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Review Article

A Narrative Review of SARS-CoV-2 Pathogenesis, Transmission, and Clinical Manifestations

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ABSTRACT

Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become a major global concern. As of writing this manuscript, there are over 224 million cases diagnosed, and 4.5 million recorded deaths with the Coronavirus Disease 2019 (COVID-19).

Objectives: This article reviews the studies conducted on SARS-CoV-2 pathogenesis, transmission, and different clinical manifestations.

Methods: An extensive online search was conducted on PubMed and Google Scholar search engines. The following keywords and their combinations were used to complete this review: "SARS-CoV-2", "COVID-19", "virology", "mechanism of action", "transmission", "clinical manifestations", "laboratory findings", and "comorbidities."

Results: The SARS-CoV-2 spike glycoprotein recognizes the human angiotensin-converting enzyme 2 receptors, and through that, the virus can enter its host cell. The virus is mainly transmitted via respiratory and or airborne droplets. The severity of the COVID-19 clinical manifestations relies on the associated comorbidities and or old age, which ranges from little-to-no symptoms to severe and critical conditions. Fever, loss of appetite and or smell, fatigue, and dry cough are among the most reported symptoms. Underlying conditions may lead to severe or critical stages of COVID-19.

Conclusion: The SARS-CoV-2 nucleocapsid and receptor-binding domain could be two potential targets for future vaccines and drugs. It appears that the virus is adapting to each region's specific environment; therefore, new endemic variants are forming.

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Introduction

The detection of pneumonia of an unknown origin at Wuhan, Hubei Province, China, was first reported on December 31, 2019. Later, it was suggested that the cause of the disease had a similar structure to a virus that was previously responsible for an infection known as a severe acute respiratory syndrome. The virus was initially proposed to be called HCoV-19 (Human Coronavirus 2019) or 2019-nCoV (2019 Novel Coronavirus) [1]; however, the new emerging virus was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for a disease known as the coronavirus disease 2019 (COVID-19) [2]. Analysis speculates that the first cluster of COVID-19 was at a seafood market in Wuhan, China. This may be the point where a zoonotic transmission may have occurred [3]. The World Health Organization's (WHO) Director-General declared the new virus outbreak a "public health emergency of international concern" on January 30, 2020. The WHO reported more than a 10-fold increase in cases diagnosed with COVID-19 in less than one month on April 4, 2020, rising the recorded global infected cases to over a million. Since then, there has been an increase in both cases and mortalities worldwide (Figure 1).

It is believed that SARS-CoV-2 is an RNA virus that consists of 3 main proteins each responsible for a part of the viral infection cycle [4]. This virus infects its host cell mainly via attaching to the human angiotensin-converting enzyme 2 (hACE2) receptor [5]. The new virions are formed inside the reticulum endoplasmic compartment of the cell after the virus has successfully entered its host cell, and the infectious stage inside the host's body will initiate. At this point, the infected individual may infect others through either direct or indirect contact [6]. However, the infected person may not necessarily develop symptoms in this phase of infection. Patients diagnosed with COVID-19 may develop a wide range of symptoms that could be fatal [7]. This review article aims to investigate the pathogenesis, transmission, and clinical manifestations of SARS-CoV-2 infection in more detail.

Materials and Methods

An online search was conducted from October to December 2020 for information and manuscripts available on the WHO, The Centers for Disease Control and Prevention (CDC), PubMed, and Google Scholar search engines using the following keywords and their combinations: "SARS-CoV-2", "COVID-19", "pathogenesis", "virology", "mechanism of action", "transmission", "clinical manifestations", "laboratory findings", "underlying conditions", and "comorbidities." The articles included in this manuscript reported the molecular characteristics of SARS-CoV-2, the way SARS-CoV-2 infects its host cell, modes of COVID-19 transmission, and the manifestations of the disease in patients regardless of their age and gender. While writing the clinical manifestations of COVID-19, a precise focus was dedicated to the age and underlying conditions of the patients with different types of clinical manifestations. All included articles were peer-reviewed, written in English, and published. Special attention was given to the papers published in the year 2020. Applicable data was collected from the respective parts of these articles. Articles' references were downloaded using the citation tool provided by each journal, and they were cited according to the Pharmaceutical and Biomedical Research journal's instructions. No ethical statements were needed for this manuscript since the data mentioned in the articles were already published, and no animal models or patients were directly involved while gathering the data for this article.

Results

Pathogenesis

SARS-CoV-2 is a member of the Coronaviridae family. This virus contains a single positive-stranded RNA, nucleocapsid protein, envelope protein, membrane protein, and spike glycoprotein [4]. The nucleocapsid protein is abundant among different viruses and is responsible for developing the ribonucleoprotein core inside the host cell [8]. The membrane protein is believed to be embedded within the viral membrane and its function is to neutralize antibodies that are developed against the virus [9]. The envelope protein disrupts the tight junctions' stability, compromising the epithelial barrier, which may lead to further inflammatory reactions caused by the virus [10]. The membrane and envelope proteins form the viral envelope together. The spike glycoprotein is divided into S_1 and S_2 subunits [4]. This glycoprotein contains a receptor binding domain (RBD) on the S_1 subunit, which enables the virus to recognize the hACE2 receptor and interact with it; hence, it is suggested that the hACE2 receptor acts as the SARS-CoV-2 receptor [5, 11, 12]. RBD segment is the most immunogenic part of the SARS-CoV-2 spike glycoprotein and the fact that it is hidden makes it difficult for both drugs and vaccines to reach it. Furthermore, RBD disables the body's immunological system from identifying it [13]. This part of the virus may prove useful in future research to find a suitable drug against COVID-19. However, as stated by Shang et al., finding the right way to deliver the drug to its target could be challenging [13].

