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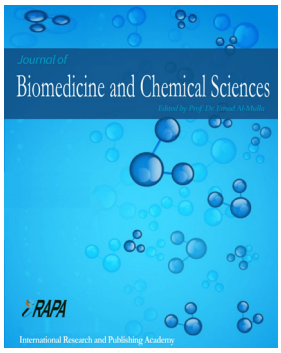

Latest Insights on the Diagnostic Approaches and Treatment Strategies of Epidemiology, Pathogenesis, Diagnosis and Possible Treatment of COVID–19 Infection

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ABSTRACT

Coronaviruses are a large family of viruses that cause a variety of illnesses, from the common cold to severe acute respiratory syndrome. The SARS–CoV–2 outbreak was first reported by the World Health Organization in China and has now become an epidemic, reflecting the extremely high transmissibility of the virus, which has caused great concern and stress among people around the world. Research suggests that prevention, risk education, and promotion of self–care behaviours can slow the spread of the disease in communities, and identifying sources of transmission can be effective in controlling it. The mortality rate of this virus is significantly higher in the elderly and people with underlying diseases compared to healthy people. Coronavirus is a challenging disease and can be easily transmitted in public places, and the number of people infected with this virus is increasing exponentially across all ages and groups. Therefore, increasing public awareness of this disease and providing positive psychological programs and teaching prevention methods in the media can reduce mental problems in society, in addition to reducing mortality and the number of patients.

INTRODUCTION

Coronaviruses are a group of viruses that were first identified in 1960. These viruses infect humans and other vertebrates. In recent decades, infections of the coronavirus family have affected the respiratory system, digestive system, liver, and central nervous system of humans, livestock, birds, bats, mice, and many other wild animals, and have manifested themselves with mild to moderate symptoms, often in the form of common colds. Its new mutant type, called COVID–19, emerged and spread in China at the end of 2019 (beginning of December 2019), and the pandemic of this virus caused about 140 countries around the world to be infected with this disease in the last week of 2019. Our country is no exception to this rule. The first cases of the disease were found and announced in Qom on Wednesday, February 19, and by the time this article was submitted, cases of the disease had been reported in all provinces of the country. Studies suggest that SARS and MERS originated in bats, infected an intermediate host, and then jumped to humans. It is possible that COVID–19 also originated in bats, which varies depending on the region and species of bat (Al-Mhyawi, 2014). In general, coronaviruses cause mild respiratory illness in humans with symptoms similar to the common cold. Of the seven coronaviruses that can infect people, four cause the common cold, alpha coronaviruses NL63 and 229E, and beta coronaviruses HKU1 and OC43, and three cause more severe disease, including severe acute

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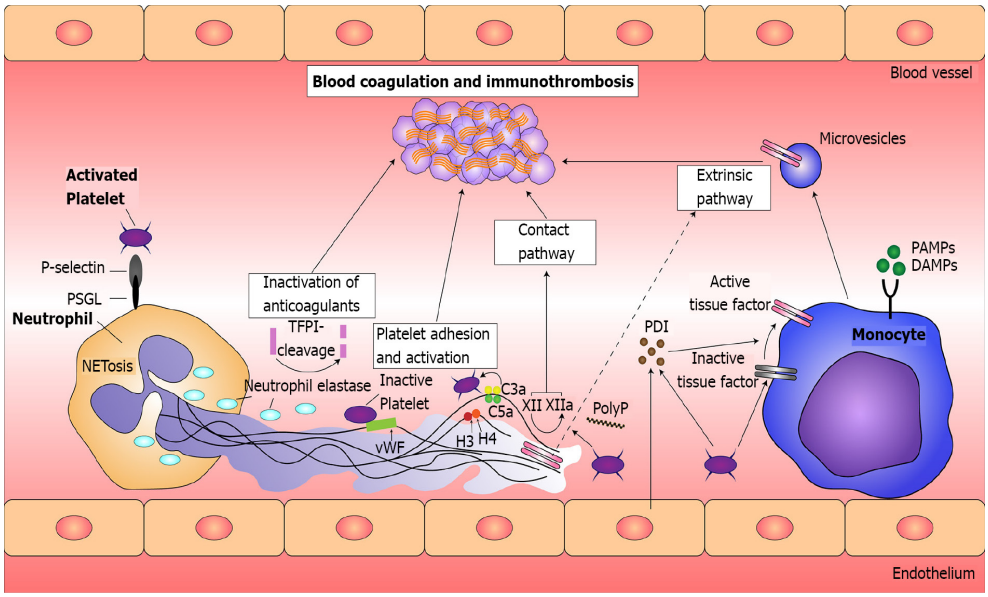
respiratory syndrome coronavirus (SARS), Middle East respiratory syndrome coronavirus (MERS), and a novel coronavirus identified in 2019 (Abeng et al., 2021). These have also been shown to cause severe and even fatal respiratory illness. For example, the outbreak of the severe acute respiratory syndrome (SARS–CoV–1) in 2002 or the Middle East respiratory syndrome (MERS) in 2012, both caused by coronaviruses. Coronaviruses are members of the Coronaries family. They also have a common RNA genome. Both viruses are transmitted from animals to humans and cause inflammation of the upper respiratory tract and then affect the lower respiratory tract, often resulting in fatal lung damage and death (Beltran-Perez et al., 2022; Bostan et al., 2012). The average incubation period, the time between infection with the infectious virus and the onset of symptoms and disease, is about 5–7 days (range 2–14 days). Coronaviruses have typically caused severe disease that is limited to a specific country or region in recent years (Callister Jr & Rethwisch, 2020). The main and initial symptom of COVID–19 is fever, and acute respiratory symptoms appear about 5 days later. People with chronic underlying diseases and healthcare workers are at high risk of infection (Li et al., 1999). In order to help healthcare workers in the country better cope with the novel coronavirus–2019, we review the available studies and evidence related to it and present scientific and practical information in the present study.

