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Epidemiology, transmission and pathogenesis of SARS-CoV-2

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2.1 Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), has resulted in more than 205 million confirmed cases and 4.3 million deaths (<https://covid19.who.int>). Coronavirus term is derived from Latin word “Corona” meaning crown. The name suggests the unique appearance of the virus under an electron microscope that contains round particles with a rim of projection. Coronavirus is an enveloped, single-stranded ribonucleic acid (RNA), positive sense virus that was first isolated from humans in 1965 (Tyrrell & Bynoe, 1966). Coronaviruses belong to the family *Coronaviridae*, which produce mild to severe respiratory disease in humans. Coronaviruses are found in various animals, including bats, birds, cattle, cats, and pigs. In recent decades, there have been three major Coronavirus outbreaks worldwide. In 2002 and 2012, two highly pathogenic Coronaviruses with the zoonotic origin, severe acute respiratory syndrome Coronavirus (SARS-CoV) [Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, \(2020\)](#) and Middle East respiratory syndrome-Coronavirus (MERS-CoV), respectively, caused fatal respiratory illness, making these Coronaviruses a new public health concern in the 21st century (Zumla et al., 2015). Key differences among SARS-CoV, MERS, and SARS-CoV-2 are summarized in [Table 2.1](#).

Till the writing of this chapter, several countries have experienced at least two waves of COVID-19. Several vaccines have been approved by the Federal Drug Agency (FDA), the European agency, Central Drugs Standard Control Organization, New Delhi. COVID-19 vaccination has decreased the severity of the disease in the exposed individuals. Several SARS-CoV-2 variants of concern (VoC) that alter transmission or disease characteristics or impact vaccine, therapeutics, diagnostics, or effectiveness preventive and social measures have been detected. These VoC pose challenges for the eradication of the COVID-19 pandemic.

TABLE 2.1 Key differences among severe acute respiratory syndrome-Coronavirus-2, severe acute respiratory syndrome-Coronavirus, and Middle East respiratory syndrome-Coronavirus.

	SARS-CoV-2	SARS-CoV	MERS-CoV
Genus	Clade I, lineage B	Clade I, lineage B	Clade II, lineage C
Length of nucleotides	29.9 kilobases	29.75 kilobases	30.11 kilobases
Emergence date	December 7, 2019 Wuhan, China	November 16, 2002 Foshan, China	April 4, 2012, Zarqa, Jordan
Virus identification first	Jan-20	Mar-03	Jun-12
Possibly natural reservoir	Bat	Bat	Bat
Possibly intermediate host	Malayan Pangolins & turtle	Palm Civets	Camel
Predominant cellular receptors	Angiotensin-converting enzyme receptor-2	Angiotensin-converting enzyme receptor-2	Dipeptidyl peptidase-4 receptor
Current status	Pandemic ongoing	Completely control	Sporadic continuous
Symptoms	Severe acute respiratory syndrome, 4.2% mortality rate	Severe acute respiratory syndrome, 11% mortality rate	Severe acute respiratory syndrome, 34% mortality rate

2.2 The emergence of Coronavirus disease-2019 as a pandemic

At the end of 2019, a novel Coronavirus emerged in Wuhan, China ([Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020](#)) and caused an outbreak of unusual viral pneumonia. The virus began its spread in the seafood wholesale market in the Wuhan, Hubei province of China. It was proposed that an infected animal, an intermediate host of the virus, was sold in the market, causing the spread of the virus in the marketplace. Growing evidence that bats are the natural host of SARS-CoV-2, which might have infected humans through an intermediate host such as pangolins and civet cats ([Zhou et al., 2020](#)). Owing to the high transmission rate of SARS-CoV-2, it spread quickly to the entire globe. On January 7, 2020, the Chinese Center for Disease Control and Prevention isolated a Coronavirus strain from a swab of a hospitalized patient ([Chen, 2020](#)). Outside mainland China, the first laboratory-confirmed case of SARS-CoV-2 infection was reported by Thailand on January 13, 2020 ([Boldog et al., 2020](#)). Subsequently, on February 11, 2020, the International Committee on Taxonomy of Viruses named the novel Coronavirus as “SARS-CoV-2” and the WHO named the disease “COVID-19” [naming the Coronavirus disease (COVID-19) and the virus that causes it]. According to the 11th situation report of WHO on novel Coronavirus, by the end of January 2020, SARS-CoV-2 spread to 19 countries outside Mainland China and 9826 confirmed cases were reported ([World Health Organization, Novel Coronavirus \(2019-NCoV\) Situation Report-11, 2020](#)). On the recommendations of the Emergency Committee, on January 30, 2020, the WHO

declared the outbreak to be a public health emergency of international concern (World Health Organization, Novel Coronavirus (2019-NCoV) Situation Report-11, 2020). Considering the global threat due to the widespread SARS-CoV-2 infection in more than 100 countries, on March 11, 2020, the WHO declared COVID-19 as a pandemic (World Health Organization, Coronavirus Disease 2019 (COVID-19) Situation Report-52, 2020). Till August 2021, North America has reported the highest number of confirmed cases, followed by Europe and Asia Fig. 2.1A. In terms of a total of COVID-19 cases and the number of deaths, the United States of America (USA) tops the list, followed by India, Brazil, and Russia Fig. 2.1B and C (World Health Organization, WHO Coronavirus COVID-19, n.d.). The chronology of important events is given in Figs. 2.1 and 2.2.

2.3 Origin and transmission of severe acute respiratory syndrome-Coronavirus-2

The transmission mode of SARS-CoV-2 is mainly person-to-person. The exact transmission route in “the patient zero” and primary transmission of SRAS-CoV-2 is not known. However, it became clear that it is zoonotic transmission (Chen, 2020). Bats are the natural reservoir of Coronaviruses, including SARS-CoV and MERS-CoV, and are considered as a potential reservoir of SARS-CoV-2 (Guo et al., 2020; Mahdy et al., 2020). Indeed, the SARS-CoV-2 genome shows 96.2 % nucleotide sequence similarity to RaTG13, a bat Coronavirus, suggesting that SARS-CoV-2 might have originated and transmitted from bats. Bats are not available for sale in the Wuhan seafood market, suggesting that the virus might have been transmitted to humans through some other intermediate hosts. Pangolins, civet cats, and snakes have been suggested as intermediate hosts of SARS-CoV-2 (Guo et al., 2020). SARS-CoV-2 might have also been transmitted from wild animals to pets and farm animals that infect human beings (Mahdy et al., 2020) Fig. 2.3.

Among all carriers of SARS-CoV-2, *Rhinolophids* bats are more dangerous carriers that do not exhibit any clinical signs of infection.