When SARS-CoV-2 binds to the hACE2 receptor, a series of activities results in the shedding of the S_1 subunit, and, subsequently, the fusion activity of the S_2 subunit will be triggered at low pH [6, 12]. The infectivity of SARS-CoV-2 is influenced by its fusion capacity [14]. Moreover, the activity of the transmembrane serine protease 2 (TMPRSS2) in the infected cell is another necessary factor for the pathogenesis and transmission of the virus [15].

The presence of furin enables SARS-CoV-2 to enter the host cell without requiring the host's protease enzymes [13]. For the SARS-CoV-2 spike glycoprotein to become activated, furin-like enzymes should cleave a proteolytic site at the S_2 subunit known as S_2', which is located next to the fusion peptide at the S_1/S_2 junction [16, 17]. This cleavage results in the priming of the spike glycoprotein by TMPRSS2, leading to the fusion of the viral membrane to its host cell [17, 18]. Pre cleavage at S_2' site by furin in the infected cell facilitates TMPRSS2-dependent cell entry of the virus [15]. It is noteworthy to mention that the polybasic S_2' site is necessary for SARS-CoV-2 to enter human lung cells. This site is also responsible for the improved pathogenicity of SARS-CoV-2 compared to SARS-CoV [18]. However, the furin-cleavage site presence is not vital to promoting viral entry to the cell, and the SARS-CoV-2 spike glycoprotein's features and structure are responsible for the efficient viral fusion to its host [14]. Several other factors that facilitate SARS-CoV-2 entry to the host cell have also been proposed. Neuropilin-1 cofactor may be responsible for SARS-CoV-2 entrance to the cells that have lower expression of hACE2 receptors on their surface [19]. Heparan sulfate can also help SARS-CoV-2 bind more efficiently to hACE2 receptors by directly attaching to viral spikes and increasing viral concentration on the cell's surface [20]. These factors may contribute to SARS-CoV-2 potential for infecting different types of cells and resulting in a variety of symptoms associated with COVID-19.

When the viral nucleocapsid has successfully entered its host cell, the proteasomes help with the uncoating process of SARS-CoV-2, and the viral genome is released into the cell [6]. Viral RNA promotes its host's ribosomes to generate necessary components for its replication by non-structural proteins. These proteins form the replication/transcription complex. Afterward, the host's ribosomes initiate the production of the vital parts of the virus, including new mRNAs and full-length RNA genomes for more viral particles [6, 21]. Replicated RNA will then be translated to the envelope, membrane, and spike proteins inside the cell's cytoplasm. These proteins are first inserted into the endoplasmic reticulum. Then, they reach the Golgi intermediate compartment, where eventually mature viruses are formed. The ribonucleoprotein consisting of the SARS-CoV-2 RNA and nucleocapsids will merge with other components of the virus in the endoplasmic reticulum-Golgi intermediate compartment to form new virions. After being assembled, virions will be transported to the cell's surface and eventually leave the cell via exocytosis. The high number of viruses produced in the endoplasmic reticulum will ultimately lead to cell death [6].

Transmission

The epidemiological triad explains 3 factors that connect in complicated ways to produce the disease (Figure 2). Transmission of an infectious agent may be categorized as direct or indirect [22]. Infected patients with SARS-CoV-2 may transmit the disease 2 days before developing the symptoms. This is acknowledged as one of the important factors of the ongoing pandemic since the infected individuals are infectious without showing any symptoms before becoming symptomatic. There are 3 common ways for SARS-CoV-2 transmission. The respiratory transmission of SARS-CoV-2 is the primary route of transmission, which occurs mostly via respiratory droplets produced by an infected person's coughing, sneezing, or speaking. If susceptible hosts breathe in these expelled droplets, they may become infected. Moreover, the closer a person is to these droplets, the higher the risk of being infected [23, 24]. Since SARS-CoV-2 is considered to be heavy, chances are that the viral particles of an infected person may not be able to reach a greater distance of 1.5 meters. The second way of transmission is by airborne microdroplets, which are also known as aerosols. It is suggested that SARS-CoV-2 can spread through the air given the increasing number of cases globally [25]. In addition, air samples were SARS-CoV-2 RNA positive using PCR, and it is believed that under certain circumstances, this virus can be airborne transmitted [26, 27]. Thirdly, it has been indicated that SARS-CoV-2 can be transmitted by fomite. SARS-CoV-2 can survive and remain infectious for days on surfaces under certain conditions. A person must touch their mouth, eyes, or nose after touching a contaminated surface without washing their hands to become infected [28, 29]. It is suggested that the virus is mainly spread through respiratory droplets, aerosols, or airborne transmission, and the chance of being infected by fomite surfaces is considered lower than the former modes [30]. A report suggests that for a person to get infected by SARS-CoV-2 through contaminated inanimate surfaces, they must touch the infected surface within 1 to 2 h after

an infectious person has contaminated that surface via sneezing, coughing, and or touching. Hence, inanimate surfaces in places (other than hospitals) that were not in contact with an infected person for some time may not pose a risk for transmission [31]. When outside its host and on inanimate surfaces, SARS-CoV-2 is highly vulnerable to changes in the environment, for instance, pH, osmolarity, and temperature. This phenomenon may be responsible for several paradoxical results between in vitro and clinical studies that have researched different therapeutical agents.

