

# Epidemiology of COVID-19: An updated review

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a zoonotic infection, is responsible for COVID-19 pandemic and also is known as a public health concern. However, so far, the origin of the causative virus and its intermediate hosts is yet to be fully determined. SARS-CoV-2 contains nearly 30,000 letters of RNA that allows the virus to infect cells and hijack them to make new viruses. On the other hand, among 14 detected mutations in the SARS-CoV-2 S protein that provide advantages to virus for transmission and evasion form treatment, the D614G mutation (substitution of aspartic acid [D] with glycine [G] in codon 614 was particular which could provide the facilitation of the transmission of the virus and virulence. To date, in contrary to the global effort to come up with various aspects of SARS-CoV-2, there are still great pitfalls in the knowledge of this disease and many angles remain unclear. That's why, the monitoring and periodical investigation of this emerging infection in an epidemiological study seems to be essential. The present study characterizes the current epidemiological status (i.e., possible transmission route, mortality and morbidity risk, emerging SARS-CoV-2 variants, and clinical feature) of the SARS-CoV-2 in the world during these pandemic.

**Keywords:** COVID-19, pandemics, SARS-CoV-2 variants, transmission

**How to cite this article:** Halaji M, Heiat M, Faraji N, Ranjbar R. Epidemiology of COVID-19: An updated review. J Res Med Sci 2021;26:82.

## INTRODUCTION

In late December 2019, hospital physicians in Wuhan, China, reported unusual cases of pneumonia. Subsequent studies have shown that the origin of this disease is from the food market in Wuhan City, Hubei Province, in Central China. By confirmation of the Chinese section of the Centers for Disease Control and Prevention (CDC), on January 2, 2020, the cause of the disease was announced to be a new coronavirus called nCoV-2019. The World Health Organization (WHO) approved the results of isolation of genome and genomic sequencing of the nCoV-2019 on February 11, 2020.<sup>[1]</sup> The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, positive single-stranded RNA virus, belongs to the Riboviria Realm, Orthornavirae Kingdom, Pisuviricota Phylum, Pisoniviricetes class, Nidovirales order, Coronaviridae family, Coronavirinae subfamily and

beta-coronavirus ( $\beta$ -CoV) genus, *Sarbecovirus* subgenus, and SARS-related coronavirus species.<sup>[2]</sup>

SARS-CoV-2 contains nearly 30,000 letters of RNA (29,903) (GenBank: MN908947.3)<sup>[3]</sup> that allows the virus to infect cells and hijack them to make new viruses. Studies have shown that this virus applies its spike protein to bind to cell receptors such as the angiotensin-converting enzyme 2 (ACE2) receptor protein and transmembrane serine protease 2 (TMPRSS2) protease, to enter cells. Findings confirmed that the spike protein structure with 3822 nucleotides is the main reason for higher infectivity of SARS-CoV-2 than its ancestors.<sup>[4,5]</sup>

The most common clinical symptoms of the COVID-19 patients are fever, cough, shortness of breath, and other breathing difficulties in addition to other nonspecific symptoms including headache, dyspnea, fatigue, and muscle pain and digestive symptoms such

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10.4103/jrms.JRMS\_506\_20

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**Submitted:** 20-May-2020; **Revised:** 30-Dec-2020; **Accepted:** 25-Apr-2021; **Published:** 30-Sep-2021

as diarrhea and vomiting.<sup>[6]</sup> The incidence of COVID-19 continues to increase. Globally, up to February 10, 2021, 106,797,721 infected cases, including 2,341,145 deaths, have been reported.

To date, in contrary to the global effort to come up with various aspects of SARS-CoV-2, including clinical manifestations, epidemiology, mortality and morbidity, and diagnosis, there are still great pitfalls in the knowledge of this disease and many angles remain unclear. That's why, the monitoring and periodical investigation of this emerging infection is an essential issue. The present study characterizes the current epidemiological status (i.e., possible transmission route, mortality and morbidity risk, emerging SARS-CoV-2 variants, and clinical feature) of the SARS-CoV-2 in the world in 2020–2021.