2.3.1 Human-to-human transmission

Currently, available data shows that the main mode of transmission of SARS-CoV-2 is human-to-human transmission. It is thought to occur mainly through close contact, either in the form of respiratory droplets or aerosols. Droplets can be broadly described as macro entities ($> 5 \mu\text{m}$) that can gravitate to the ground, that is, approximately within 3–6 feet of the source person (Klompas et al., 2020). Viruses present in respiratory secretion in infected persons spread via coughing, sneezing, talking, or through contaminated surface contact. The mean incubation period for the disease is 5–6 days. When a healthy person comes in contact with an infected person, either direct or indirect (inhalation) may cause disease Fig. 2.3. Infection might also occur through touching the infected surface and, after that, touching the face, nose, and mouth. This type of transmission can be prevented by frequent hand wash, sanitizing hands with alcohol-based sanitizer, and avoiding touching the face, nose, and mouth through the contaminated hand. SARS-CoV-2 transmission for

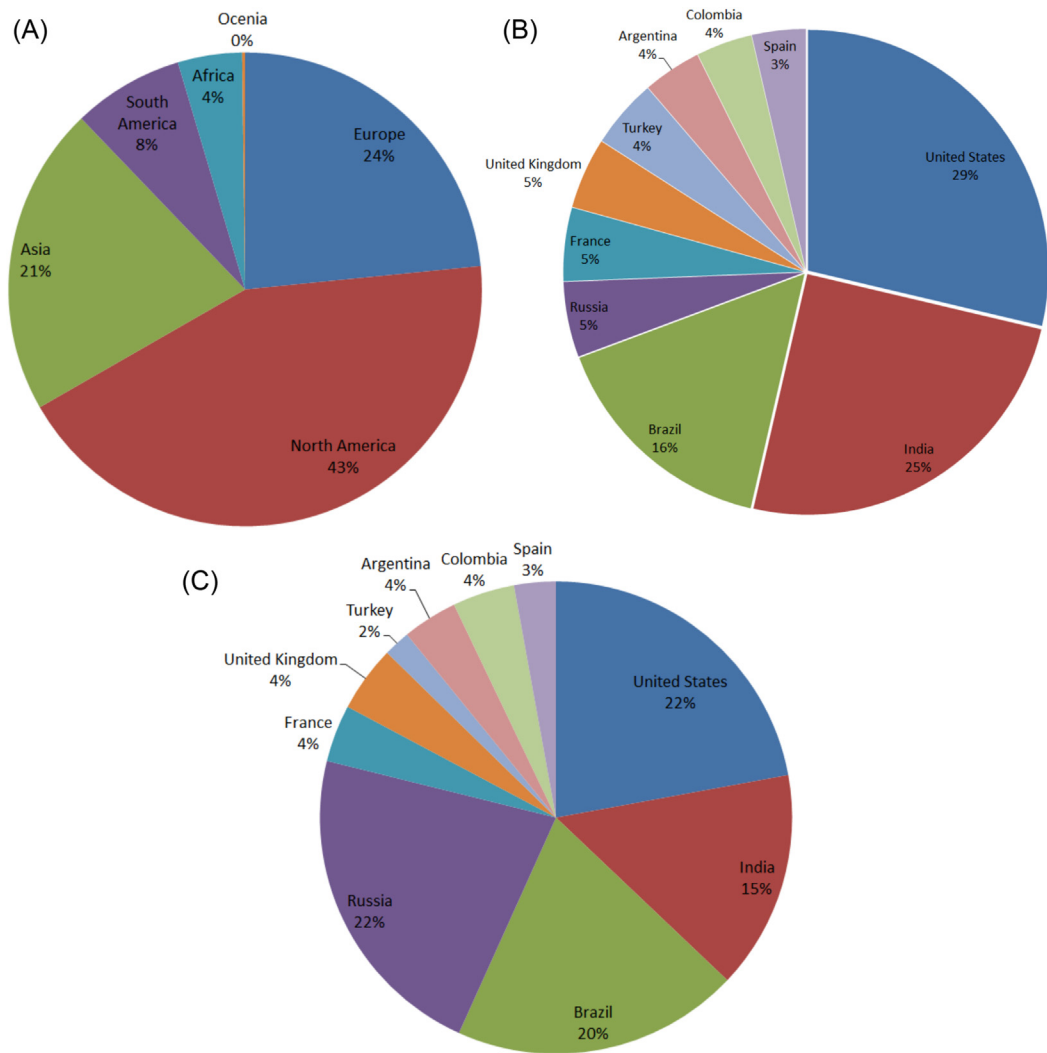


FIGURE 2.1 Geographical distribution of Coronavirus disease-2019 cases. (A) Proportion of COVID-19 cases in different continents; (B) Top 10 affected countries in terms of a total number of COVID-19 cases; (C) Top 10 affected countries in terms of a total number of deaths caused due to COVID-19 (till August 11, 2021).

long distances may also occur through aerosols (small droplets that are suspended in air) through inhalation, but the extent to which this mode of transmission is contributed is controversial (Klompas et al., 2020). Generally, many symptomatic COVID-19 patients may infect other human beings who come in close contact. However, most of the asymptomatic patients can serve as carriers of COVID-19, and can unknowingly transmit infection. This may be one of the reasons for drastically and rapidly increased infection worldwide and that lax in the practice of isolation and social distancing and also within

December 8, 2019	Pneumonia like symptoms with unknown etiology firstly reported in Wuhan, China
January 7, 2020	The Chinese Centre for Disease Control and Prevention isolated coronavirus strain from swab of a hospitalized patient
January 13, 2020	The first case was reported in Thailand, outside China
January 20, 2020	WHO released a situational report 1 for COVID-19 pandemic indicating 282 laboratories confirmed cases & 6 death globally
January 30, 2020	The first case reported in India WHO declared SARS-CoV-2 outbreak as public health emergency of International concern.
February 11, 2020	Diseased caused by SARS-CoV2 was named as COVID-19
March 19, 2020	WHO released its situational reports

FIGURE 2.2 Chronology of events related to Coronavirus disease-2019 pandemic.

families having asymptomatic carrier patients (Phan et al., 2020; Riley et al., 2003). Another way of transmission is dust particles laden with the virus. They will enter and get themselves deep-seated in the respiratory tract. When the dust particles or droplet nuclei are less than $5\ \mu\text{m}$, they can travel greater than 1-meter distance and become much more problematic. It becomes a threat when there is aerosolization of particles, especially during endobronchial intubation, bronchoscopy, cardio-pulmonary resuscitation, and other procedures.