Structure of the Novel Coronavirus

Coronavirus belongs to the family Coronaries and is a member of the order Noroviruses. Viruses in this family are enveloped viruses with a helical capsid and have a diameter of about 80 to 220 nm. On the surface of the lipid envelope of these viruses, there are glycoprotein appendages that give the virus a petal–shaped or crown–shaped appearance (Figure 1). The genome of these viruses consists of single–stranded RNA with positive polarity. Among viruses with RNA genomes, coronaviruses have the longest genome with a length of about 29 to 22 thousand base pairs (Chahul et al., 2015).

So far, four genera of coronaviruses have been identified, namely alpha, beta, gamma and delta, and COVID–19 is placed in the genus beta coronavirus of the subfamily Coronaries (Chavan & Vijayakumar, 2024; Chi & Zhao, 2009; Sun et al., 2016). Beta and alpha viruses infect only mammals and typically cause respiratory disease in humans and the stomachs of animals. Gamma and delta viruses infect birds, but some can also infect mammals (Ebenso et al., 2008). The coronavirus family has two different types of surface proteins and is named for this characteristic appearance.

COVID–19 is the third known animal coronavirus disease agent after SARS and MERS, which also belong to the beta coronavirus family (Chahul et al., 2015). Two highly pathogenic viruses, SARS and MERS, cause severe acute respiratory syndrome in humans, and the other four human agents (HCoV–NL63, HCoV–229E, HCoV–OC43, and HKU1) induce only mild upper respiratory disease. However, some can cause severe infection in immunocompromised individuals, infants, young children, and the elderly (Eddy & Ebenso, 2010; Fu et al., 2010; Fu et al., 2012).



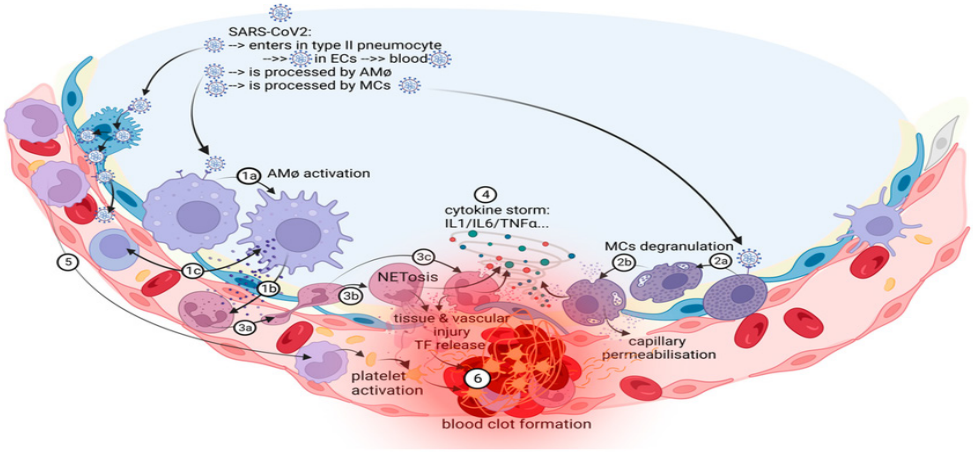


Fig. 1. Coronavirus body (enveloped with a helical capsid, approximately 80 to 220 nm in diameter and with glycoprotein appendages on the surface of the lipid envelope) (10)

