

Original Article

Emerging SARS-Cov-2 Infection in a Rapidly Changing World

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Abstract

Background and objectives: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh member of the coronavirus family to infect humans. The coronavirus disease was first identified in late 2019 in Wuhan, China. More than five million people in different countries have been infected with the virus in a matter of months. Although many studies have been done on the molecular immune pathogenesis and genetics of SARS-CoV-2, there is still not enough information about the virus. The purpose of this study is to summarize the latest information on SARS-CoV-2 characteristics, transmission, prevention and management to increase awareness and stop the virus transmission cycle.

Conclusion: The incidence of post-tonsillectomy hemorrhage, the methods for its management and the need for re-admission are quite different in different age groups.

Keywords: COVID-19; Corona virus; SARS-CoV-2

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INTRODUCTION

Over the past 18 years, the world has witnessed three deadly outbreaks of emerging coronaviruses (CoVs), known to cause gastrointestinal and respiratory problems in humans. The first outbreak of severe acute respiratory syndrome (SARS) was caused by SARS-CoV in 2002 in Guangdong, China, which affected 8,098 persons in 37 provinces (1). In 2012, another outbreak called the Middle East Respiratory Syndrome (MERS-CoV) occurred in the Middle East (2). Recently, a new outbreak of coronavirus disease (COVID-19) appeared in Wuhan, China that spread rapidly around the globe. The causative agent of COVID-19 was first identified in late January 2020 as SARS-CoV-2 or 2019-nCoV (3). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh member of the CoVs family to infect humans (4). China started to investigate symptomatic patients who had been in close contact with wet markets and declared that the infection may be caused by a new virus. According to the World Health Organization (WHO) report on July 20th, 2020, there are 14,664,054 laboratory-confirmed cases of COVID-19 and 609,279 deaths in 213 countries (5). China, Italy, the United States, Spain and Germany currently have the highest mortality rates (6). The WHO conducted further studies on the virus's genome and concluded that the virus had more than 95% homology with the CoV in bats. Although it is assumed that the source of the virus is *Rhinolophus affinis* species from Yunnan Province, the intermediate animal that could transmit the virus to humans remains unknown (7). Many have reported pangolins to be the main suspects because of 91% homology between SARS-CoV-2 and pangolin-CoV. In addition, the S protein has a similar structure in both viruses (8). The Coronaviridae family is placed in the Nidovirales order that has two subfamilies namely Coronavirinae and Torovirinae. There are also four groups for

Coronavirinae based on phylogenetic clustering: alpha, beta, gamma and delta CoVs (9, 10). The SARS-CoV-2 has a crown like appearance under electron microscope. They are enveloped viruses with a single strand, positive-sense RNA genome with variable GC content, which is the largest known genome for an RNA virus. The RNA genome contains seven genes (27-31 kB), 14 open reading frames (ORFs) that encode 27 proteins. The diameter of this enveloped virus varies between 14-60 nm (11). It has four major structural proteins: the spike surface glycoprotein, small envelope protein, matrix protein and nucleocapsid protein, which is increased in patients with no history of contact with live animals indicating that virus is spread via human-to-human transmission or contaminated surfaces (11). Patients with severe conditions are more contagious than those with mild to moderate symptoms. Asymptomatic patients as well as those in the incubation period with no sign of respiratory infection are potential sources of infection (12). In terms of infection spectrum, the disease is considered as self-limiting and most cases can be cured with mild symptoms in 1-2 weeks (12). The frequency of asymptomatic, mild to moderate, severe and critical cases is estimated to be 1.2%, 80.9%, 13.8% and 4.7%, respectively. In addition, there is an estimated 2.3% mortality rate. Recent studies have shown that the rate of asymptomatic infection in children under 10 years of age is 15.8% (13, 14). Overall, 98% of patients had bilateral involvement in chest CT scans. Patients with underlying disorders have poor diagnosis and the mortality rate in non-underlying disorders was 0.9%. Moreover, the mortality rate in patients with cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancer was 10.5%, 7.3%, 6.3%, 6.0% and 5.6%, respectively (15). Older people and those with underlying

diseases like asthma, diabetes, cardiovascular disease and cancer may be more susceptible to the virus, while smoking and obesity are predisposing factors. Those in close contact with the infected individuals including healthcare workers and patients' family members are also at high risk of contracting the virus (16).