Other modes of transmission, including fecal aerosolization, urine contact, blood transfusion, and sexual transmission, have also been proposed aside from the 3 discussed routes of transmission for SARS-CoV-2. Evidence suggests that viable SARS-CoV-2 can be isolated from the feces of patients with COVID-19 [32, 33]. One report claims the isolated viable and infectious SARS-CoV-2 from the urine sample of COVID-19 patients could infect healthy vulnerable cells through in vitro examination [34]. Moreover, one study holds fecal aerosol transmission of the virus responsible for a community outbreak [35]. Two reports also detected SARS-CoV-2 in blood samples of patients before the development of COVID-19 symptoms [36, 37]. However, a case report indicates that a patient receiving apheresis platelet transfusion from an infected person with SARS-CoV-2 did not develop COVID-19 afterward [38]. In addition, there has not been a report of infection with SARS-CoV-2 through blood transfusion [39]. As for the sexual transmission of SARS-CoV-2, the vaginal fluid of a patient diagnosed with COVID-19 was positive for SARS-CoV-2 using the reverse transcription polymerase chain reaction [40]. However, COVID-19 is not characterized as a sexually transmitted disease [41]. The oral cavity could also be a potential route for SARS-CoV-2 infection since the virus was detected in saliva samples of patients with COVID-19 [42]. Although these ways have been proposed as potential routes for the transmission of SARS-CoV-2, results show that it is unlikely for the community to become infected with the virus through these paths. However, individuals with close contact with the infected patient, for instance, families, relatives, roommates, or health care workers, could be potentially in danger of being infected. Still, transmission through droplets remains a major way and the most probable route of transmitting the virus.

Clinical manifestations

COVID-19 has a widespread variety of symptoms ranging from asymptomatic cases to critically ill patients that may require special care (Table 1) [7]. It is estimated that the mean incubation period of SARS-CoV-2 is approximately 5 days, and most cases will develop symptoms within 14 days after being infected [43]. Although the symptoms of COVID-19 are not specific to the disease, shortness of breath and olfactory dysfunction could be marked as alarming signs of the infection. As the disease progresses to severe stages, the symptoms become worse. In the later stages of the disease, the vital organs may malfunction, which could be fatal.

Asymptomatic cases

Some COVID-19 patients may be asymptomatic or may develop mild symptoms [7, 44–49]. These patients would not seek medical care since they might not be aware of their infection. SARS-CoV-2 is found in the pharyngeal samples of asymptomatic cases, however, the virus does not stimulate the innate immunologic response. Thereby, fatigue, fever, cough, sore throat, and gastrointestinal signs are not present in some of the asymptomatic patients [7, 44, 46]. These cases are estimated to include approximately 10% to 30% of the patients that are infected with SARS-CoV-2. Moreover, the asymptomatic infection can be developed in all age groups [50]. It is suggested that negative results of reverse transcription polymerase chain reaction in asymptomatic cases may be due to the low load of the virus in these cases [45]. Though asymptomatic patients may develop no obvious clinical presentations, their laboratory results, including a low level of C-reactive protein and alanine aminotransferase (implementing no inflammation or liver damage, respectively), and radiologic findings, such as patchy shadows in the computed tomography scan, may present traces of SARS-CoV-2 and its replication [46, 47, 50].

What makes asymptomatic cases a concern for public health is that these cases are difficult to identify and can contaminate their nearby environment. Hence, they are considered a major factor in the current COVID-19 pandemic. This raises the need for detecting infected cases with methods other than symptom-based screenings [51, 52]. One study suggests that asymptomatic cases can significantly infect lower proportions of other individuals compared to symptomatic cases [53]. Interestingly, it is assumed that the spread of COVID-19 by asymptomatic patients is likely to result in more asymptomatic infections, which has been backed up by the Diamond

Table 1. Clinical manifestations of the Coronavirus Disease 2019 (COVID-19)

Variables	
General Manifestations	Asthenia
	Myalgia
	Fever
	Sore throat
	Joint pain
Respiratory Manifestations	Nasal obstruction
	Cough
	Rhinorrhea
	Shortness of breath
	Production of sputum
	Dyspnea
	Respiratory rate ≥ 30 breathes per minute (severe cases)
	Respiratory failure (critical cases)
Gastrointestinal Manifestations	Diarrhea
	Nausea
	Vomiting
	Abdominal pain
Neurological Manifestations	Gustatory dysfunction
	Olfactory dysfunction
	Headache

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Notes: This table summarizes the clinical manifestations of COVID-19 found in different studies with various cases (56–58,64,71)420 patients completed the study (962 females, 30.7% of healthcare workers.