2.3.1.1 Fecal–oral route transmission

Besides airborne, SARS-CoV-2 can also be transmitted via other routes. The virus is shed in the feces of the COVID-19 patient. But the fecal–oral route transmission of the disease is still not clear. It has been observed that patients who have been discharged after completing the treatment and whose throat swabs tested negative for the virus showed a positive result for the virus in the stool samples. A study has shown that even asymptomatic COVID-19 patients shed the virus in the stools. This shedding of virus in stool samples is much more common in pediatric patients (Xu et al., 2020). The spread of the virus through this route occurs due to poor sanitation. Therefore, stool samples of COVID-19 patients should also be handled very carefully.

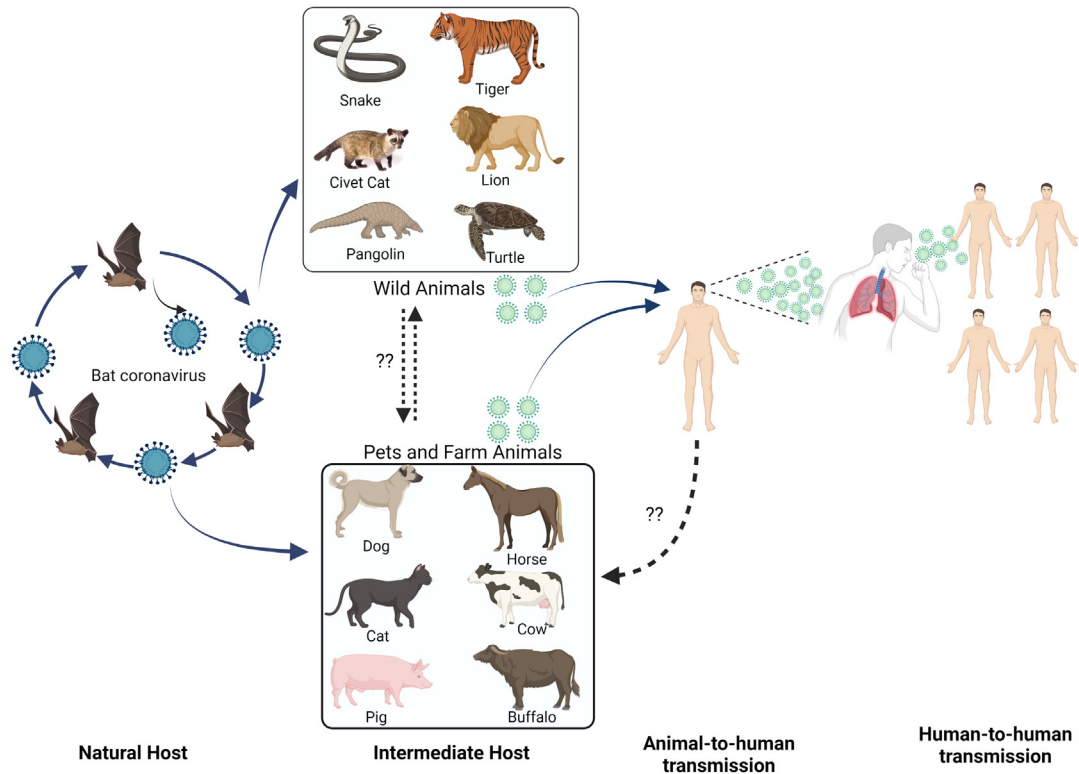


FIGURE 2.3 Transmission of severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) through an intermediate host. SARS-CoV-2 might have evolved from a bat virus. SARS-CoV-2 might have reached humans through intermediate hosts (wild animals or pet and farm animals).

2.3.1.2 Vertical transmission

The transmission of Coronaviruses from mother to baby is not fully understood (Kotlyar et al., 2021). However, babies born to COVID-19 patients showed an elevated titer of IgM antibodies as early as 2 hours after the birth (Dong et al., 2020), raising the possibility of vertical transmission of the virus. No vertical transmission was reported to the newborns in the case of cesarean section (Chen, 2020), but the presence of the SARS-CoV-2 genome in one out of 32 specimens of umbilical cord blood, at-term placenta, vaginal mucosa of pregnant women and breast milk specimen has been reported (Fenizia et al., 2020). Thus, based on the current evidence, the possibility of vertical transmission either through vaginal delivery or through cesarean is very low.

2.3.1.3 Sexual route

Seminal fluid from COVID-19 patients who recovered from the disease tested negative. However, semen testing for SARS-CoV-2 resulted in 15.8% positivity in 15.8% COVID-19 patients, of which some were in the acute stage of infection and others were in the recovery phase (Li et al., 2020). The study by Pan et al. showed that there was a low expression

of ACE2 and TMPRSS2 in human testes, and SARS-CoV-2 was not detected in the semen of recovered patients (Pan et al., 2020). Considering the fact that SARS-CoV-2 was detected in the semen of recovering patients, thus there is a risk of transmission through the sexual route, and safe practices should be followed.

2.3.1.4 Ocular route

The ocular surface may also serve as a reservoir and source of SARS-CoV-2 infection. It could be transmitted through hand–eye contact or aerosol or the nasolacrimal route (Qu et al., 2021).

2.4 Infectiousness and transmissibility severe acute respiratory syndrome-Coronavirus-2

The basic reproduction number (R_0) is the expected number of secondary cases that could arise from a single case in a susceptible population (Dhar Chowdhury & Oommen, 2020). R_0 is a very important parameter in the epidemiology of infectious diseases and it is used to measure the infectiousness or transmission potential of a communicable disease (Viceconte & Petrosillo, 2020). R_0 represents the number of people each infected person will infect on average, assuming that there is no preexisting immunity in the population. Whereas effective reproduction number (R_e) is the number of people that can be infected by an infected person at any specific time, and it changes as the community becomes increasingly immunized. When R_e is greater than 1, it means each person affected by the transmittable disease is expected to infect a number of subjects that increase exponentially related to R_0 value, and the disease is expected to spread through the susceptible population. If R_e is less than 1, it means each case transmits the disease to one or less than one individual, and the disease is expected to die out in a population (Mahase, 2020). The concept of R_0 is based on a complex model and may lead to misinterpretations, especially for the concerns about the spreading of infectious disease and the feasibility of controlling epidemics (20). The World Health Organization (WHO) has estimated the R_0 for COVID-19, which ranges between 1.4 and 2.5 (Dhar Chowdhury & Oommen, 2020).

2.5 Pathogenesis of Coronavirus disease-2019

The genome of SARS-CoV-2 is comprised of approximately 29 kilobases of single-stranded positive-sense RNA. The envelope surrounding the genome consists of four structural proteins: (1) a membrane protein (M), (2) an envelope protein (E), (3) a nucleoprotein, and (4) a spike protein (S). Spike glycoprotein is a very important component because it is responsible for the entry of the virus into the host cell. The detailed structure, genome, and proteomic markers of SARS-CoV-2 have been described in Chapter 4.