## **DOMINANT TRANSMISSION ROUTES**

SARS-CoV-2 can be transmitted directly from human to human and indirectly via contaminated objects.<sup>[7]</sup> Person-to-person transmission of SARS-CoV-2 occurs mainly via respiratory droplets spread by coughs, sneezes, or even talking. Droplets usually cannot proceed more than six feet. SARS-CoV-2 remains contagious in droplets and suspends in the air for maximum 3 h.<sup>[8]</sup> However, the WHO demonstrated that airborne transmission is not a significant route in disease transmission on 75,465 confirmed COVID-19 cases in China as of March 27, 2020.<sup>[9]</sup> In order to prevent aerosol spread of SARS-CoV-2, room ventilation and airborne isolation can be useful.<sup>[10]</sup>

Direct contact of a contaminated hand with mucous membranes such as the eyes, nose, or mouth can also transmit the virus.<sup>[11]</sup> Therefore, handwashing with soap and water or using sanitizers can be helpful. Transmission of SARS-CoV-2 from asymptomatic cases without any paraclinical findings may also occur.<sup>[12-14]</sup> Hence, there is an urgent need for sensitive and fast diagnosis of suspected individuals.

In a multicenter study while each patient showed at least two nonpolymerase chain reaction (PCR) negative tests, the reverse transcription-PCR remained still positive up to 13 days after discharge.<sup>[15]</sup> Viral shedding in the stool takes place up to 5 weeks<sup>[16]</sup> with a mean of 11.2 days after a negative respiratory test.<sup>[17]</sup>

Although positive blood and stool samples for SARS-CoV-2 RNA have been reported and some COVID-19 patients had positive stool cultures for living SARS-CoV-2,<sup>[18]</sup> a WHO-China report showed that fecal-oral transmission is not a major route.<sup>[11]</sup> However, a recent study in China with 1070 specimens collected from 205 COVID-19 patients

showed that 29% of positive COVID-19 individuals have been infected by transmission via feces.<sup>[18]</sup>

Based on studies of semen and testicular samples of COVID-19 patients, SARS-CoV-2 is not sexually transmitted.<sup>[19]</sup> In a recent case report, an infant delivered from a COVID-19-positive mother was tested negative for 7 samples of pharynx, blood, and stool;<sup>[20]</sup> on the other hand, some studies demonstrated that immunoglobulin M against SARS-CoV-2 was detected in blood samples of newborns; therefore, vertical transmission of SARS-CoV-2 is still a matter of conflict.<sup>[21,22]</sup>

Although it is not clear that SARS-CoV-2 can be transmitted from infected animals to humans, this phenomenon needs to be considered as a possibility.<sup>[23]</sup> SARS-CoV-2 is able to infect dogs, cats, and some other animals.<sup>[24]</sup> A German shepherd dog was reported dead (with unclear cause of death and no autopsy) 2 days after quarantining the pet owner because of COVID-19. Cat-to-cat transmission of SARS-CoV-2 has been reported, but it is not clear if cat-to-human transmission is possible.<sup>[9]</sup>

## **FACTORS CONTRIBUTING TO RISK OF THE DISEASE**

SARS-CoV-2 can spread through direct and indirect contact (human-to-human and contaminated objects). Meantime personal protective equipment could also be considered as the possible source of airborne infections.<sup>[7]</sup> Transmission factors are varied from environmental, behavioral, and physical to virological (viral loading, location of virus receptor, etc.) features which can infected individuals and cause serious problems.<sup>[25]</sup> SARS-CoV-2 aerosol spread can occur when a person touches a contaminated surface, and then, the hands contact with mucous membranes such as the mouth, nose, or eyes. Therefore, proper sanitizers or washing hands with soap and water is recommended.<sup>[25]</sup> Despite RNA of SARS-CoV-2 has been detected in blood and stool sample, a joint WHO-China report indicated that fecal-oral transmission did not seem to be an important spread factor.<sup>[25,26]</sup> Consequently, Xiao *et al.* documented evidence of gastrointestinal SARS-CoV-2 infection and represented the risk of virus transmission via the fecal-oral route, which can be as a possible route for SARS-CoV-2 transmission.<sup>[27]</sup> It seems that the risk of virus transmission is greater than what we think. Vivanti *et al.* reported a case of SARS-CoV-2 transplacental transmission from a pregnant woman infected by COVID-19 during late pregnancy to her fetus. The load of virus was much more higher in the placental tissue than in the amniotic fluid or maternal blood which based on the European Centre for Disease Control (<https://www.ecdc.europa.eu/en/all-topics/coronavirus/threatsand-outbreaks/covid19/>