Princess cruise ship's outbreak [53, 54]. Another study states that there are no evidence of infectious asymptomatic cases and the transmission of the virus to their close contacts. Also, samples taken from these cases were negative for viable SARS-CoV-2 [48]. However, an investigation claims that asymptomatic patients had considerable viral shedding in a skilled nursing facility [49].

Mild to moderate cases

Though some patients may be asymptomatic during the whole course of the infection, some may gradually develop symptoms. In one study, an estimate of 81% of patients among 44 415 cases had mild symptoms without the need of being hospitalized [55]. Studies indicate that fever, fatigue, headache, respiratory symptoms, such as nasal obstruction, dry cough, and gastrointestinal complications, including nausea, diarrhea, and abdominal pain, are among the most common symptoms in mild to moderate cases of COVID-19 [56–58]. Also, olfactory dysfunction (i.e., anosmia, dysgeusia, and ageusia) have been reported among other symptoms in these cases [56, 58, 59]. It may take approximately 12 days for symptoms to subside in mild to moderate cases [56]. Consolidation or ground-glass opacity may be found in the chest computed tomography scan of these cases [60]. Laboratory findings of patients admitted to hospitals, including ferritin, aspartate aminotransferase, D-dimer, and C-reactive protein levels, were significantly higher in moderate cases of COVID-19 compared to mild cases. It may take

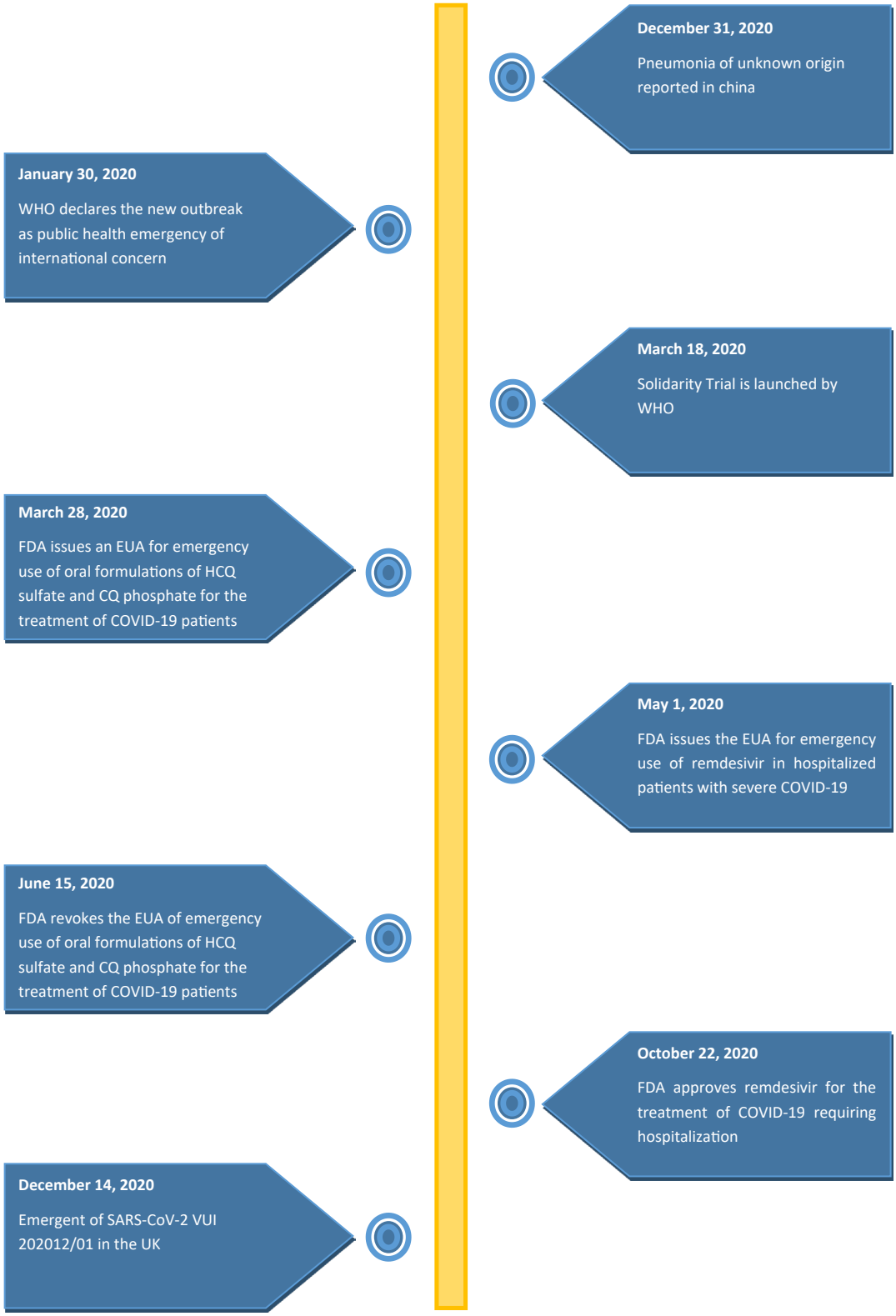

Figure 1. Key dates related to severe acute respiratory Syndrome Coronavirus 2 (SARS-CoV-2) timeline

Abbreviations: WHO: World Health Organization; FDA: U.S. Food and Drug Administration; EUA: emergency use authorization; HCQ: hydroxychloroquine; CQ: chloroquine; COVID-19: coronavirus disease 2019; SARS-CoV-2 VUI 202012/01, severe acute respiratory syndrome coronavirus 2 variant under investigation, year 2020, month 12, variant 01; UK, United Kingdom.