Life cycle of SARS-CoV-2 in host cells

Although many proteins are involved in virus production and host invasion, spike proteins (S protein) are the most important factor in determining host domain. Glycoproteins play an essential role in binding to receptors on host cells, membrane fusion, host tropism, transmission capacity and determining host tissue orientation. The S protein is a type 1 transmembrane protein with a separable N-terminal peptide signal, a large and heavy actinomycin n, a membrane transregion and a cytoplasmic tail containing a cluster of s-acylated cysts. Each monomer termeric protein is approximately 180 kD, which includes two subunits S1 and S2. The second S1 carries the binder-receptor activity, and the second protected s2 catalyzes the membrane fusion. The second S1 is divided into two parts: N-terminal domain (ntd) and C-terminal domain (ctd). Ntd is shown as a structural fold such as human galactin, in order to be a binding factor. The ctd in SARS-CoV and ncov-2019 is responsible for binding to angiotensin-converting enzyme 2 (ACE2) receptor and consists of two subdomains: a nuclear structure consisting of a 5-strand antiparallel plate and a real receptor binding motif (RBM) that determines the receiver's connection characteristics. Based on the RBM-ACE2 complex, most S residues in contact with the ACE2 receptor are shared

between SARS-CoV and SARS-CoV-2. However, some are unique including an important salt bridge that contains various amino acids in ACE2 in order to bind to SARS-CoV and SARS-CoV-2. These minor differences may explain the more effective connection of SARS-CoV-2 S protein to ACE2. However, this has not been observed in other preliminary studies.

Variety of receiver usage is a prominent feature of CoVs (assuming they are all derived from a common ancestor) that they have already changed the connection feature of their receiver several times during evolution. Depending on the virus, the second ntd or ctd can act as a receptor binding domain (rbd). Depending on the virus type and the cell type, the spike CoV protein may be synthesized by one or more proteins, including furin, trypsin, cathepsins, transmembrane protease serine protease-2 and -4 or human airway trypsin-like protease. The availability of these proteases on the target cell determines whether CoVs enter the cell through the plasma membrane or endocytosis (17). An important feature of the SARS-CoV-2 is having a polybasic cleavage site where S1 and S2 are connected. This feature is important for effective cutting by furin and other proteases to generate S1 and S2 (18). N protein binds to the nucleic acid of the virus; therefore, it plays a role in replication and host response. It seems that phosphorylation of protein N and structural changes play a role in viral genomes (19). The main structural protein in the virus is M protein, which binds to N protein and is involved in its stability and the formation of N-RNA complexes (20). The N protein is also involved in virus maturation. The largest gene for SARS-CoV-2 is ORF1ab, which encodes pplab protein and non-structural proteins (Figure 1).