laboratory-support/questions) detecting both “E” and “S” genes of SARS-CoV-2 is confirming positive result. The viral load in the placental tissue was much higher than in amniotic fluid or maternal blood.<sup>[28]</sup> Furthermore, some systematic reviews demonstrated vertical transmission of SARS-CoV-2, vaginal delivery from mother to neonate 9.6%–21%,<sup>[29,30]</sup> and maternal immune cells. Nevertheless, vertical transmission of mother-to-infant hypothesis requires further investigation. One of the major problems of SARS CoV-2 pandemic is decreasing transplant rate which leads to increasing mortality on the waiting list, for instance, in Spain as a great pandemic area for SARS-CoV-2, on March 13, 2020, the mean number of donors has declined from 7.2 to 1.2 per day, and the mean number of transplants from 16.1 to 2.1 per day.<sup>[31]</sup>

## NOSOCOMIAL TRANSMISSION

Nosocomial transmission of SARS-CoV-2 is a serious health center problem which is facilitated by mobile phones of health-care workers and hospital equipment.<sup>[32]</sup> One case report study showed a person-to-person transmission between health-care workers and patients. Of forty-eight study cases, six out of twelve patients had SARS-CoV-2-positive results by RT-PCR and had shown symptoms at the time of examination.<sup>[33]</sup> Among high-risk professionals at SARS-CoV-2 outbreak, dental professionals are at the top of the nosocomial transmission and infection list that make them to become as a disease potential carriers.<sup>[34]</sup> The previous studies showed the existence of SARS-CoV-2 in patient’s face and saliva,<sup>[35,36]</sup> in which SARS-CoV-2 was able to bind to the receptors of ACE2 indicating a remarkable reason for the existence of COVID-19 in the secretory saliva.<sup>[1,37]</sup> Consequently, the transmission of SARS-CoV-2 via aerosol or fomites and health-care facilities is plausible, which may be related to person-to-person transmission in the dental clinics.<sup>[38]</sup> The Epidemiology Team of Coronavirus Pneumonia Emergency Response (2020) represented that COVID-19 nosocomial coughing transmission is still imprecise, but in China, around 1716 hospital staff have been infected by February 2020 during their makeshift. Those huge infections numbers probably have been occurred by the person-to-person transmission of viral-loaded aerosol.

The CDC has declared that till April 2020, in the USA, around 9000 medical center staff have been identified with SARS-CoV-2-positive results, which could be related to airborne aerosol cloud nosocomial transmission.<sup>[39]</sup> Therefore, combination of handwashing and surgical face mask effectively decreases the rate of nosocomial transmission.<sup>[40]</sup> Among patients who were hospitalized or admitted, about 15 individuals (4.9%) were identified as a COVID-19 nosocomial infected patients.<sup>[41]</sup>

## MORBIDITY AND MORTALITY

According to the WHO, by February 2021, there have been 109,068,745 confirmed cases of SARS-CoV-19, including 2,409,011 deaths.<sup>[9]</sup> The mortality of COVID-19 is associated with some health conditions including older age (>60 years), gender, smoking history, preexisting pneumonia, and significant comorbid illnesses (such as immunocompromised states, chronic cardiovascular, cerebrovascular, pulmonary, kidney disease, diabetes mellitus, fulminant inflammation, lactic acid accumulation, and thrombotic events).<sup>[42-44]</sup> A meta-regression study has reported that hypertension is considered as a risk factor for both mortality and severity.<sup>[45]</sup> Although there is no sufficient documentation to display the association of this fatality with fever in SARS-CoV-2, fever and cough are the most frequent symptoms which have been related to death or sever acute condition in infected patients.<sup>[44]</sup> Children are less affected than adults, and clinical attack rates in the 0–19 age group are low and usually present as a mild disease.<sup>[46]</sup> Zhao *et al.* investigated association between the blood group and the SARS-CoV-2 among 2173 patients and compared them with normal patients in Wuhan and Shenzhen, China. The results showed that the proportion of blood group A in SARS-CoV-2 patients was significantly higher indicating it as a risk factor for the individuals.<sup>[47]</sup> SARS-CoV-2 has the ability to infect neurons *in vitro* and leads to neuronal death, but the data from CSF and autopsy examinations do not show consistent evidence of direct CNS invasion. Nevertheless, effects on the median eminence and other circumventricular organs cannot be prevented and may play an important role in the disease systemic expression.<sup>[2]</sup>