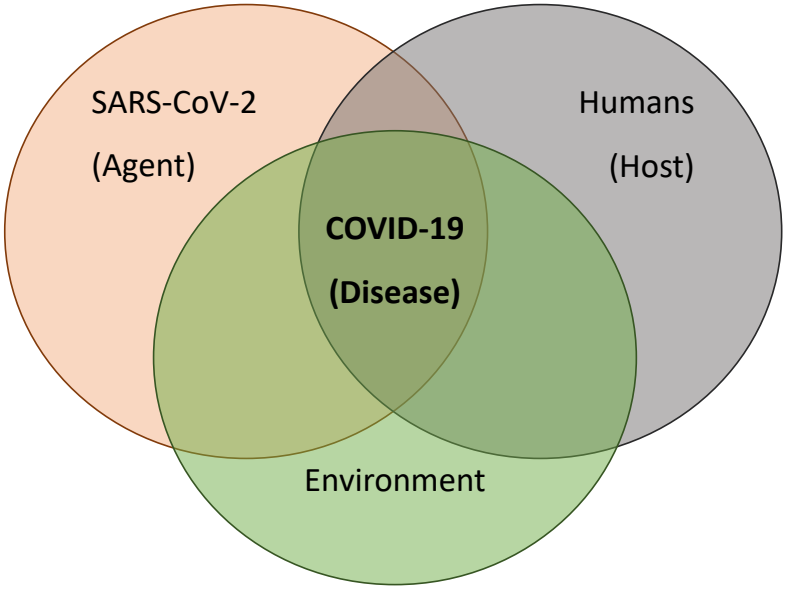

Figure 2. Epidemiological triad of the Coronavirus Disease 2019 (COVID-19).

Notes: This illustration indicates that under certain conditions (environment) infectious agent (SARS-CoV-2) may interact with its susceptible host (humans), and this could result in the disease (COVID-19).

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a shorter hospitalization for mild COVID-19 cases. Nevertheless, moderate cases may take more time to develop a negative PCR test result for viable SARS-CoV-2 [57].

Severe to critical cases

People at higher risk of developing severe to critical COVID-19 are those in the old age group and or with an already coexisting condition(s) that may be fatal [61]. These underlying conditions include autoimmune and cardiovascular diseases, diabetes, and respiratory complications, including chronic obstructive pulmonary disease, smoking, severe asthma, hypertension, cancer, and obesity [61–63]. One investigation points out that critically ill COVID-19 cases admitted to the intensive care unit had low blood pressure that needed vasopressor to manage the condition and or mechanical ventilation because of type 1 hypoxemic respiratory failure [64]. Hypoxemia and dyspnea may eventually lead to end organ failure, a life-threatening respiratory disorder known as acute respiratory distress syndrome or death [65]. A cohort study of 928 COVID-19 cases indicated that patients with cancer, regardless of the presence of active cancer, anticancer therapy, or both, are at increased risk of developing severe COVID-19 that may result in mortality [66].

It is suggested that the high death rates in the old age population might be the result of less vigorous immune responses against SARS-CoV-2 [65]. At the severe stage of the disease, lung inflammation may be a key factor for acute respiratory distress syndrome [67]. Symptoms of severe or critical COVID-19 include chest congestion, chest pain, shortness of breath, cough, fever, lack of appetite, diarrhea, vomiting, weakness, fatigue, and muscle pain [58, 64]. Gastrointestinal symptoms become more noticeable as COVID-19 becomes more severe [58]. Other complications, such as pulmonary edema, multiple organ failure, pneumonia, and acute respiratory distress syndrome may also become apparent in later courses of the disease [62]. Immune response in patients with poor prognosis may also be challenging. One study suggests that the immune system may act differently in 2 phases. During the first phase, the immune defense system tries to fight the virus, and it needs to be boosted; however, the immunological response could result in a phenomenon known as cytokine storm syndrome in the second phase that needs to be inhibited as this syndrome may lead to pulmonary damage and even death [67, 68]. COVID-19 cases are also susceptible to thrombosis and thromboembolic events with the release of inflammatory cytokines throughout the body [69].

Laboratory findings of severe to critical cases of COVID-19 indicate elevated innate immune response, reduced biological markers associated with adaptive immune response, tissue damage, and increased biological markers related to major organ failure [70]. An elevated level of D-dimer in the blood is also considered a risk

factor for developing severe COVID-19 as this factor is associated with pneumonia and the initiation of the coagulation cascade [71, 72]. The computed tomography scan of these cases shows a higher amount of consolidation, crazy-paving pattern, bronchial wall thickening, and linear opacities compared to patients who have less severe symptoms, which may indicate pneumonia in patients with COVID-19 [62].