2.5.1 Lung pathogenesis

Upon exposure of a healthy person to a SARS-CoV-2 infected person, viral particles reach the superficial epithelium of the nasal cavity. The viral spike glycoprotein of SARS-CoV-2 binds to the target cells by ACE2, present on the epithelial cells of the nasal cavity. The entry of the virus into the epithelial cells is facilitated by transmembrane serine protease 2 (TMPRSS2), which helps in the fusion of the membrane. Children have a low-level expression of this ACE2 receptor, which explains the reason for the lower severity of the disease in children. From nasal epithelial cells, the pathway by which it enters into lower respiratory tract is not much clear. But there are two proposed theories. According to the first theory, microaspiration of virus particles leads to the spread of the virus to the lower respiratory tract. The other theory is the direct entry of virus particles into the lower respiratory tract by bypassing the nasal cavity. Neuropilin-1 is abundantly expressed in the respiratory and olfactory epithelium and enhances the SARS-CoV-2 infectivity (Cantuti-Castelvetri et al., 2020). Once the viral genome enters the host cell, its genes replicate, undergo transcription, and form new virions (Shanmugam et al., 2020). After reaching the lower respiratory tract, the virus attaches to the alveolar epithelial cells through ACE2 receptors present on them. Type-2 alveolar epithelial cells are more involved than type-1. SARS-CoV-2 has a unique polybasic S1/S2 protease cleavage site and an insertion of tetrapeptide SPRR, which increases cleavage efficiency. Consequent to the engagement of spike with ACE2, TMPRSS2 present in the host cell membrane cleaves the above site and thus exposing S2 fusion protein, resulting in the fusion of the virus with the host cell membrane. After the membrane fusion, the internalization of viral RNA occurs, resulting in the replication and formation of viral proteins. SARS-CoV-2 nucleocapsid proteins bind with the viral RNA, covered by envelope and membrane proteins resulting in complete virion formation (Fig. 2.4) (Shanmugam et al., 2020).

SARS-CoV-2 damages type-2 alveolar cells, which are essential for surfactant synthesis and repair of damaged tissues. Thus, there will be an increase in the surface tension, causing dyspnoea. In addition, the viral genome and proteins act as a pathogen-associated molecular pattern (PAMP) and stimulate the innate immune system. In the cytoplasm, viral RNA is recognized by cytosolic receptor melanoma differentiation-associated gene 5 (MDA5), the viral RNA receptor retinoic-acid inducible gene I (RIG-I), and nucleotidyl transferase cyclic GMP-AMP synthase (cGAS). In the endosome, viral RNA is recognized by endosomal TLRs, leading to activation of downstream cascades, resulting in cytokine production, especially type-1I interferon (IFN-1). Other cytokines such as IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (MCSF), granulocyte-colony stimulating factor (G-CSF), MCP-1, macrophage inflammatory protein-1 alpha (MIP-1 α), interferon gamma-induced protein-10 (IP-10), IFN- γ , TNF- α , and hepatocyte growth factor (HGF) levels also increase during COVID-19 infection, causing massive a cytokine storm and thus worsening the patient's condition (Tahaghoghi-Hajghorbani et al., 2020). Monocytes release proinflammatory cytokines responsible for pneumocyte apoptosis. Macrophages release chemokines and cytokines, which increase capillary permeability and also cause the recruitment of neutrophils. Excessive degranulation of neutrophils causes permanent damage to pneumocytes breaking the alveolar–capillary barrier. The end result of all these mechanisms is a transmigration of blood proteins resulting in alveolar and interstitial edema (Batah & Fabro, 2021).

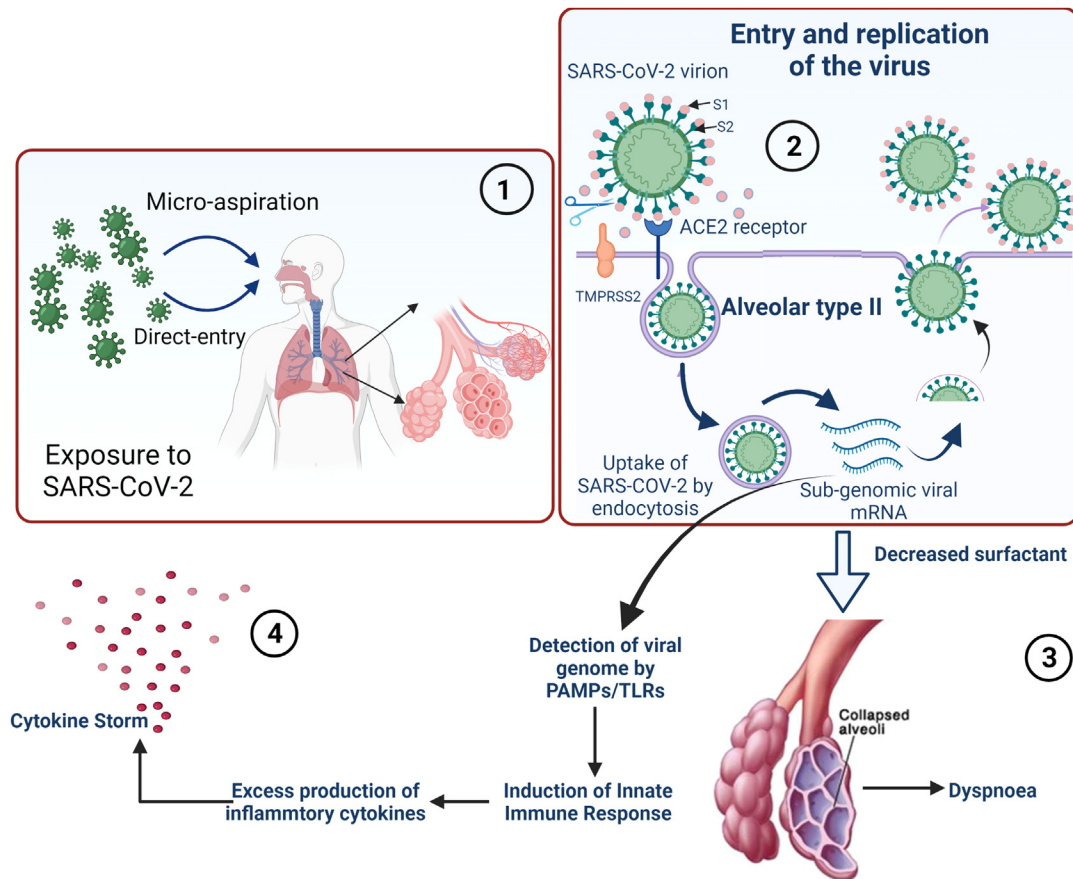


FIGURE 2.4 Pathophysiology of severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) induced lung injury. Following inhalation (1), SARS-CoV-2 infects type-2 alveolar cells, epithelial cells, and endothelial cells through binding of its spike protein with angiotensin-converting enzyme 2 (ACE2) receptor. The serine protease type-2 transmembrane serine protease (TMPRSS2) promotes viral uptake by cleaving spike. SARS-CoV-2 replicates in the host cells and generates new virions (2). SARS-CoV-2 damages type-2 alveolar cells and reduce surfactant synthesis, thereby increasing surface tension causing the collapse of alveoli (3). Damage-associated molecular pattern (DAMP) released by macrophages and alveolar cells recruit T lymphocytes, monocytes, and neutrophils. These cells secrete an excess amount of inflammatory cytokines resulting in a cytokine storm (4).