Furthermore, according to some case-cohort studies, there are some blood markers which can be related to mortality of SARS-CoV-2 in hospitalized patients, including lower oxygenation index, serum urea nitrogen, total bilirubin, lactate dehydrogenase (LDH), aspartate aminotransferase/alanine aminotransferase ratio, C-reactive protein (CRP), D-dimer, fibrin/fibrinogen (FIB) degradation products, FIB, erythrocyte sedimentation rate, and prolactin.<sup>[48-50]</sup> In a meta-analysis, Lippi *et al.* showed the remarkably lower level of platelet in patients with more severe COVID-19. Consequently, thrombocytopenia could be a clinical indicator and is also considered as a risk for severe disease and mortality in COVID-19 patients.<sup>[51]</sup>

Furthermore, some molecular investigations on SARS-CoV-2-infected patients have revealed a significant role of some molecular features and gene expression in susceptibility of infection and symptoms indication, such as ACE2, ACE1/ACE2, ACE2/TMPRSS2, renin-angiotensin system pathway, CD147, CD26-related molecules, and IFITM3.<sup>[52,53]</sup> Shi *et al.* represented that IFITM3 plasma

membrane localization increases SARS-CoV-2 infection, while IFITM3 endocytosis successfully restricts the virus.<sup>[54]</sup> FITM3 with IFITM2 was shown to enhance SARS-CoV-2 infection, quite than restrict it, both in the absence and presence of interferon.<sup>[55]</sup> Zhang *et al.* suggested that rs12252:G is the risk allele of COVID-19 in Chinese patients.<sup>[56]</sup> Devarajan *et al.* studied the single-nucleotide polymorphism rs12252-C/C in the gene IFITM3 as a risk factor that is associated with severe influenza in patients with COVID-19. However, they have suggested that further investigation of the IFITM3-rs12252-C/C allele in a large population is needed.

Although there are few reports of studies investigating the association of human leukocyte antigen (HLA) genetic variation and the immune response against SARS-CoV-2, Lin *et al.* represented that the HLA-B\*46:01 has been significantly related to the severity of SARS in Asian populations.<sup>[57]</sup> Another study showed that HLA-A\*24:02 is associated with SARS-CoV-2 susceptibility after noticing this allele in four of five patients from Wuhan.<sup>[58]</sup> The severity of SARS-CoV-2 disease is associated with elevation of IL-2R, IL-6, IL-10, and TNF- due to “cytokine storming”. It is related to the development of severe alveolar damage and lung inflammation as a distinctive pathological picture of the acute respiratory distress syndrome.<sup>[59]</sup> Among all previously mentioned risk factors, male gender, diabetes, age, and chronic heart and pulmonary conditions show higher morbidity or mortality associated by SARS-CoV-2.<sup>[60,61]</sup>

## NOTABLE FEATURES OF POSSIBLE ORIGINS, SOURCES, AND RESERVOIRS OF THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Zoonotic diseases are type of illnesses which normally exist in animals and could infect humans. Understanding the source of a zoonosis infection is very critical for health authorities to separate humans from infected animals, in the outbreaks or pandemics of zoonotic agents. SARS-CoV-2 as a zoonotic infection is responsible for COVID-19 pandemic and also is known as a public health concern. However, so far, the origin of the causative virus and its intermediate hosts is yet to be fully determined.<sup>[62]</sup>

Commonly, the SARS-CoV, MERS-CoV, and SARS-CoV-2 are known as highly zoonotic pathogenic  $\beta$ -CoVs with bat origin which caused tree pandemics in the 21<sup>th</sup> century.<sup>[20]</sup>

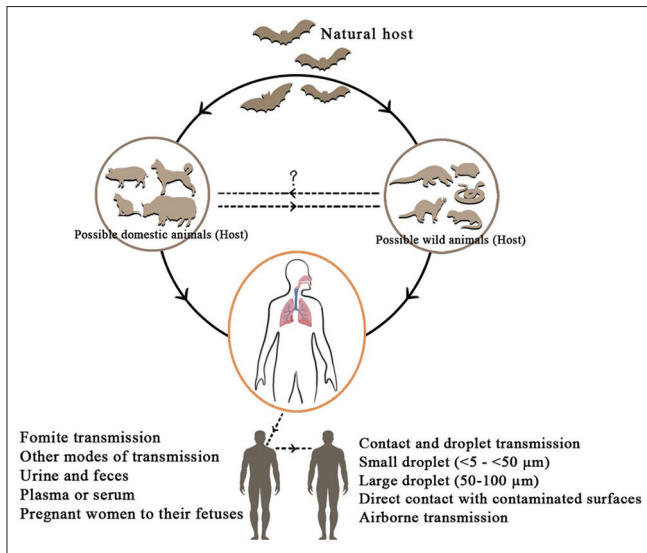
Previous reports have revealed that SARS-CoV and MERS-CoV have been spread from the source origin (bats) to the intermediate host (palm civets for SARS-CoV and camels for MERS-CoV) and then transmission circle has been completed by the transmission of the virus from the