Origin of the Novel Coronavirus

The source of pneumonia was first discovered in December 2019 by doctors in Wuhan, China, and a novel coronavirus was isolated from the respiratory epithelium of patients, which belongs to the coronavirus family. On February 11, 2020, the new coronavirus was officially renamed from "SARS–CoV–2" to "COVID–2019" (Gece & Bilgiç, 2010). According to data released by the National Health Commission of the Republic of China, COVID–19 is most likely to have originated from wild cats and from seafood, poultry, and live animal markets located in Wuhan, Hubei Province, central China, and all three coronaviruses can be transmitted from person to person (Dos Santos et al., 2017; Goyal et al., 2018; Hussin & Kassim, 2011). On January 1, 2020, the market was closed and decontaminated (Wantulok et al., 2020). On the same day, Wuhan authorities released information about the outbreak to the public (Kadapparambil et al., 2017). Today, the number of COVID–19 cases worldwide is increasing exponentially.

The first genome sequence of COVID–19 was published online one day after it was confirmed by Zhang and other scientists at Fudan University in Shanghai. Following this, on January 11, five additional genome sequences of the virus were uploaded to the GSAID database by various initiatives across China, allowing researchers around the world to begin research on this novel coronavirus (Kiani et al., 2008). By January 17, 62 cases of this coronavirus had been confirmed in China and three outside China (two in Thailand and one in Japan). Subsequently, the genome sequences of all coronaviruses isolated in China and abroad were determined and uploaded to the database. Following the development of appropriate diagnostic kits, other suspected cases of the disease were identified in other parts of the world, including Vietnam, Singapore, and Hong Kong (Ramachandran & Nosonovsky, 2015). The successful isolation and sequencing of the 2010–nCOV genome has greatly contributed to understanding the origin of the virus and its infectious properties. However, many uncertainties remain, and scientists are currently conducting extensive research on this new virus.

Following the increase in cases and the global spread of this virus, the World Health Organization (WHO) declared the outbreak of the new coronavirus the sixth global public health emergency of international concern on January 30, 2020, which was considered a threat not only to China but also to all countries. As a populous country, China has previously fought viral epidemics, including SARS in 2003. The recent outbreak of COVID–19 has already caused great damage to the global economy, and the national growth of the world, and especially China, in 2019 decreased for the past 30 years. Therefore, the cooperation of health workers, governments and the public is needed to prevent the spread of the new coronavirus. On 11 February, the World Health Organization named the new coronavirus disease COVID–19 (Ramachandran & Nosonovsky, 2015), and on the same day, the International Committee on Taxonomy of Viruses (ICTV) changed the name of the virus that causes the disease from 2010–nCOV to SARS–Cov–2 (Pavithra et al., 2012).

Epidemiological Features of COVID–19

Coronaviruses have a broad host range and are responsible for 15–30% of all colds. Immunity to viral surface antigens is likely to play a major role in protecting individuals, but reinfection with similar strains is common (Qiang et al., 2018). Heidari (2017) reported that from January 10 to 24, 2020, the number of COVID–19 cases in China increased 31.4–fold. On

February 23, 2020, the number of COVID–19 cases in China were 1,879, compared to January 10, 2020. They estimated the mortality rate for COVID–19 based on their patient population to be 84.2%. The researchers also found that the male–to–female mortality ratio was 25.3:1, the median age at death was 75 years, the median time from onset of symptoms to death was 14 days, and the median time from onset of symptoms to death was 11.5 days in those aged 70 years and older and 20 days in those aged <70 years. These findings suggest that the disease may progress more rapidly in older adults than in younger individuals.