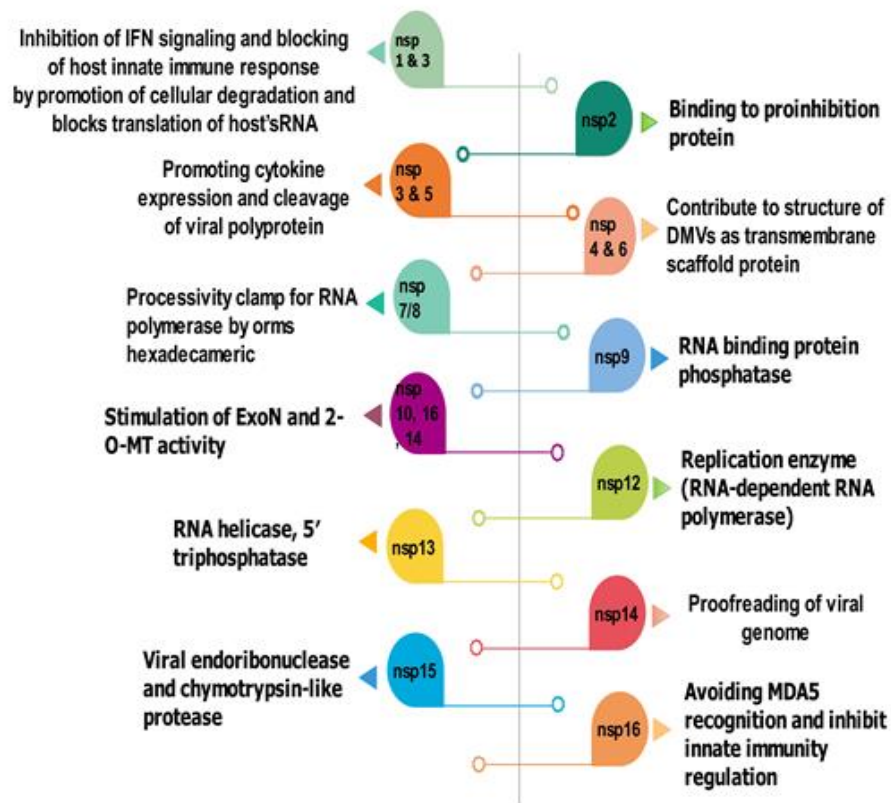


Figure 1. Non-structure proteins (nsps) and their function in coronaviruses. All Figures were drawn using the Edraw Max 10.0.4 software.

Polyproteins are completed by a protein similar to papain and a similar protease encoded by chemotripicin 3clpro (encoded in nsp3 and nsp5). Compared to SARS-CoV, 8a protein is absent and the level of 8b and 3c proteins is higher and lower in SARS-CoV-2, respectively (Figure 2) (21, 22).

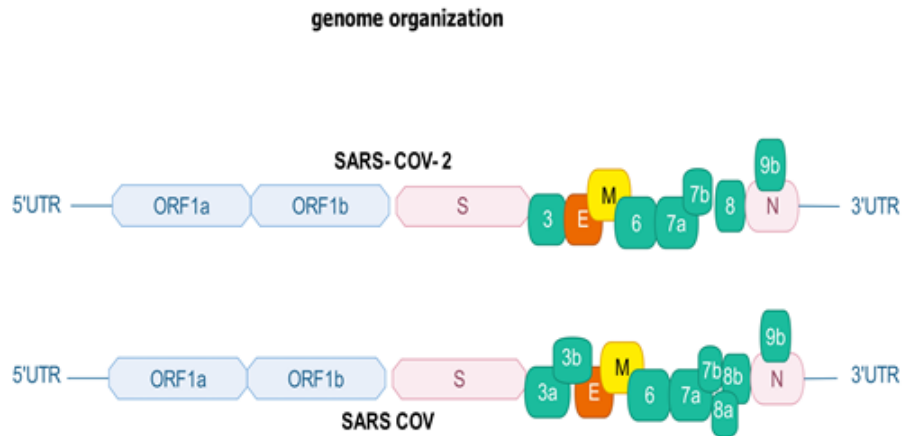


Figure 2. Genome structure in SARS-CoV and SARS-CoV-2

Two important proteins are known to be the main causes of viral penetration: ACE2 and TMPRSS2 (23). As figure 3 illustrates, the binding of glycoprotein S to the ACE2 receptor in the lower respiratory tract, is the starting point for the virus to enter the host cell (24). It is necessary to connect to the ACE2 receptors, five of which are different between SARS-CoV-2 and SARS-CoV. A mutation (N501T) has been found in the S protein of the virus that increases the binding affinity to the receptor. This binding of the membrane to the host cell and the virus is associated with fusion (25) and activation of the S

protein, which changes the conformation and leads to viral entry. The genomic material of the virus is released into the cytoplasm, which can be translated into proteins. Structural and peripheral proteins translated from subgenomic proteins and genomes containing the N protein are transferred to the endoplasmic reticulum and then to the endoplasmic reticulum-Golgi intermediate compartment, forming a complete virus-containing vesicle and exiting the virus by exocytosis (25, 26).