interface hosts to the humans. Most likely, it seems that the SARS-CoV-2 may have been transmitted to subjects via the intermediate host.

Phylogenetic analysis is one of the good approaches to finding the possible sources and reservoirs of zoonotic agents. Phylogenetic data have shown that genomes of SARS-CoV-2, SARS-CoV, and MERS-CoV share noticeable similarities with each other.<sup>[63]</sup> To date, a large number of phylogenomic analysis investigations have reported that the complete genome sequence (~29.9 kb size) of SARS-CoV-2 had almost 80% and 96% similarity with human SARS-CoV and bat coronavirus at nucleic acid level, respectively, suggesting that the bats' CoV and SARS-CoV-2 might be generated from the common ancestor.<sup>[64,65]</sup> Furthermore, the recent studies have confirmed that bats are the primary reservoir of SARS-CoV and MERS-CoV.<sup>[66-68]</sup> Another report has introduced the pangolins as natural reservoirs for SARS-CoV-2-like CoVs, but there is no conclusive document that SARS-CoV-2 has a specific wildlife host as a virus reservoir.<sup>[69,70]</sup>

Besides bats, CoVs have been isolated from various animals such as snakes, minks, and pangolins and these animals have considered as a possible intermediate host for SARS-CoV-2.<sup>[71]</sup> Anyway, there is no experimental data to support the hypothesis of being of snakes and minks as interface hosts of the SARS-CoV-2. At the front, more advanced molecular analysis and virological studies suggested that pangolins are the most likely candidate for intermediate hosts and this suggestion is supported by phylogenetic analysis studies. For example, original papers have identified 99% and 85.5%–92.4% similarity in complete genome sequence of pangolin-CoV and SARS-CoV-2.<sup>[72]</sup> Meanwhile, another research has identified that S protein in receptor-binding domain (RBD) of isolated Malayan pangolin-CoV was almost the same as that of SARS-CoV-2.<sup>[73]</sup> The current main suggestion is that the CoVs derived from bat have infected the pangolins and then some genetical variations such as mutations and recombination phenomena evolved this pathogen for transmission to human.<sup>[24]</sup> Figure 1 represents the potential and possible transmission routs of SARS-CoV-2.

The S protein of SARS-CoV-2 is responsible for virus entry into the cells and beginning the infection in human. This viral protein shares approximately 80% similarity with the SARS-CoV ones in amino acid level, however, there are some difference in amino acid residues of the RBD-S protein between SARS-CoV and SARS-CoV2.<sup>[74]</sup> It seems that humans are infected with the virus directly from intermediate animal hosts through contact.<sup>[75]</sup> Now, it is obvious that the animals are main intermediate hosts for the evolution of SARS-CoV-2 via recombination and



**Figure 1:** Potential and possible transmission routes of severe acute respiratory syndrome coronavirus 2

mutation events. Nevertheless, further investigation and analysis may be needed to find the intermediate hosts and other sources.<sup>[76]</sup>

## INCUBATION PERIOD AND CLINICAL CHARACTERIZATION

The incubation period of an infectious disease is the time interval between the exposures to an infectious agent until signs and symptoms of the disease appear.<sup>[77]</sup> The incubation period of a disease can widely vary from one person to another. Understanding the incubation period data of a novel infectious agent is useful to estimating the size of the transmission potential and the pandemic, finding the active cases, assessing the effectiveness of entry screening and contact tracing, and relative infectiousness of a pathogen.<sup>[63,78]</sup>