Heidari (2017) reported a median age of 59 years among 425 patients infected with COVID–19, 56% of whom were male, a median incubation period of 2.5 days, and approximately half of the adult patients were 60 years or older. In the early stages, the number of infected patients doubled. The transmission rate from an infected person was 2.2. Although 55% of the first patients infected with the 2019 novel coronavirus were not from the Hana Seafood Market, the number of unrelated cases has been increasing exponentially since late December 2019.

COVID–19 Outbreak in the World

Epidemiological studies have shown that coastal cats in the wildlife market in China were the direct source of SARS–CoV (Talari et al., 2017). From the beginning of the outbreak to April 26, 2020, the latest global statistics on the spread of the coronavirus show that all countries on all continents of the world (Figure 2) are affected by this virus and the disease COVID–19, which has an overall mortality rate (2.98%) and a recovery rate (74.29%) (Figure 2).

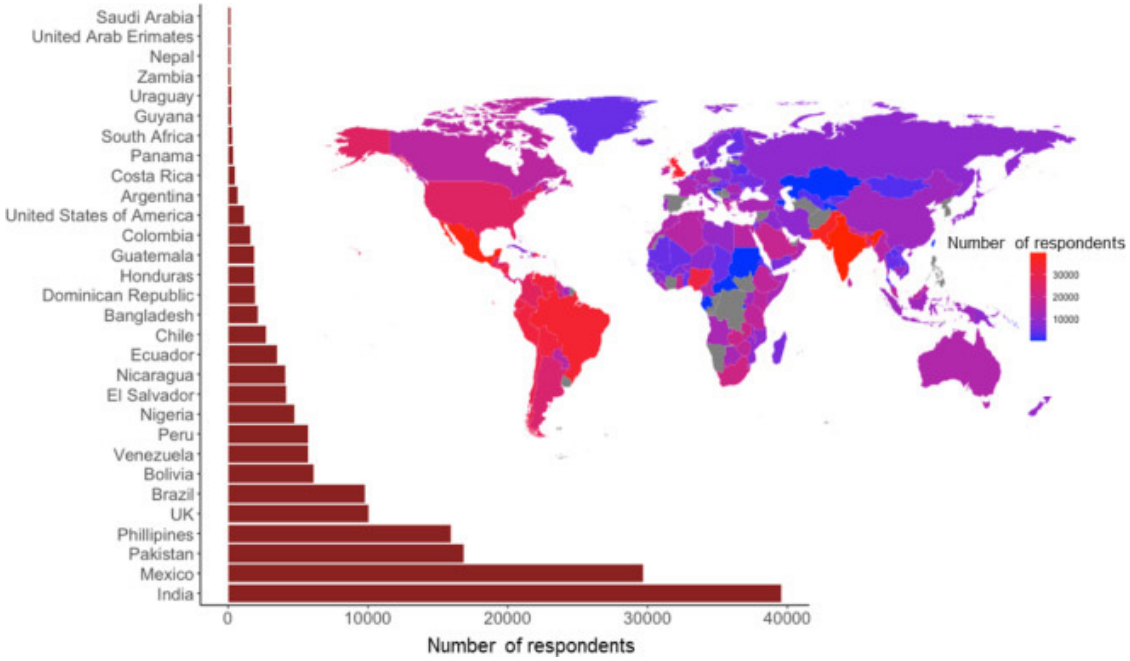


Fig. 2. Global spread of COVID–19 (dark areas indicate affected countries) (Talbot & Talbot, 2018)

Transmission Routes of COVID–19

The 2019 novel coronavirus is thought to be transmitted by droplets, close contact, aerosols, and perhaps fecal–oral transmission, and patients during the incubation period can transmit the virus to others. The distribution of the viral receptor may explain the pathogenic mechanisms, clinical manifestations, and transmission routes of the 2019 novel coronavirus. Angiotensin–converting enzyme 2 (ACE2) has been proposed as a receptor for COVID–19 that is essential for its entry. The ubiquitous expression of ACE2 in various cells, such as AT2 cells of the lung, upper esophagus, epithelial cells, and absorptive enterocytes of the ileum and colon, has been implicated in multi–tissue infection with COVID–19 (Umoren et al., 2006; Verma et al., 2016). Therefore, in addition to respiratory and body contact, fecal–oral transmission is a potential route for infection with the novel coronavirus.