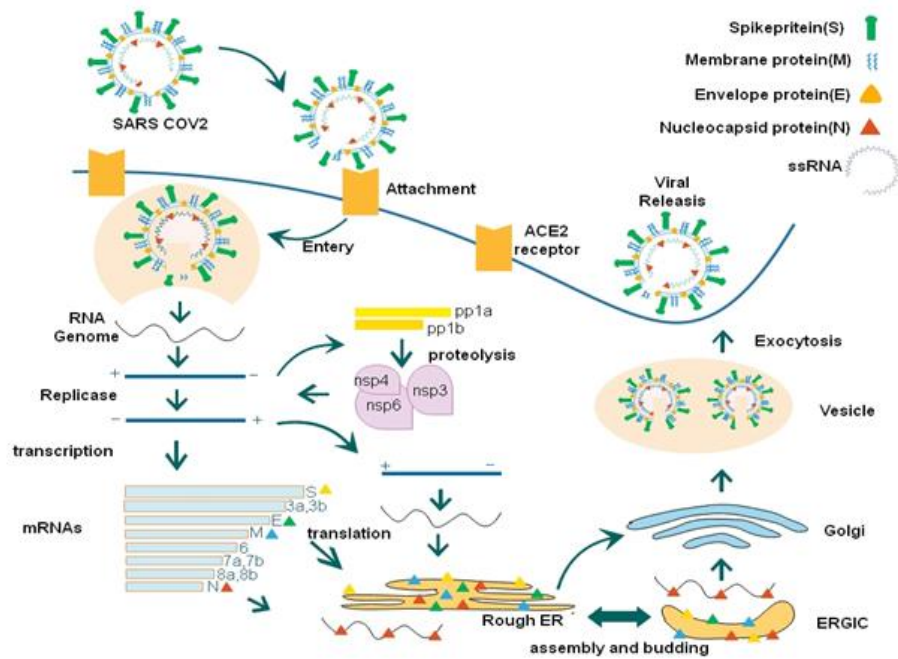


Figure3. SARS-CoV-2 life cycle in host cell.

First, the S protein binds to the ACE2 receptor, leading to fusion of the viral envelope and the cell membrane. Next, the virus enters the cell via the endosome pathway and the S protein is separated. The virus genome is released into the host cell and translates into 1a and 1b polyproteins. These proteins are broken down by proteases. Genome transcription creates a set of mRNAs. Viral genome and proteins merge into the endoplasmic reticulum and Golgi apparatus and then leave the cell by endocytosis.

The main modes of COVID-19 transmission

Knowing the routes of transmission is essential for the prevention and control of infectious diseases. Recombination in S protein has given the virus high transmission capacity compared to influenza and common cold viruses in a way that each COVID-19 patients can spread 1.8-fold more contacts compared to flu patients through infected bodily fluids (27, 28). It is important to note that if these infected respiratory droplets are present on surfaces, transmission to new host will become possible. The SARS-CoV-

2 can also be transmitted during asymptomatic periods. It is possible to

prevent the spread of infection and virus transmission through improving our knowledge about hygiene and virus's growth conditions in different conditions. The major route of SARS-CoV-2 transmission is via droplets and close contact. The SARS-CoV-2 is believed to be more transmissible than the SARS-CoV (29). Reports suggest that the SARS-CoV-2 can also be detected in urine and feces of patients. However, there is no evidence of virus transmission via consumption of virus-contaminated foods, aerosols or vertical transmission in pregnancy(30,31).

Infection prevention and control for SARS-CoV-2

The WHO has recommended several ways to prevent the transmission of SARS-CoV-2 virus. First, it is important to use a tissue when coughing and sneezing, or cough or sneeze in the elbow. Governments began

quarantining people in their homes as the best and safest way to control the virus (32). People with mild symptoms should isolate themselves and stay at home, especially if they have a fever above 37.8 °C and persistent cough. It is recommended that people do not go to hospitals and pharmacies and stay at home for 14 days. The following steps should be taken to prevent infection and reduce virus transmission: wash hands regularly with soap and water for at least 20 seconds, or soak and rub hands in alcohol, keep at least 2 meters distance from others, avoid unnecessary trips, stay away from large groups of people and follow government guidelines (32).

Clinical management of COVID-19

There is currently no specific vaccine or treatment for the SARS-CoV-2 virus, although a number of clinical trials are being carried out. Asymptomatic patients as well as those with mild clinical symptoms do not need to be hospitalized. Although clinical signs and symptoms may worsen in the second week of the illness, all patients should be closely monitored for any changes in their vital signs, oxygen saturation, respiratory rate, blood pressure, pulse and blood glucose levels (33). Intense COVID-19 management with oxygen therapy is one of the recommendations of the WHO. Plasma therapy is one of the ways to control the COVID-19 pandemic (34). Although anti-parasitic drugs such as chloroquine and hydroxychloroquine have been approved by

the US Food and Drug Administration to be tested against the SARS-CoV-2 virus, their administration should be closely monitored due to side effects. In addition, there are some other anti-inflammatory drugs and vaccine that are currently under testing (34).

Effects of temperature and humidity on SARS-CoV-2

Like many other viruses, SARS-CoV-2 is thought to be sensitive to heat and humidity, which can inactivate or reduce transmission to some extent. Temperature has a huge impact on the SARS-CoV-2 spread, while research suggests that warm and wet climates reduce the transmission of the virus (35). According to a systematic study, very hot, very cold and also warm and wet weather prevent the SARS-CoV-2 activity. Based on the information on SARS-CoV-1 and MERS-CoV, it is assumed that SARS-CoV-2 could become inactivated in warm and wet climates (35).