The reported estimate of the novel coronavirus incubation time is based on limited case data. Using the data from many online publishes, the incubation period for the novel coronavirus is estimated to be in the range of 2–14 days;<sup>[78]</sup> however, two cases with an incubation period of 19 and 27 days have been reported in other public reports.<sup>[14]</sup> Although the median incubation period of COVID-19 is variable, many public studies have estimated approximately 5-day incubation time for this viral infection.<sup>[78-80]</sup> It has been shown that the median time to confirm the virus infection after first doctor's visit is around 1 (ranged from 1 to 2 days) day.<sup>[81,82]</sup> Further studies have reported that the median time from start of manifestation to dyspnea and hospitalization was 5 and 7 days, respectively. Furthermore, the median time for ARDS was 8 days.<sup>[25]</sup> Hence, applying at least 14-day quarantine, which is longer than incubation time of virus,

is a very effective policy to avoid the risk of COVID-19 transmission from active clusters to other subjects.<sup>[83]</sup> Studies that compare the average incubation time in SARS-CoV-2, SARS-CoV, and MERS infections, statistically remarkable differences in the incubation periods between these three coronaviruses have not reported,<sup>[3]</sup> while, some studies have suggested that new emerged COVID-19 had long incubation time than MERS and SARS-CoV<sup>[84]</sup> however, most studies with large sample size around the world are needed to find this issues.

The clinical outcomes of COVID-19 are variable, and there is no complete study on its true clinical features. Although SARS-CoV-2 is a respiratory tract virus, because the presence of cellular receptors (ACE2) for virus entry into host cell in the most organs, infection does not limit to lungs and it could be considered as a multi-organ infection with pulmonary and extrapulmonary outcomes.<sup>[85]</sup> Adults infected by COVID-19 can develop a spectrum of disease and illness severity, from asymptomatic to mild, moderate, or severe disease. In approximately 80% of patients, infection is asymptomatic or mild,<sup>[86,87]</sup> and unfortunately, in the 20% of infected patients, the disease progresses to severe stage with severe respiratory manifestations.<sup>[87,88]</sup> The major presenting manifestations of COVID-19 are fever, cough, headache, fatigue, myalgia, malaise, and shortness of breath or difficulty breathing. On the other hand, sore throat, muscle ache, confusion, sputum production, rhinorrhea, chest pain, conjunctivitis, diarrhea, nausea, and vomiting are less frequently seen in these patients.<sup>[89,90]</sup> Therefore, this disease cannot be distinguished from other respiratory diseases.

COVID-19 can be divided into four levels including mild, moderate, severe, and critical, based on the severity of clinical manifestations. The details of each level are represented in Table 1.

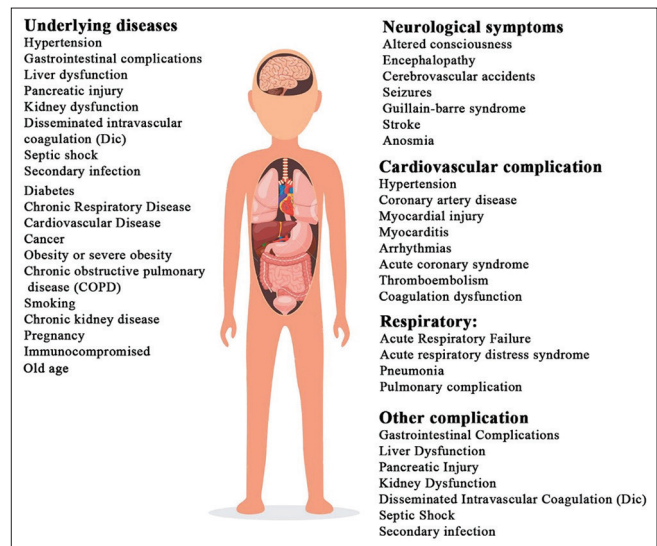
Analysis of clinical features in the young, middle-aged, and elderly SARS-CoV-2-sufferings from Hainan (China) indicated that fever was the common symptom in the all age groups and infection also followed by dry cough and sputum. Overall, the elderly and immunocompromised patients are more susceptible to the severe forms of COVID-19 and also the mortality rate in these patients is higher than young and middle-aged individuals.<sup>[20,82]</sup> Meanwhile, SARS-CoV-2 infection in neonates, infants, and children is markedly milder than their patients.<sup>[25]</sup> There are little data from SARS-CoV-2-perinatal infection, and previous studies indicated no evidence of perinatal infection during the pregnancy.<sup>[90,91]</sup> Furthermore, this virus has not been detected in the milk of mothers; however, mothers with ARS-CoV-2 infection are encouraged to use personal protective equipment during breastfeeding their babies.<sup>[92,93]</sup>