SARS-CoV-2 variants

Random mutations in the SARS-CoV-2 genome are inevitable. Although these mutations may not have considerable effects, some may have impacts on different properties of the virus, including the performance of the therapeutical agents or vaccines against the virus, the transmissibility of SARS-CoV-2, and the severity of COVID-19. On December 14, 2020, officials in the United Kingdom and Northern Ireland reported a new variant of SARS-CoV-2 referred to as "SARS-CoV-2 Variant Under Investigation, the year 2020, month 12, variant 01 (VUI 202112/01)", later named B.1.1.7 (alpha) variant, which became the dominant variant in some countries [73]. Other SARS-CoV-2 variants of concern are B.1.351 (beta) variant first reported in South Africa, P.1 (gamma) variant reported in Brazil, and B.1.617 (delta) variant that first appeared in India, which is currently on high surge in some countries. SARS-CoV-2 lineages of interest are B.1.525 (eta), B.1.526 (iota) which was first documented in the United States of America, B.1.617.1 (kappa), which was identified in India, C.37 (lambda) that was recognized in Peru, and B.1.621 (mu), which was documented first at Colombia. There are also new emerging variants that require further investigation [74].

Conclusion

SARS-CoV-2 caused a pandemic that has affected health care services, governments, and economies globally. This virus is expected to cause more damage in the body where hACE2 receptors are abundant. Moreover, the SARS-CoV-2 nucleocapsid and RBD could be 2 potential targets for future vaccines and therapeutical agents. Infection caused by the virus is mainly transmitted through droplets of infected patients to healthy individuals. Patients with COVID-19 may have a variety of symptoms. Fever, loss of appetite and or smell, fatigue, and dry cough are among the most reported symptoms. Underlying conditions, including diabetes, cardiovascular, or respiratory complications, may lead to severe or critical stages of COVID-19. The two lethal complications of the disease that may even be fatal are acute respiratory distress syndrome and cytokine storm syndrome. Newly emerging variants worldwide caused by viral mutations remain of great concern that requires further evaluation. It appears the virus is adapting to each region's specific environment; therefore, new endemic variants are being formed accordingly.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles have been considered in this article.

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Conflict of interest

The author declares no conflict of interest.

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References

[1] Jiang S, Shi Z, Shu Y, Song J, Gao GF, Tan W, et al. A distinct name is needed for the new coronavirus. Lancet (London, England). 2020; 395(10228):949. [DOI:10.1016/S0140-6736(20)30419-0]

[2] Fauci AS, Lane HC, Redfield RR. Covid-19-navigating the uncharted. N Engl J Med. 2020; 382(13):1268-9. [PMID]

[3] Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus disease 2019-COVID-19. Clin Microbiol Rev. 2020; 33(4):e00028-20. [PMID] [PMCID]

[4] Samudrala PK, Kumar P, Choudhary K, Thakur N, Wadekar GS, Dayaramani R, et al. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020; 883:173375. [PMID] [PMCID]

[5] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020; 5(4):562-9. [DOI:10.1038/s41564-020-0688-y] [PMID] [PMCID]

[6] Boopathi S, Poma AB, Kolandaivel P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. J Biomol Struct Dyn. 2021; 39(9):3409-18. [PMID] [PMCID]

[7] Dong X, Cao YY, Lu XX, Zhang JJ, Du H, Yan YQ, et al. Eleven faces of coronavirus disease 2019. Allergy. 2020; 75(7):1699-709. [PMID] [PMCID]

[8] Zeng W, Liu G, Ma H, Zhao D, Yang Y, Liu M, et al. Biochemical characterization of SARS-CoV-2 nucleocapsid protein. Biochem Biophys Res Commun. 2020; 527(3):618-23. [PMID] [PMCID]

[9] Liu J, Sun Y, Qi J, Chu F, Wu H, Gao F, et al. The membrane protein of severe acute respiratory syndrome coronavirus acts as a dominant immunogen revealed by a clustering region of novel functionally and structurally defined cytotoxic T-lymphocyte epitopes. J Infect Dis. 2010; 202(8):1171-80. [PMID] [PMCID]

[10] De Maio F, Lo Cascio E, Babini G, Sali M, Della Longa S, Tilocca B, et al. Improved binding of SARS-CoV-2 Envelope protein to tight junction-associated PALS1 could play a key role in COVID-19 pathogenesis. Microbes Infect. 2020; 22(10):592-7. [PMID] [PMCID]

[11] Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019; 17(3):181-92. [DOI:10.1038/s41579-018-0118-9] [PMID] [PMCID]

[12] Zhu Y, Yu D, Yan H, Chong H, He Y. Design of potent membrane fusion inhibitors against SARS-CoV-2, an emerging coronavirus with high fusogenic activity. J Virol. 2020; 94(14):e00635-20. [PMID] [PMCID]

[13] Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020; 117(21):11727-34. [PMID]

[14] Xia S, Lan Q, Su S, Wang X, Xu W, Liu Z, et al. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. Signal Transduct Target Ther. 2020;5(1):92. [PMID] [PMCID]