Inflammatory cytokines and chemokines, including C-C motif chemokine ligand (CCL)-2, CCL3, CCL5, C-X-C motif ligand (CXCL)-8, and CXCL9, lead to accumulation of macrophages, neutrophils, monocytes, causing damage to the lungs and other tissues (Tahaghoghi-Hajghorbani et al., 2020).

The common symptom in COVID-19 patients is hypoxia, if worsened, may lead to acute respiratory distress syndrome (ARDS). An unusual phenomenon seen in COVID patients is silent hypoxemia. The patients with silent hypoxemia experience no or mild respiratory discomfort and dyspnoea despite critically low partial pressure of oxygen (PaO₂).

(Grasselli et al., 2020). Pulmonary pathology of deceased COVID-19 subjects with ARDS shows typical features of diffuse alveolar damage (DAD) with hyaline membranes (Fig. 2.5) and AT2 cell hyperplasia (Borczuk et al., 2020). DAD has two phases; the first one is the *exudative phase*, which involves hyaline membrane formation due to the polymerization of fibrin present in plasma leaked into interstitial space. This phase is accompanied by alveolar–capillary barrier injury, resulting in red blood cell extravasation and inflammatory cell infiltration. The second phase of DAD is the *proliferative phase*, which involves excessive fibroblast and myofibroblast proliferation resulting in acute fibrinous organizing pneumonia with extracellular matrix deposition (Batah & Fabro, 2021). Radiological findings on computed tomography show bilateral ground-glass opacities along with peripheral distribution. Lung fibrosis is a complication of ARDS which occurs

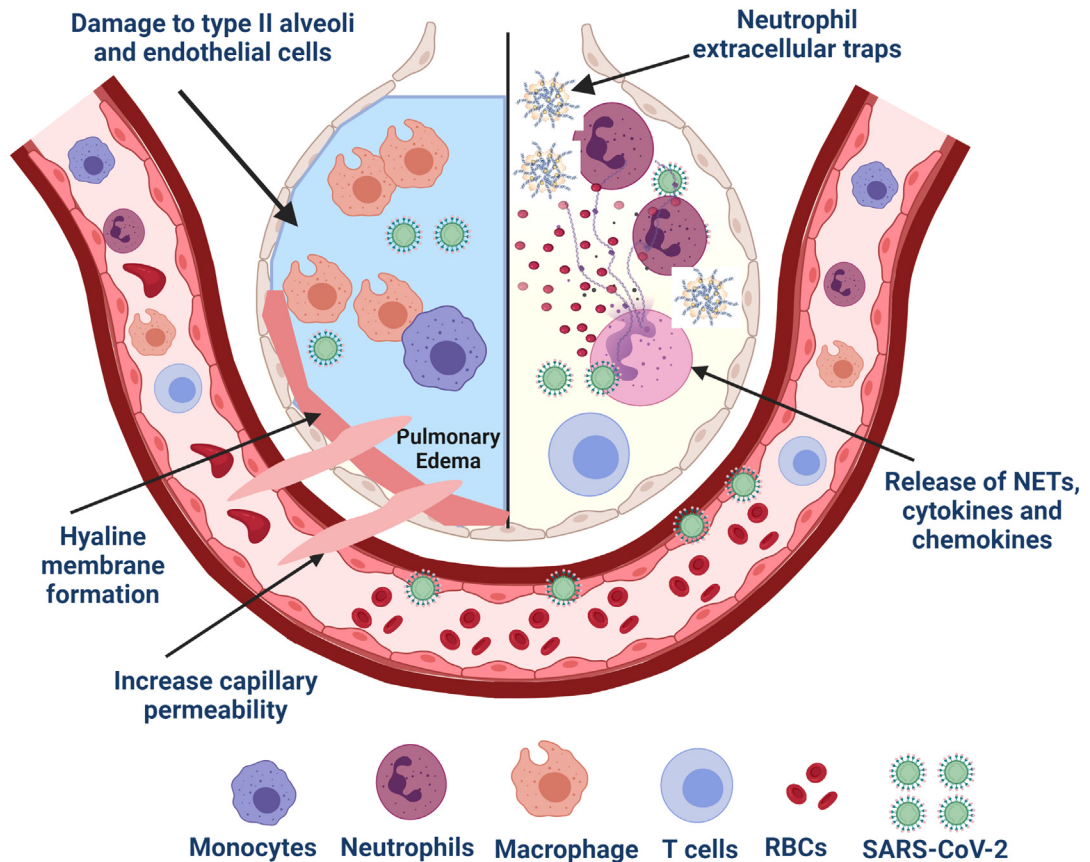


FIGURE 2.5 Pathophysiology of diffuse alveolar damage and acute respiratory distress syndrome. Diffuse alveolar has two phases; the first one is the exudative phase, which involves hyaline membrane formation. This phase is accompanied by alveolar–capillary barrier injury, resulting in red blood cell extravasation and inflammatory cell infiltration. The second phase of diffuse alveolar damage is the proliferative phase, which involves excessive fibroblast and myofibroblast proliferation resulting in acute fibrinous organizing pneumonia with extracellular matrix deposition.

in severe COVID-19 patients. It occurs due to profibrotic factors like transforming growth factor-beta (TGF-beta) released from the damaged lung tissues. Usually, it promotes tissue repair and causes resolution of infection-induced damage. But in severely affected patients, excessive secretion of TGF-beta and epithelial-to-mesenchymal transition and endothelial-to-mesenchymal transition results in fibrosis of the lung (Batah & Fabro, 2021).