**Table 1: The clinical details of four levels of COVID-19**

Disease name	Severity level of COVID-19 symptoms	Clinical symptoms
COVID-19	Mild	The patients suffer from only mild symptoms without radiographic features
	Moderate	The patients suffer from fever, respiratory signs, and radiographic features such as ground-glass opacity
	Severe	Patients have one of three criteria including Oxygen saturation <93% in ambient air Dyspnea PaO <sub>2</sub> /FiO <sub>2</sub> <300 mmHg
	Critical	Patients have all of the three criteria including Oxygen saturation <93% in ambient air Dyspnea PaO <sub>2</sub> /FiO <sub>2</sub> <300 mmHg

According to published reports, complications observed in these patients included ARDS, shock, coagulation dysfunction, metabolic acidosis, acute lung injury, acute cardiac injury, and acute kidney injury. The disease in critical patients can quickly progress to multiple organ functional failure.<sup>[25,94]</sup> Furthermore, clinical complications such as ARDS and acute heart, liver, and kidney dysfunctions in elderly patients are largely higher than young and middle-aged ones.<sup>[68]</sup> The conducted studies have found a distinct positive correlation between age and peak viral load in clinical samples; all these suggest that viral replication can lead to clinical manifestations and death among the elderly group.<sup>[35]</sup> Although 4%–11% case fatality rate was recorded for the hospitalized ARS-CoV-2-positive patients,<sup>[25]</sup> the overall case fatality rates are truly different among different countries around the world. For example, it is 4.2% in China, 7.7% in Italy, 5.7% in Iran, 3.6% in the United Kingdom, and 6.2% in the United States of America. This is may be because of differences in medical care systems, number of undiagnosed cases with mild or asymptomatic stages of illness, sensitivity of laboratory detection methods, and population heterogeneity.<sup>[95,96]</sup> Hence, precise estimation of overall case fatality rates is impossible at now.<sup>[97]</sup> Figure 2 shows the main complication and comorbidity related to coronavirus disease.

Similar to SARS and MERS, COVID-19 led to the extreme enhance in the level of inflammatory cytokines such as IL-2, IL-6, IL-7, IL-10, interferon-inducible protein 10 (IP-10), granulocyte colony-stimulating factor, monocyte chemotactic protein 1, TNF- $\alpha$ , and macrophage inflammatory protein 1A (especially in intensive care unit patients) which is named cytokine storm<sup>[25]</sup> and is responsible for severe symptoms in the pulmonary tract.<sup>[98,99]</sup> Higher viral loads in the serum and stool are associated with drastically elevated IL-6 level and diarrhea, respectively.<sup>[18]</sup> The viral load in the salivary is reached to the maximum level during the 1<sup>st</sup> week after symptom onset and then decreased over time. The viral loads in some specimens indicate that extrapulmonary viral replication contributes to clinical manifestations. The most common

**Figure 2: Main complication and comorbidity related to coronavirus disease**

laboratory findings of COVID-19 are included neutrophilia, lymphopenia, enhanced LDH, prolonged prothrombin time, increased alanine transaminase, enhanced D-dimer, creatinine kinase, and CRP.<sup>[35]</sup>

## EMERGING SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 NOTABLE VARIANTS

The genome mutation of the SARS-CoV-2 during reproducing by infected cell is one of the ways of the virus evolution and the variability of the genome, thus allowing viruses to escape from the host immune system and cause drug resistance and also have an effect on the virus transmission and the disease severity.<sup>[100]</sup>

A group of viruses that share the same distinct inherited mutations is called a variant. Most of the reported mutations in this virus is related to mutations in its spike glycoproteins.<sup>[101]</sup> Among 14 detected mutations in the SARS-CoV-2 S protein that provide advantages to virus for transmission and evasion form treatment, the D614G mutation (substitution of aspartic acid [D] with glycine [G]

in codon 614 was particularly important since enables the virus to be at least 36% more transmissible than other variants.<sup>[102]</sup>

SARS-CoV-2 spike D614G variant, also called lineage B.1.1.7 or Variant of Concern 202012/01 which has emerged in the United Kingdom (UK variant), may be associated with an increased risk of death compared to the other variants.