Survival of SARS-CoV-2 on different surfaces

In addition to person-person transmission, contact with contaminated surfaces can also cause SARS-CoV-2 infection. However, sterilizing surfaces can eliminate the virus. As shown in figure 4, the half-life of the virus on plastic and stainless steel is higher than that on other surfaces such as wood and copper. Moreover, the half-life of the virus in aerosols is about 90 minutes (29).

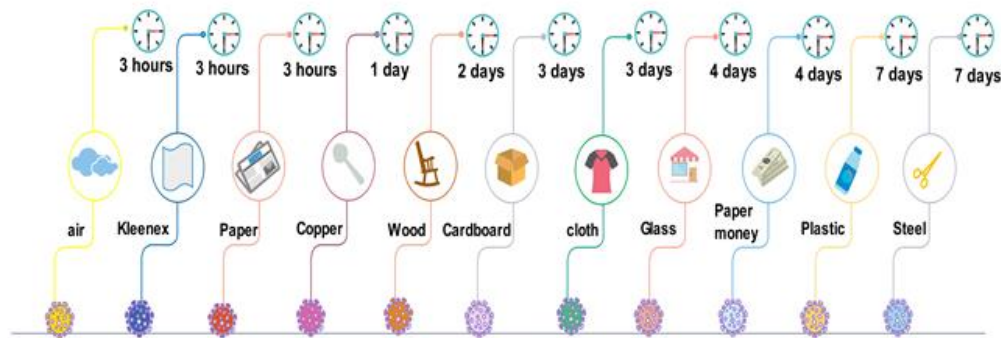


Figure 4. Stabilization time of the SARS-CoV-2 on different surfaces at room temperature

Signs and symptoms of COVID-19 infection

According to the WHO, pyrexia is the most common symptom (36). Although coughing is a common symptom, sputum is less common in patients. COVID-19 is very similar to flu and common cold in terms of clinical presentation, but it can be distinguished by certain features. For example, rhinorrhea and nasal congestion are frequent in common cold (37). Gastrointestinal-related symptoms include nausea, diarrhea, and vomiting (38). The most important complication of COVID-19 is lung damage, which affects older people and those with underlying disease. It should be noted that anosmia and ageusia are common in almost two third of patients because the virus can cause neuronal brain damage via the olfactory nerve. On the other hand, olfactory dysfunction has been considered as a marker of COVID-19 (39, 40). Other common symptoms of the disease include muscle pain and chills (41). The average age of people affected with the COVID-19 is 47 years with an estimated 2-3% mortality rate. The risk of developing COVID-19 is directly related to factors such as hypertension, diabetes, respiratory disease and cardiovascular disease (36). It has been also suggested that the level of ACE2 expression in different human tissues may be an important determinant of

susceptibility, symptoms and outcome of COVID-19. The RBD binds to the ACE2 receptor present in the heart, lungs, kidneys and gastrointestinal tract, thus facilitating the entry of the virus into the target cells. Children under the age of 14 are at lower risk of contracting the infection since they have lower ACE2 receptor expression level compared to those over 60 years of age and smokers. Of course, this difference in ACE2 receptor expression can also be affected by geographical locations as the receptors is overexpressed in Asians.

Diagnostic testing and screening for SARS-CoV-2

Due to the fact that COVID-19 is a new pandemic, there is no specific diagnostic test. After complete sequencing of the viral genome on January 12, 2020, it became possible to setup a real-time PCR test with almost 80% sensitivity. The test can be performed using respiratory samples such as sputum and throat swab. Given the relatively low sensitivity and long duration of the real-time PCR test, chest CT-scan is performed to confirm COVID-19 in hospitals (42). This test is more sensitive (95%) and specific because it can illustrate infiltrates, ground glass opacities and sub-segmental consolidation (43). Repeating the real-time

PCR testing increases the chance of correct diagnosis. It should be noted that X-ray is not sensitive enough to be used for the diagnosis of COVID-19. Serological antibody testing can also be a good diagnostic tool for the detection of the infection. In this regard, it has been shown that combined IgM-IgG testing has a high sensitivity for rapid screening for the COVID-19 (44). Other highly sensitive diagnostic methods based on nucleic acid amplification include loop-mediated isothermal amplification, specific high sensitivity enzymatic reporter unlocking and CRISPR-Cas12 (45, 46).