Mechanism of COVID–19 Pathogenesis and Receptor Utilization

There are currently few studies on the pathophysiological properties of COVID–19 and uncertainty about its mechanism of transmission. Current knowledge largely suggests that it is transmitted from person to person via respiratory secretions (Wahyuningrum et al., 2008). However, evidence suggests that human–to–human transmission occurs during the asymptomatic incubation period of

COVID–19, which may be 2–10 days after virus entry (Xhanari & Finšgar, 2016; Xiong et al., 2016).

Heidari (2017) found that ACE2 is the receptor for the 2019 novel coronavirus. In the normal human lung, ACE2 is expressed on alveolar type 1 and 2 cells, with 83% of alveolar type 2 cells expressing ACE2. Men have higher levels of ACE2 in their alveolar cells than women. Asians have higher levels of ACE2 in their alveolar cells than do whites and African Americans. Binding of the 2019 novel coronavirus to the ACE2 receptor increases the expression of the enzyme ACE2, which can lead to damage to alveolar cells. Damage to alveolar cells can in turn cause a series of systemic reactions and even death. They also confirmed that Asian men are more susceptible to COVID–19 infection. Heidari (2017) found that the receptor binding ability of COVID–19 is 10–20 times stronger than that of SARS–CoV.

Receptor binding is a prerequisite for coronavirus invasion of the host cell. After receptor binding, the viral spike protein is cleaved by acid–dependent proteolysis by cathepsin TMPRRS2 or furin, followed by proteinase cleavage, followed by fusion of the viral envelope with cell membranes. The spike is a large trimer and a surface protrusion that can be cleaved by proteases into a protein with an S1 subunit at the amino terminus. Compared with other coronavirus proteins, the Spike protein has the most variable amino acid sequence, which is the strongest candidate among all coronavirus genes for adaptation to its hosts. Recently, results showed that COVID–19 uses the same ACE2 cell entry receptor as SARS–CoV. In addition to human ACE2, COVID–19 can use ACE2 from Chinese horseshoe bats, civets, and pigs, but cannot use mouse ACE2 as an entry receptor. One reason is that human ACE2 has a high homology with Chinese horseshoe bats, cats, and pigs, with 80.7%, 83.5%, and 81.4% homology, respectively (Zhang et al., 2018; Heidari, 2017).

Clinical Symptoms and Pathogenesis of COVID–19

Coronavirus is the second most common cause of the common cold. Fever, fatigue, and dry cough are the most common symptoms, while nasal congestion, runny nose, and other upper respiratory tract symptoms are rare. The Beijing Centers for Disease Control and Prevention reported that the severity of the disease varies. According to the severity of the disease, it can be classified into mild, normal, severe, and fatal types (Heidari, 2014): 1– Mild cases: mild clinical symptoms and no pneumonia found on chest CT scan. 2– Normal cases: fever, respiratory symptoms, and patients with imaging manifestations of pneumonia. 3– Severe cases: labored breathing (more than 30 times per minute). 4. Fatal cases: One of the following three conditions: respiratory failure and need for a ventilator, shock or other organ failure and need for intensive care. Heidari (2017) reported that all individuals who have not been exposed to SARS–CoV–2 are susceptible to COVID–19. However, current clinical studies show that severe cases of COVID–19 and deaths are more common in middle–aged and elderly people and in young people with a long history of cigarette smoking or other conditions. In particular, immunocompromised patients (undergoing corticosteroid treatment, chemotherapy, organ transplant, HIV patients) and patients with underlying diseases (cardiovascular diseases, hypertension, diabetes, underlying respiratory disease, BMI>40) are likely to experience severe symptoms (Heidari, 2017b).

According to the first study of patients infected with the novel coronavirus, the incubation period of this virus is about 2 to 14 days and more commonly 3 to 7 days. The incubation period is the period when the virus is present in the body and symptoms have not yet appeared. During this incubation period, patients are contagious, and it has been reported that each case infects an average of 3.77 other people. For this reason, it is necessary for family members to take precautions when they are forced to be in an environment other than the safe environment of the home.

In a study by Heidari (2017), 98% of COVID–19 patients had fever. Of these, 78% had a temperature above 38°C. They reported that 76% of patients had cough, 44% had fatigue and muscle aches, and 55% had shortness of breath. A small number of patients also had sputum (28%), headache (8%), bleeding (5%), and diarrhea (3%). Laboratory tests showed that 25% of infected patients had leukopenia and 63% had lymphocytopenia. Aspartate aminotransferase levels were elevated in 37% of patients. Myocarditis was diagnosed in 12% of patients, and the level of highly sensitive profaning I was significantly increased in these patients. Abnormalities were observed on chest CT images in 100% of patients.

