVID-19 patients [108]. Notably, critically ill COVID-19 patients who received CRRT treatment demonstrated significantly longer survival than other ICU COVID-19 patients [109]. These findings highlight the potential of CRRT as a valuable intervention in managing COVID-19 cases.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial agent showing

efficacy against SARS-CoV-2 *in vitro* [110]. However, the administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than the standard of care alone in mild to moderate COVID-19 patients admitted to 16 treatment centers in China [111]. Several randomized controlled trials suggested that hydroxychloroquine treatment in patients with COVID-19 had no significant clinical benefit in terms of mortality, the risk of mechanical ventilation, and the rate of ICU transfer compared with standard treatment. In addition, it could increase the incidence of adverse events [112]. Therefore, hydroxychloroquine is not currently recommended for treating the COVID-19.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) secrete stem cell growth factor, vascular endothelial growth factor, and keratinocyte growth factor to promote the regeneration of type II alveolar epithelial cells. In addition, MSCs are attracted to sites of inflammation by different chemokines and play an immunomodulatory role through direct contact and paracrine. As one of the treatment options for patients with severe COVID-19, MSCs contribute to the recovery of lung injury, inhibit the excessive activation of the inflammatory response, and affect the progression of pulmonary fibrosis. Phase I and phase II clinical trials of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) therapy in COVID-19 patients showed that UC-MSCs tended to improve the whole lung lesions of COVID-19 patients and significantly increased the regression of lung solid component lesions [113,114]. Although the efficacy of UC-MSCs treatment cannot sustain through the end of the 2-year follow-up period, the short and long-term safety of UC-MSCs therapy has been demonstrated in COVID-19 patients [115]. UC-MSCs therapy is a viable option as an adjunct to standard treatment for COVID-19 patients.

Prone positioning

The beneficial effects of prone positioning have been widely established in patients with non-COVID-19 related acute respiratory distress syndrome. In the prone position, the dorsal ventilation is improved, the poorly ventilated alveoli behind the heart are significantly reduced, the collapsed alveoli are re-expanded, and the ventilation/blood flow ratio is better. At the same time, the secretions in the airway are well drained under gravity. Awake-prone positioning reduces the risk of endotracheal intubation in adults with hypoxemic respiratory failure due to COVID-19 but has little to no effect on other secondary endpoints, such as mortality and ICU length of stay [116].

Convalescent plasma therapy

Convalescent plasma therapy is the infusion of plasma from individuals recovering from infectious diseases into patients. Convalescent plasma containing high titer and bioactive neutralizing antibodies treats recipients by passive immunization. The short-term benefits of early use of convalescent plasma therapy with high antibody titers in severe COVID-19 patients were first demonstrated in China during the early COVID-19 outbreak [117,118]. The current view is that non-selective administration of convalescent plasma is not recommended. Early administration of high titer convalescent plasma is recommended for patients at risk of severe illness, patients with no detectable SARS-CoV-2 antibodies and immunosuppressed patients [119–122], while infusion of convalescent plasma is not recommended for patients with advanced COVID-19. The role of convalescent plasma is mainly related to its neutralizing antibodies against SARS-CoV-2 to clear the virus, so the patients who benefit from convalescent plasma therapy are those who did not produce neutralizing antibodies early or whose immune function is suppressed. With the progress of the disease, symptoms may be more closely related to the host inflammatory response caused by the virus than to the effects of the virus itself. Prophylactic transfusion of convalescent plasma is not recommended for uninfected patients with a history of exposure to COVID-19 [123].

Possible future outlook

In this review, we try to give an overview of the emergence, spread, and evolution of SARS-CoV-2, describe the clinical and pathological characteristics of patients with different severity, and introduce the latest progress in the treatment and prevention of COVID-19. Over the past three years, countries worldwide have made tremendous efforts to respond to the COVID-19 pandemic. China has achieved major achievements by relying on her unique public health management strategies. Although China recently downgraded COVID-19 to Category B management and the WHO declared an end to the global public health emergency [124], the ongoing health risks from COVID-19 and other emerging viruses persist. In ongoing efforts to address COVID-19 in the future, public health management strategies, such as NPIs, should be objectively and thoughtfully evaluated. Balancing the effectiveness of epidemic prevention with economic costs in public health is crucial. Simultaneously, vaccinating high-risk groups with newly developed vaccines is crucial. With the continuous emergence of SARS-CoV-2 variants, new generation vaccines designed to cover current circulating strains may

provide appropriate protection. Meanwhile, promising antiviral drugs and treatment modalities need further verification by ongoing clinical trials.

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Compliance with ethics guidelines

Conflicts of interest Dong Wei, Yusang Xie, Xuefei Liu, Rong Chen, Min Zhou, Xinxin Zhang, and Jieming Qu declare that they have no conflict of interest.

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