[15] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2):271-80.e8. [PMID] [PMCID]

[16] Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 2020; 176:104742. [PMID] [PMCID]

[17] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020; 181(2):281-292.e6. [PMID]

[18] Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell. 2020; 78(4):779-84.e5. [PMID] [PMCID]

[19] Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 2020; 370(6518):856-60. [PMID] [PMCID]

[20] Zhang Q, Chen CZ, Swaroop M, Xu M, Wang L, Lee J, et al. Heparan sulfate assists SARS-CoV-2 in cell entry and can be targeted by approved drugs in vitro. Cell Discov. 2020; 6(1):80. [PMID] [PMCID]

[21] Romano M, Ruggiero A, Squeglia F, Maga G, Berisio R. A structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. Cells. 2020; 9(5):1267. [PMID] [PMCID]

[22] van Seventer JM, Hochberg NS. Principles of infectious diseases: Transmission, diagnosis, prevention, and control. Int Encycl Public Health. 2017; 22-39. [PMCID]

[23] Dhand R, Li J. Coughs and sneezes: Their role in transmission of respiratory viral infections, including SARS-CoV-2. Am J Respir Crit Care Med. 2020; 202(5):651-9. [DOI:10.1164/rccm.202004-1263PP] [PMID] [PMCID]

[24] Ma J, Qi X, Chen H, Li X, Zhang Z, Wang H, et al. Coronavirus disease 2019 patients in earlier stages exhaled millions of severe acute respiratory syndrome coronavirus 2 per hour. Clin Infect Dis. 2021; 72(10):e652-4. [PMID]

[25] Morawska L, Cao J. Airborne transmission of SARS-CoV-2: The world should face the reality. Environ Int. 2020; 105730. [PMID]

[26] Morawska L, Tang JW, Bahnfleth W, Bluyssen PM, Boerstra A, Buonanno G, et al. How can airborne transmission of COVID-19 indoors be minimised? Environ Int. 2020; 142:105832. [PMID] [PMCID]

[27] Ma J, Qi X, Chen H, Li X, Zhang Z, Wang H, et al. COVID-19 patients in earlier stages exhaled millions of SARS-CoV-2 per hour. Clin Infect Dis. 2021; 72(10):e652-4. [PMID]

[28] Lake MA. What we know so far: COVID-19 current clinical knowledge and research. Clin Med (Northfield Il). 2020; 20(2):124-7. [PMID] [PMCID]

[29] Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020; 382(16):1564-7. [PMID] [PMCID]

[30] Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A review of viral, host, and environmental factors. Ann Intern Med. 2021; 174(1):69-79. [PMID]

[31] Goldman E. Exaggerated risk of transmission of COVID-19 by fomites. Lancet Infect Dis. 2020; 20(8):892-3. [DOI:10.1016/S1473-3099(20)30561-2]

[32] Xiao F, Sun J, Xu Y, Li F, Huang X, Li H, et al. Infectious SARS-CoV-2 in feces of patient with severe COVID-19. Emerg Infect Dis. 2020; 26(8):1920-2. [PMID] [PMCID]

[33] Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of sars-cov-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. Gastroenterology. 2020; 159(1):81-95. [PMID] [PMCID]

[34] Sun J, Zhu A, Li H, Zheng K, Zhuang Z, Chen Z, et al. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerg Microbes Infect. 2020; 9(1):991-3. [PMID] [PMCID]

[35] Kang M, Wei J, Yuan J, Guo J, Zhang Y, Hang J, et al. Probable evidence of fecal aerosol transmission of SARS-CoV-2 in a high-rise building. Ann Intern Med. 2020; 173(12):974-80. [PMID] [PMCID]

[36] Chang L, Zhao L, Gong H, Wang L, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. Emerg Infect Dis. 2020; 26(7):1631-3. [DOI:10.3201/eid2607.200839] [PMID] [PMCID]

[37] Di Cristanziano V, Meyer-Schwickerath C, Eberhardt KA, Rybniker J, Heger E, Knops E, et al. Detection of SARS-CoV-2 viremia before onset of COVID-19 symptoms in an allo-transplanted patient with acute leukemia. Bone Marrow Transplant. 2021; 56(3):716-9. [PMID]

[38] Cho HJ, Koo JW, Roh SK, Kim YK, Suh JS, Moon JH, et al. COVID-19 transmission and blood transfusion: A case report. J Infect Public Health. 2020; 13(11):1678-9. [PMID]

[39] Bassil J, Rassy E, Kattan J. Is blood transfusion safe during the COVID-19 pandemic? Futur Sci OA. 2020; 6(9):FSO626. [PMID] [PMCID]

[40] Scorzolini L, Corpolongo A, Castilletti C, Lalle E, Mariano A, Nicastri E. Comment on the potential risks of sexual and vertical transmission of covid-19. Clin Infect Dis. 2020; 71(16):2298. [PMID] [PMCID]

[41] Tur-Kaspa T, Hildebrand G, Cohen D, Tur-Kaspa I. Is COVID-19 a sexually transmitted disease? A systematic review. Fertil Steril. 2020; 114(3):e522-8. [DOI:10.1016/j.fertnstert.2020.09.018] [PMCID]