2.5.2 Hematological manifestations

The hematological manifestations in COVID-19 patients include both thrombotic and bleeding disorders. Disseminated-intravascular coagulation (DIC) has been noted in COVID-19 patients. There are two types of DIC (1) enhanced fibrinolytic DIC and (2) suppressed fibrinolytic DIC. In enhanced fibrinolytic DIC, the thrombus is formed and is broken by fibrinolytic activation. D-Dimer is an important marker in the determination of the prognosis of COVID-19 patients. It is formed as a result of the degradation of fibrin polymer by plasmin. In suppressed fibrinolytic DIC, the thrombus is not broken down, resulting in only a mild increase in D-Dimer levels (Asakura & Ogawa, 2021). Several mechanisms have been proposed to explain the DIC in COVID-19 patients (Lo et al., 2020). One of the mechanisms responsible for thrombotic manifestations is endothelial cell disruption. Inflammatory cytokines released due to SARS-CoV-2 infection activate endothelial activation, which also causes thrombosis. Damaged endothelial cells and/or activated endothelial cells release Weibel-Palade granules containing ultra-large molecular-weight multimers of von Willebrand factor (vWF). These ultra-large granules spontaneously bind to the platelets and cause microthrombosis. Usually, these large granules are broken down by ADAMTS13, a vWF-cleaving protease. But the activity of ADAMTS13 is reduced in COVID-19 patients. The elevated levels of vWF and increased clotting activity of factor-VIII are due to the acute phase reaction, resulting in thrombosis (Lo et al., 2020).

Complement activation is another mechanism responsible for hematological manifestations observed in COVID-19 patients. The complement pathway mediates during mild-to-moderate inflammation, leading to the removal of harmful agents and thus helping in tissue regeneration (Lo et al., 2020). Complement activation and cytokine production are interlinked to each other. Low complement levels inhibit cytokine production; however, uncontrolled action of complement pathway results in hyperinflammation and much collateral damage, which include excess production of cytokines by macrophages. The antimicrobial activity of neutrophils gets reduced, and endothelial cells produce tissue factor which increases thrombosis resulting in DIC. Adding to these, SARS-CoV-2 can increase the transcription of complement (C1r, C1s, C3) and coagulation genes (fibrinogen) in the lungs and in the liver (Lo et al., 2020).

COVID-19 patients present with various forms of thrombosis, including retiform purpura with extensive deposition of C3d, C4d, MAC, and viral spike protein (Lo et al., 2020). Moreover, SARS-CoV-2 nucleocapsid (N) protein has been shown to directly activate the complement pathway. It can increase mannose-binding lectin (MBL)-associated serine protease-2 (MASP-2)-dependent complement activation. Ficolin-2 expression gets upregulated in monocyte-derived macrophages, which further increases the MBL pathway of complement activation. This results in degranulation and increased production of

cytokines, NETosis, increased production of reactive oxygen species and eicosanoids. Owing to the membrane activation complex (MAC)-mediated cell death, damage-associated molecular patterns (DAMPs) are released, which acts as positive feedback and further increases complement production (Lo et al., 2020). Notably, N-protein-mediated complement activation occurs only in the absence of an envelope membrane (Lo et al., 2020). In mild disease, a complete virus with an envelope is released. But in severe cases, due to the collateral damage to the cells, immature virions lacking the envelope are released and thus expose N-protein, resulting in enhanced complement activation and elevated thrombosis (Lo et al., 2020). The complement and coagulation pathways are inter-linked in two ways. MAC and MASP2 can cleave prothrombin. Factor 10a, plasmin, thrombin can cleave C3. In this way, they together interact and cause an increase in thrombosis and thus explain inflammation around retiform purpura in COVID-19 patients (Lo et al., 2020).

2.5.3 Cardiovascular manifestations

The frequent cardiovascular complications observed in COVID-19 patients are myocardial infarction, heart failure, venous-thromboembolic episodes, and palpitations. Acute myocardial infarction is due to atherosclerotic plaque rupture due to inflammation and hyperstability (Long et al., 2020). Some of the COVID-19 patients experience palpitations which may be due to hypoxia, abnormal metabolism, and inflammatory stress. The pathology involved in heart failure is not known, but it is most likely due to the exacerbation of previously undiagnosed heart failure. So, immune system dysregulation, hypercoagulability, increased metabolic demand are some causes of cardiovascular diseases in COVID-19 patients (Long et al., 2020).

2.5.4 Kidney and excretory system

COVID-19 patients with preexisting renal diseases have a poor prognosis and have high mortality. So, understanding the pathogenesis of kidney involvement and treating it is very much essential to reduce mortality in COVID-19 patients. In COVID-19 patients, acute kidney injury increases the severity of the disease, resulting in increased mortality and morbidity in the patients (Han & Ye, 2020). Kidney damage involves tubular damage, impaired glomerular filtration, proteinuria and is associated with elevated levels of serum urea and serum creatinine (Han & Ye, 2020). The virus can gain entry through ACE2 receptors present in proximal kidney tubules, making tubular damage more common (Han & Ye, 2020). Inflammatory cytokines and hypoxia also aggravate sepsis-induced acute kidney injury (AKI). Rhabdomyolysis caused due to further hypoxia increases the damage to the kidney. Diarrhea caused due to GI injury leads to dehydration which may also play some role in damaging kidney function Fig. 2.6.