Routine laboratory tests

Routine blood tests are usually nonspecific to COVID-19 diagnosis, but there is an increase in C-reactive protein, erythrocyte sedimentation rate, alanine aminotransferase/aspartate transaminase ratio, prothrombin time, creatinine, D-dimer, creatine kinase and lactic acid dehydrogenase level in severe cases. On the other hand, standard blood investigations revealed that most patients with COVID-19 have normal or decreased leucocytes as well as lymphocytopenia. Common clinical laboratory findings include leucopenia and lymphopenia. Half of patients have abnormal liver function with elevated alanine aminotransferase or aspartate aminotransferase. Most patients have abnormal myocardial zymogram, which is accompanied with elevation of creatine kinase and lactate dehydrogenase. Furthermore, most patients show normal serum levels of procalcitonin, but the C-reactive protein is above the normal range (47).

Immune responses in COVID-19

The innate immune system is essential for virus detection. In order to induce a sufficient antiviral inflammatory response, it is essential to activate certain pathways. First, the single stranded RNA of SARS-CoV-2 is identified as pathogen-associated molecular pattern by cytosolic receptors

such as toll-like receptors, retinoid-inducible gene and melanoma differentiation-associated gene 5. These receptors can initiate inflammatory signals through nuclear factor κ B, activator protein 1 and interferon response factor 3 in order to produce inflammatory cytokines and chemokines (48). It is noteworthy that type I interferons (α and β), which are important in antiviral responses are suppressed by the SARS-CoV-2 (49). Following the innate immune response, in order to have an adoptive immune response, the viral antigenic peptides must be presented to cytotoxic T lymphocytes by major histocompatibility complex (MHC) or human leukocyte antigen (HLA) in humans on antigen presenting cells (50). The type and manner of antigen presentation to immune cells is crucial for treatment and prevention of infectious diseases. As mentioned, HLA plays a key role in initiating immune responses because the antigen receptors on T lymphocytes can detect antigen peptides. Therefore, genetic and haplotype diversity can be a significant factor in detection of the virus. According to previous studies, HLA loci polymorphisms affect disease susceptibility. Therefore, HLA loci could be an important candidate for treatment and even prevention of COVID-19 (50).

Humoral immunity response

Humoral and cell-mediated immunity are two components of the adoptive immune system. In the humoral immune response, IgM and IgA are the first traceable antibodies in serum, but IgG which is produced against the N protein can be detected in the serum after 10 days. Nine days after contracting the disease, IgM levels increase, and class switching to IgG can be identified in about 14 days (44).

Cellular immune response

In the case of cellular immunity, infection is accompanied with a decrease in T lymphocyte subsets and an increase in the production of inflammatory cytokines that

has a positive correlation with disease severity. Reduction in T lymphocytes subsets can be a differential diagnosis for SARS viruses. Interestingly, the cytotoxic T lymphocytes and CD4+/CD8+ ratio have a meaningful association with the inflammatory condition in COVID-19 patients. The lack of memory cells in COVID-19 is controversial (51). In fact, it is considered an important barrier to vaccination against the disease.

Cytokine and chemokine storm

Uncontrolled activation of inflammatory pathways and production of cytokines and inflammatory chemokines can damage body organs. Among the important produced cytokines (IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , TGF β , etc.), an increased production of chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10 have been reported in inflammatory conditions. In addition, increased activation of markers such as HLA-DR and CD45RO and even IL-2 receptor has been reported in patients with COVID-19 (52). On the contrary, co-stimulatory molecule CD28, natural regulatory T cells, dendritic cells and B cells activation were all decreased in extremely severe patients. The most important complication of COVID-19 is a systemic inflammatory disease called acute respiratory distress syndrome, which is also the main cause of mortality (51).

CONCLUSION

To date, COVID-19 could be a once-in-a-century pandemic that is affecting millions of people worldwide. Due to the alarming rate of COVID-19 spread, medical professionals are investigating strategies for the diagnosis, management and containment of the disease. Although developing a preventive vaccine is of utmost importance, research is also essential for establishing effective treatment methods, particularly against the resistant strains of the virus.

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Conflict of interest

The author declares that there is no conflict of interest regarding publication of this article.

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