This variant has an unusually large number of mutations such as nonsynonymous mutations, deletions, and synonymous mutations that some of them resulted in amino acid changes in the spike protein including ΔH69/V70, ΔY144, D614G, N501Y, A570D, P681H, T716I, S982A, and D1118H. These mutations are important. For instance, the spike protein with N501Y mutation that is located in the receptor-binding site (spike protein's RBD) binds more tightly to its cellular receptor, ACE-2.

The other variant 501Y.V2 that has been identified in South Africa was called B.1.351 lineage. The last three changes are located within the RBD which is estimated to cause 50% more transmissibility than previously circulating variants in South Africa.<sup>[103]</sup>

One novel variant which was described in Brazil, P. 1 variant (VOC202101/02, 20J/501Y.V3), is not tightly related to VOC 202012/01 or 501Y.V2 and has eleven amino acid alterations, L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, T1027I, and V1176F. Three of them (K417T, E484K, and N501Y) are located in the RBD. Due to the presence of N501Y, the increased transmissibility is assumed for this variant.<sup>[104]</sup> Another variant has been also reported in Brazil that was called as VUI202101/01, P. 2 which owns less mutation than P. 1 variants. Figure 3 reveals the global distribution of emerging variants of SARS-CoV-2. Another variant, an Indian type, Delta SARS-CoV-2 (B.1.617.2. AY.1, AY.2, AY.3 lineage), was detected in October

2020<sup>[105]</sup>, and spread drastically in many countries. A study demonstrated that the spread ability of variant delta (55% more transmissible than variant Alpha, said WHO) is due to its potency to escape to antibodies targeting non-RBD and RBD Spike epitopes<sup>[106]</sup>.

At the beginning of the COVID-19, numerous scientists and biopharmaceutical manufacturers have attended in research collaboration for developing medications, vaccine discovery, and manufacturing. To the best of our knowledge, about 100 vaccines reached the final testing stages. Most of the vaccine designs are based on two different variants of SARS-CoV-2 genomes, called L and S.<sup>[105]</sup> Some antiviral medications are prepared for clinical trials.<sup>[61,105]</sup>

Tracking the novel variants of SARS-CoV-2 is one of the important global issues. Some variants including 501Y.V2, B.1.351 and P. 1 could represent more transmissibility and impact on incidence of this pandemic.<sup>[107]</sup> Moreover, some concerns are growing about the impact of introduced vaccines and medications on newly discovered variants. For example, E484K in 501Y.V2 and P. 1 variants could cause a reduction in neutralization by the anti-RBD monoclonal antibodies.<sup>[108]</sup> There are also some evidences that this mutation has significant effects on viral sustainability and adaptive evolution which could decline vaccines efficiency.<sup>[109]</sup> Fortunately, almost all vaccines have maintained their efficacy to acceptable levels, but not favorable. However, it requires more evidences and studies to confirm their efficiencies against new variants.

## CONCLUSIONS

This article is an overview of the current researches on epidemiology in response to the outbreak of COVID-19. In the present review, we summarized the latest reports of transmission route and risk of transmission, mortality and morbidity risk factor, possible origins and reservoirs, and clinical outcomes of SARS-CoV-2 infection. On the other hand, notable variants of SARS-CoV-2 that are the important challenge were investigated. However, further investigations on all aspects of the illness are urgently needed to overcome this viral infectious pandemic.

## Acknowledgments

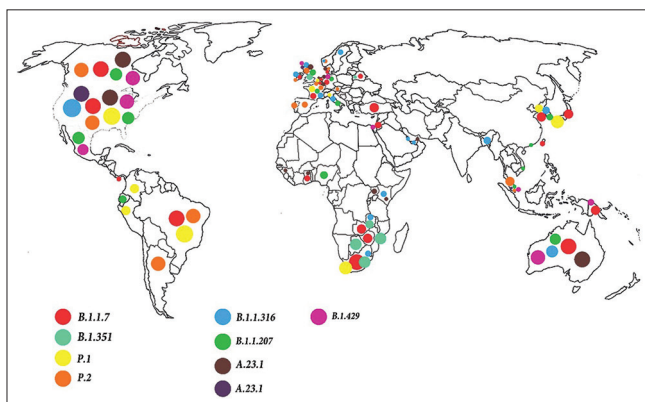
We would like to thank to guidance and advice from the Clinical Research Development Unit of Baqiyatallah Hospital, Tehran, Iran.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.



**Figure 3:** The global distribution of emerging variants of severe acute respiratory syndrome coronavirus 2

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