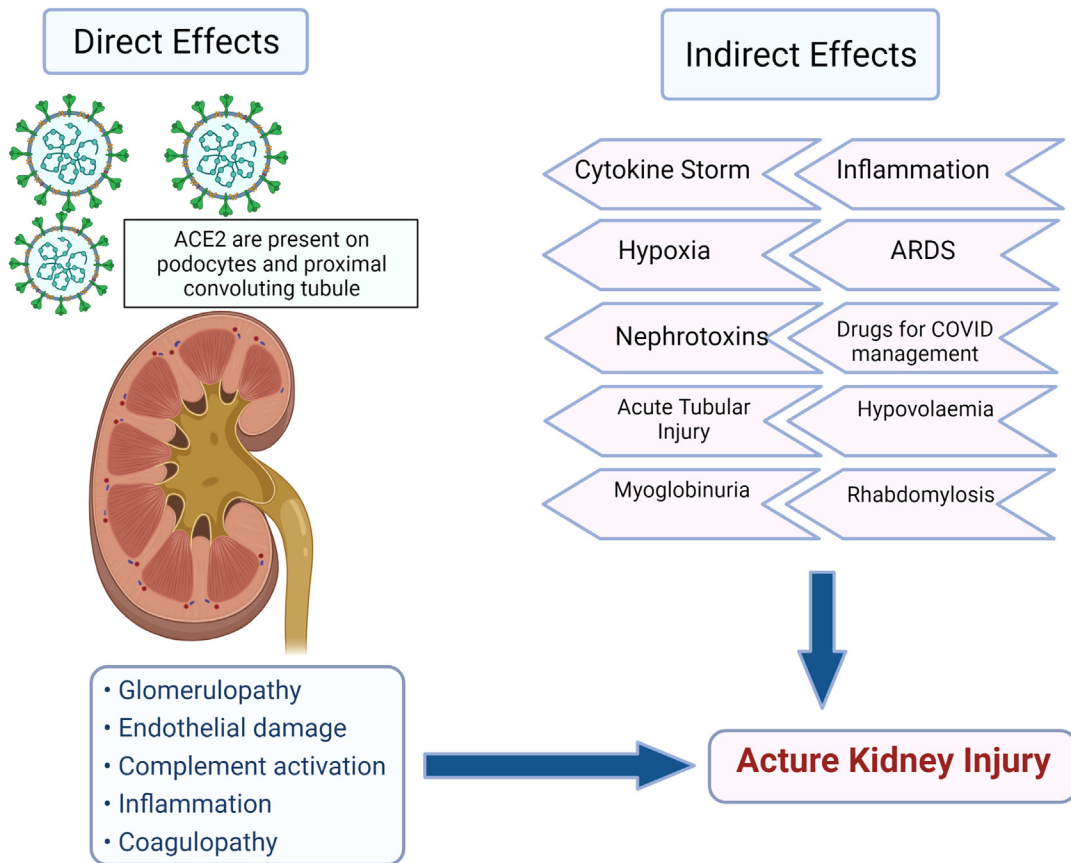


FIGURE 2.6 Pathophysiology of renal injury by severe acute respiratory syndrome-Coronavirus-2. Acute renal injury in Coronavirus disease-2019 patients involves tubular damage, impaired glomerular filtration, and myoglobinuria. The virus can directly cause harm to the kidney by binding to angiotensin-converting enzyme 2 present in proximal renal tubules. Inflammatory cytokines, rhabdomyolysis, nephrotoxins, and hypoxia also aggravate acute kidney injury (Han & Ye, 2020).

2.5.5 Neurological manifestations

The neurological manifestations in COVID-19 can be divided into two groups: central nervous system (CNS) manifestations and peripheral nervous system (PNS) manifestations. The symptoms in CNS manifestations include headache and dizziness, and PNS include dysgeusia and hyposmia (Pryce-Roberts et al., 2020). One of the most common symptoms experienced by COVID-19 patients is anosmia. ACE2 and TMPRSS2 are expressed in vascular pericytes of the olfactory bulb as well as in the olfactory neuroepithelium (Lin et al., 2021). SARS-CoV-2 binds ACE2 present on the olfactory bulb; thus, via olfactory nerves, it spreads into the CNS through the cribriform plate, thus causing anosmia. Another way of transmission is the retrograde pathway through trigeminal and vagus nerves and also by entry of infected

leucocytes through the blood–brain barrier (BBB) into the CNS, causing anosmia (Lin et al., 2021).

BBB is involved in many pathophysiological mechanisms resulting in neurological manifestations of COVID-19. ACE2 is expressed in varying levels on the vascular endothelium of BBB, which gets infected by SARS-CoV-2 triggers proinflammatory and procoagulable states and leads to vasculitis (Johansson et al., 2021). SARS-CoV-2 binding to ACE2 receptors present in sympathoadrenal systems may disrupt the autoregulation of systemic and intracranial blood pressure, thus causing dysregulation of blood pressure (Johansson et al., 2021). Systemic inflammatory responses also affect the integrity of BBB. Blood vessel-associated microglia maintain the integrity of BBB through tight junction proteins. Astrocytes help in the maintenance of BBB endothelium via posttranslational modifications of occludin, a component of tight junction proteins. Microglia gets activated by a systemic inflammatory response and thus disrupts the BBB, which further leads to increased neuro-inflammation and hyperexcitability, resulting in seizures, functional disturbance, fatigue, encephalopathy, and neuronal death. Severe hypoxia due to respiratory complications cause cerebral vasodilation and interstitial edema (Johansson et al., 2021). Headache experienced by COVID-19 patients is due to the invasion of trigeminal nerve endings directly by the virus in the nasal cavity. Elevated levels of proinflammatory cytokines also affect the perivascular nerve endings, resulting in headaches (Sharifian-Dorche et al., 2020).

2.5.5.1 Acute cerebrovascular events

Acute ischemic stroke and intracranial hemorrhage have been noted in COVID-19 patients. SARS-CoV-2 infection induces coagulation abnormalities, resulting in elevated levels of procoagulant factors, including fibrinogen, IL-6, D-Dimer, and platelets that contribute to many thrombo-embolic events. Furthermore, the elevated inflammatory markers such as CRP, IL-6, IL-7 increase the vulnerability of atherosclerotic plaque to rupture. Imbalance in rennin–angiotensin-system (RAS) results in endothelial dysfunction. All the above-stated reasons contribute to ischemic stroke (Sharifian-Dorche et al., 2020). Several hematological manifestations of COVID-19, including DIC, thrombocytopenia, increased prothrombin time, may cause intracranial hemorrhage. The RAS system plays a very important role in blood pressure regulation. Downregulation of ACE2 receptors is an important component of the RAS system. ACE2 catalyzes the conversion of angiotensin 2 (Ang 2) to Ang 1. Ang 1 is a potent vasoconstrictor and atherogenic molecule, and the balance between Ang 2 and Ang 1 regulate blood pressure, and ACE2 plays a critical role in this balance. ACE2 after SARS-CoV-2 binding is internalized and degraded. Hence ACE2 activity on the cell surface is reduced, leading to an increase in the concentration of Ang 2 and a decrease in the concentration of Ang (1–7). The downregulation of ACE2 results in dysfunction of cerebral autoregulation, and an increase in blood pressure results in arterial rupture and hemorrhage (Dettlaff-Pokora & Swierczynski, 2021; Sharifian-Dorche et al., 2020).

2.5.6 Psychiatric manifestations

The SARS-CoV-2 infection also results in psychiatric manifestations like psychosis, post-traumatic stress disorder, and even suicide in some patients (Orsini et al., 2020). Sleep

deprivation and feeling excessive fear are some of the reasons for depression and posttraumatic stress disorder in these patients. The psychiatric symptoms may be due to a direct neurotropic effect or may be due to a systemic immune-inflammatory response (Orsini et al., 2020). The proinflammatory cytokines, including TNF-alpha, IL-1, IL-6 produced by cytokine storm, exert their effect on indoleamine-2, 3-dioxygenase. This enzyme is responsible for the degradation of tryptophan which is important for the synthesis of serotonin, a mood elevator. The increase in the activity of this enzyme results in depletion of serotonin causing depressive symptoms and other psychiatric manifestations. Furthermore, prolonged stay of COVID-19 in the intensive care unit causes psychosis, delirium in some patients (Orsini et al., 2020).