Diagnosis of COVID–19

The early symptoms of COVID–19 are very similar to those of winter influenza, and current diagnosis of coronavirus disease relies on radiological and laboratory findings. Radiological studies are of paramount importance in the early diagnosis and management of COVID–19 (Heidari, 2015). The most important diagnostic methods for laboratory testing include nasopharyngeal swabs, sputum, or lower respiratory tract aspirates. The confirmatory diagnostic test is usually RT–PCR, which detects the

viral RNA polymerase (RdRp) genome. The region detected by this technique typically includes the RdRp genomic region, along with other regions such as the E or N genomic regions (Heidari, 2017).

Prevention and Control of COVID–19 Infection

As the number of COVID–19 patients in China and other countries are rapidly increasing, the most important and urgent task is to prevent the spread of COVID–19. Early detection and isolation are essential to reduce virus transmission. In addition, close surveillance in crowded places is also important. Both SARS and COVID–19 potential pathogens are obtained from wild animals. Therefore, hunting, selling, and eating wild animals not only cause serious damage to the ecosystem but also lead to the spread of epidemics. Therefore, banning the trade of wild animals is an effective measure to prevent viral spread. Given the lack of standard treatment and effective vaccine for the novel coronavirus, the best way to prevent infection and prevent its spread is to avoid it. However, on January 26, 2020, the Chinese CDC began developing a new vaccine for SARS–CoV–2. Ways to prevent transmission include: covering your mouth and nose when sneezing and coughing, washing your hands with soap and water for at least 20 seconds or using alcohol–based hand sanitizers (at least 60% alcohol), avoiding eating raw or undercooked animal products, and maintaining a distance of at least 1–2 meters from a person with respiratory symptoms.

Treatment

Currently, antiviral therapies are mainly approved for the treatment of COVID–19. Hormones and interferons can also be used as effective drugs for the treatment of COVID–19. Lopinavir or ritonavir is a protease inhibitor used to treat HIV infection and is effective. Lopinavir has antiviral activity in vitro. Lopinavir or ritonavir has also been clinically tested in the treatment of COVID–19 and has significantly reduced viral titers and improved patient conditions, but the overall clinical effect has not been determined. In this regard, new studies are still exploring more effective treatments: On January 25, 2020, a joint study from the Shanghai Institute of Materia Medica, the Chinese Academy of Sciences, and the Shanghai University of Technology tested and identified 30 potential drugs that are reported to be effective against COVID.

RESULTS & DISCUSSION

Coronaviruses were not considered highly pathogenic until the outbreak of severe acute respiratory syndrome (SARS) in Guangdong Province, China, in 2002–2003, because the coronaviruses that circulated in humans before that time mostly caused mild infections in immunocompromised individuals. Some of the genome sequences of COVID–19 also show similarities to MERS. It would be interesting to study the relationship between SARS, MERS, and COVID–19, which could be used to develop broad–spectrum antiviral therapies. Since a large number of people have left Wuhan, controlling the epidemic is urgent. Coronaviruses cause mild to severe respiratory and enteric syndromes in animals and humans. However, some genera in this family can cause severe infections in infants, young children, and the elderly. The most recent case is COVID–19. Due to the lack of effective antiviral drugs, the prognosis of patients depends solely on their age and physical condition (Heidari, 2018). However, the number of positive cases and deaths continues to increase. The mortality rate for COVID–19 in infants is about 3.4%, for SARS 9.6%, and for MERS 34.4%.

CONCLUSION

In addition to the physical problems it causes, COVID–19 also has psychological impacts on the general population, especially on vulnerable groups. Therefore, it is essential to design psychological interventions to improve mental health during pandemics. Also, increasing public awareness of government measures to counter the spread of rumors and increasing public awareness by providing information on the recovery process of patients can reduce anxiety in the community (78). It is likely that the number of clinically recovered patients will exceed the number of deaths, but most patients are still not treated in the hospital. In addition, the potential adaptive mutation of the coronavirus is of particular importance for vaccine development. Therefore, it is essential for us to develop more sensitive methods and effective drugs.

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Competing Interest

The authors had no competing interests.

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