[42] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020; 12(1):8. [PMID]

[43] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med. 2020; 172(9):577-82. [PMID] [PMCID]

[44] Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020; 323(14):1406-7. [PMID] [PMCID]

[45] Zhu CQ, Gao SD, Xu Y, Yang XH, Ye FQ, Ai LL, et al. A COVID-19 case report from asymptomatic contact: Implication for contact isolation and incubation management. Infect Dis Poverty. 2020; 9(1):70. [PMID]

[46] Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020; 63(5):706-11. [PMID]

[47] Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet. 2020; 395(10223):514-23. [DOI:10.1016/S0140-6736(20)30154-9]

[48] Cao S, Gan Y, Wang C, Bachmann M, Wei S, Gong J, et al. Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China. Nat Commun. 2020; 11(1):5917. [PMID]

[49] Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med. 2020; 382(22):2081-90. [PMID] [PMCID]

[50] Yu C, Zhou M, Liu Y, Guo T, Ou C, Yang L, et al. Characteristics of asymptomatic COVID-19 infection and progression: A multicenter, retrospective study. Virulence. 2020; 11(1):1006-14. [DOI:10.1080/21505594.2020.1802194]

[51] Wei L, Lin J, Duan X, Huang W, Lu X, Zhou J, et al. Asymptomatic COVID-19 patients can contaminate their surroundings: An environment sampling study. mSphere. 2020; 5(3):e00442-20. [PMID] [PMCID]

[52] Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control COVID-19. N Engl J Med. 2020; 382(22):2158-60. [PMID]

[53] He D, Zhao S, Lin Q, Zhuang Z, Cao P, Wang MH, et al. The relative transmissibility of asymptomatic COVID-19 infections among close contacts. Int J Infect Dis. 2020; 94:145-7. [PMID]

[54] Chen Y, Wang AH, Yi B, Ding KQ, Wang HB, Wang JM, et al. [The epidemiological characteristics of infection in close contacts of COVID-19 in Ningbo city (Chinese)]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020; 41(5):667-71. [PMID]

[55] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13):1239-42. [PMID]

[56] Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020; 288(3):335-44. [PMID]

[57] Al Mutair A, Alhumaid S, Alhuqbani WN, Zaidi ARZ, Alkoraisi S, Al-Subaie MF, et al. Clinical, epidemiological, and laboratory characteristics of mild-to-moderate COVID-19 patients in Saudi Arabia: An observational cohort study. Eur J Med Res. 2020; 25(1):61 [PMID]

[58] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020; 115(5):766-73. [PMID]

[59] Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. Am J Otolaryngol. 2020; 41(5):102581. [PMID]

[60] Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes at chest CT during recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020; 295(3):715-21. [PMID] [PMCID]

[61] Jordan RE, Adab P, Cheng KK. Covid-19: Risk factors for severe disease and death. BMJ. 2020; 368:m1198. [PMID]

[62] Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The clinical and chest ct features associated with severe and critical covid-19 pneumonia. Invest Radiol. 2020; 55(6):327-31. [PMID]

[63] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020; 584(7821):430-6. [PMID] [PMCID]

[64] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically Ill patients in the seattle region - case series. N Engl J Med. 2020; 382(21):2012-22. [PMID] [PMCID]

[65] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumo-

nia in Wuhan, China. JAMA Intern Med. 2020; 180(7):934-43. [PMID] [PMCID]

[66] Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): A cohort study. Lancet (London, England). 2020; 395(10241):1907-18. [PMID]

[67] Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: The perspectives on immune responses. Cell Death Differ. 2020; 27(5):1451-4. [PMID] [PMCID]

[68] Brennecke A, Villar L, Wang Z, Doyle LM, Meek A, Reed M, et al. Is inhaled furosemide a potential therapeutic for covid-19? Am J Med Sci. 2020; 360(3):216-21. [DOI:10.22541/au.158817616.62606783/v2]

[69] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol. 2020; 75(23):2950-73. [PMID]

[70] Moutchia J, Pokharel P, Kerri A, McGaw K, Uchai S, Nji M, et al. Clinical laboratory parameters associated with severe or critical novel coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. PLoS One. 2020; 15(10):e0239802. [PMID] [PMCID]

[71] Dixon DL, Van Tassell BW, Vecchié A, Bonaventura A, Talasaz AH, Kakavand H, et al. Cardiovascular considerations in treating patients with coronavirus disease 2019 (covid-19). J Cardiovasc Pharmacol. 2020; 75(5):359-67. [PMID]

[72] Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020; 395(10229):1014-5. [DOI:10.1016/S0140-6736(20)30633-4]

[73] Abdool Karim SS, de Oliveira T. New SARS-CoV-2 variants - clinical, public health, and vaccine implications. N Engl J Med. 2021; 384(19):1866-8. [PMID] [PMCID]

[74] Oude Munnink BB, Worp N, Nieuwenhuijse DF, Sikkema RS, Haagmans B, Fouchier RAM, et al. The next phase of SARS-CoV-2 surveillance: Real-time molecular epidemiology. Nat Med. 2021; 27(9):1518-24. [PMID]

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