2.5.7 Dermatological manifestations

Common dermatological manifestations observed in COVID-19 patients are maculopapular eruptions, acral areas of erythema with vesicles and pustules, urticarial lesions, vesicular eruptions, livedo or necrosis (Kaya et al., 2020). The pathophysiological mechanism behind dermatological manifestations is the cytokine storm, which stimulates the dermal dendritic cells, macrophages, neutrophils, lymphocytes and promotes erythema, urticarial lesions, and eruptions (Kaya et al., 2020). Obliterative microangiopathy due to endothelial and myointimal growth has also been reported in COVID-19 patients (Kaya et al., 2020). This occurs due to complement activation resulting in pseudo-chilblain and purpuric lesions. ACE2 receptors are also present in the basal layer of the epidermis and in the endothelial cells of dermal blood vessels, which form the target site for the action of the virus and result in acantholysis and dyskeratosis (Kaya et al., 2020).

2.5.8 Reproductive system manifestations

ACE2 receptors and Ang 2 are widely expressed on all the components of the female reproductive system, including the ovary, uterus, and vagina (Jing et al., 2020). ACE2 and Ang 1 regulate follicle development, ovulation, luteal angiogenesis, and degeneration. Ang 1 is an endogenous ligand for the G protein-coupled receptor Mas and specifically inhibits Ang 2 by the antagonism of AT1 receptors (Jing et al., 2020). Thus, SARS-CoV-2 affects ovarian tissue, granulosa cells and affects ovarian function, oocyte viability, resulting in infertility and miscarriage. It also damages endometrial cells and thus distressing the implantation of the embryo. In pregnant women, it causes vascular mal-perfusion of the placental bed, chorangio-hemangioma, and intervillous fibrin deposition (Jing et al., 2020). Male gender serves as a risk factor for COVID-19. TMPRSS2 receptor expression is enhanced by the androgen receptor. TMPRSS2 gene is expressed more in the adult prostate. In the same way, ACE2 expression is enhanced and causes the passage of virus into cells by androgens.

2.5.9 Gastrointestinal and hepatic manifestations

The most common gastrointestinal (GI) symptom observed in COVID-19 patients is diarrhea. Other symptoms include nausea, vomiting, abdominal discomfort, abdominal

pain, and dysgeusia (Cha et al., 2020). The symptoms related to the involvement of the liver mostly include a change in the laboratory parameters. These include elevated levels of serum aspartate aminotransferase, alanine aminotransferase, bilirubin, prolonged prothrombin time, and elevated lactate dehydrogenase (Cha et al., 2020). Some of the symptoms are thought to be due to the interaction between CNS and the gut. The proinflammatory cytokines cause alteration in the gut-CNS axis of the vagal nerve or through the lymphatic or vascular system. The lateral hypothalamic nuclei control nausea and vomiting, and if it is affected due to neurological damage, it may also become the cause of vomiting and diarrhea (Perisetti et al., 2020). ACE2 receptor is abundantly expressed in the GI tract, including the tongue, esophagus, stomach, ileum, rectum, and possess mucosa. The gastric acid secreted in the stomach kills the virus, but still, the virus finds its way into the duodenum and distal ileum, showing its effect (Perisetti et al., 2020). Once the virus gains entry into the cells, it divides rapidly and proliferates, resulting in cytopathic changes causing viral cytopathic effects. In addition to these, COVID-19 patients are given many antibiotics which cause alteration of gut flora. The cytokine storm seen in COVID-19 patients increases IL-2, IL-7, GM-CSF, TNF-alpha, which causes alteration in the GI motility and also plays a role in alteration of GI flora resulting in diarrhea. Also, medications used in the treatment of COVID-19 have side effects like diarrhea (Perisetti et al., 2020). The liver is much less affected in COVID-19 patients because it does not express many ACE2 receptors (Perisetti et al., 2020, PMID: 32807535). But the cholangiocytes and biliary epithelium have more of these receptors, making them a potential site for the virus to act. The virus gains access into the biliary system through the portal vein. This way, it can directly cause hepatocytes' cytopathic effect, resulting in microvesicular steatosis (Perisetti et al., 2020).

2.6 Effect of host factors on Coronavirus disease-2019 pathogenesis

The disease outcome depends not only on the virulence factors but also on some host factors like gender, age, obesity, tobacco consumption/smoking, and comorbidities like preexisting respiratory disease, cardiovascular disease, genetic factors, cerebrovascular diseases, diabetes, hypertension. The severity of the disease is different in males and females. Females have a better prognosis compared to males. This might be due to the immunomodulatory effect of estrogen. Virus replication is suppressed by estrogen, resulting in less viral load in females (Shanmugam et al., 2020). Estrogen causes suppression of some micro-RNA like miR125 and let7A, resulting in repression of monocyte-macrophage infiltration (Shanmugam et al., 2020). Some genes present on the X-chromosome like TLR-7, which upregulates IFN-beta in dendritic cells and provides protection (Shanmugam et al., 2020). Obesity causes the release of certain cytokines like TGF-beta, TNF-alpha, IL-6, which delay innate and acquired immunity and result in the fast spread of the virus. Attenuation of cytokine signaling proteins in the peripheral blood mononuclear cells and lungs, which reduces the production of IFN-1, and proinflammatory cytokines. In people with hypertension, ACE inhibitors, angiotensin receptor blockers (ARBs), cause an increase in the production of ACE receptors, making them more prone to the virus. In addition, in diabetic patients, MHC-1 expression and antibody production is reduced due to glycation.

Furthermore, decreased production of IFN-gamma and TNF-alpha by NK cells and macrophages results in immune paralysis (Shanmugam et al., 2020). The macrophages present in the lungs of smokers produce fewer amounts of IL-1, -6, and TNF-alpha. In smokers, decreased NK cell activity and increased production of ACE receptors make them more prone to COVID-19.

2.7 Conclusion

COVID-19 primarily affects the respiratory system, vasculature, and immune system. SARS-CoV-2 infected patients can have a range of clinical manifestations ranging from no symptoms to critical illness associated with ARDS, septic shock, and multiorgan failure. Effective antiviral drugs for SARS-CoV-2 are still not available. Therefore, preventive measures such as social distancing, personal hygiene, and usage of masks along with vaccination are key armor for the containment of the COVID-19 pandemic. Owing to evolutionary pressure, SARS-CoV-2 is rapidly mutating, and several VOC have emerged that have further spread to several countries. The emergence of SARS-CoV-2 VOC with increased contagiousness or escaping neutralizing antibodies poses challenges in eradicating SARS-CoV-2. Thus, the development of an effective antiviral drug is the need of the hour.

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