REVIEW ARTICLE

Pathogenesis of COVID-19: ACE2, Cytokine Storm and Extrapulmonary Manifestations

Abdul Muhaymin[1], Hyder Wajid Abbasi[2], Naeem Ullah[3], Adnan Haider[4], Syed Babar Jamal[4], Fazli Subhan[4], Muhammad Naeem[4*]

ABSTRACT

The coronavirus disease 19 (COVID-19) is a global pandemic of the twenty-first century and currently fourth wave is creating fear and panic worldwide. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), a highly contagious viral infection of humans. The COVID-19 can be spread mainly through respiratory droplet particles and in contact with a COVID-19 infected person. Clinical manifestation of COVID-19 patients includes cough, fever, diarrhea, loss of taste and smell. In critical cases of COVID-19, the development of pneumonia and dyspnea leads to acute respiratory distress syndrome that may cause the death of the patient. It is well established that Angiotensin-Converting Enzyme 2 (ACE2) receptors on alveolar cells act as an entry gate for the SARS-COV-2. However, ACE2 is also highly expressed in multiple extrapulmonary vital organs such as the gastrointestinal system, cardiovascular system, kidney, etc. Therefore, the direct viral entry in these organs can be a likely pathway of injury. In addition, decoupling of immune responses leads to the cytokines storm, which might contribute to the injury of extrapulmonary organs. In this review, we report the multiple organ pathogenesis and clinical manifestations of COVID-19 patients, which could aid clinicians and researchers in prioritizing therapeutics remedies and developing research for all vital body systems involved.

Key Words: *ACE2, COVID-19 Pathogenesis, Cytokines Storm, Extrapulmonary Manifestations.*

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Introduction

The COVID-19 pandemic emerged in Wuhan, China, by 12th December 2019. Clinical manifestations of infected patients included high fever, cough, and diarrhea. In critical cases of COVID-19, pneumonia and dyspnea developed, leading to acute respiratory distress and death of the patient.[1] The infection was spread swiftly to the other parts of China and around the world, aided by the ease of global travel and possibly by the prevalence of asymptomatic spreaders. The association of COVID-19 with the Huanan live animal "wet market" is notable. Live animals such as rats, frogs, bats, frogs, rats, snakes, rabbits, and marmots are usually sold, along with seafood, at the Huanan market.[2] Several potential etiological agents, including severe acute respiratory syndrome-corona virus (SARS-COV), Middle East respiratory syndrome-corona virus (MERS-COV), avian influenza virus, and other specific respiratory pathogens, were excluded to identify the etiology of the proliferated virus. Finally, a novel coronavirus 19 (2019-nCOV), later known as severe acute respiratory syndrome-corona virus 2 (SARS-COV-2), was identified as a seventh member of the family of coronaviruses known to infect humans and capable of human to human transmission.[3] WHO named the disease "COVID-19" on 11 Feb, 2020.[4,5] COVID-19 was declared as a global pandemic by WHO on 11 Mar, 2020.[6] Until 02 Apr, 2021, the COVID-19 had spread in 221 countries with 130,291,660 and 2,842,323 deaths worldwide.[7]

Corona Viruses and Human Diseases

In Latin, corona means crown. Coronaviruses (COVs) contain crown-like spikes proteins on the outer surface; thus, they were named coronavirus. COVs

[1]*Preston Institute of of Nanoscience and Technology*
Preston University, Kohat, Islamabad Campus, Islamabad
[2]*Department of Gastroenterology*
Pakistan Institute of Medical Sciences, Islamabad
[3]*Department of Pediatric Medicine*
National Institute of Child Health, Karachi
[4]*Department of Biological Sciences*
National University of Medical Sciences, Rawalpindi
Correspondence:
Dr. Muhammad Naeem
Assistant Professor, Biological Science
National University of Medical Sciences, Rawalpindi
E-mail: m.naeem@numspak.edu.pk

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size ranging from 65 to125 nm in diameter. COVs contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length. COVs are further divided into subgroups: alpha (α), beta (β), gamma (γ), and delta (δ).[8]

COVs have lasted as prominent pathogens infecting humans' respiratory tracts and causing mild and severe respiratory diseases. Seven COVs, including COV-229E, COV-NL63, HCOV-HKU1, HCOV-OC43, SARS-COV, MERS-COV, and SARS-COV-2, have been identified that infect the human respiratory system. The first four mildly pathogenic HCOVs (COV-229E, COV-NL63, HCOV-HKU1, HCOV-OC43) infect the upper respiratory tract and cause seasonal, mild to moderate cold-like respiratory diseases in healthy individuals.[9] However, SARS-COV, MERS-COV, and SARS-COV-2 cause fatal pneumonia, leading to acute lung injury and acute respiratory distress syndrome (ARDS). SARS-COV pandemic was originated in Guangdong province of China in 2002, transmitted globally to 37 countries, and caused 8,096 cases and 774 deaths.[10] SARS-COV natural reservoir hosts were Chinese horseshoe bats.[11] Transmission to humans was through civet cats (intermediate host) sold as a meat source in Chinese wet markets.[12,13] MERS-COV was spread to 27 countries, causing 2494 infected cases and 858 deaths worldwide. In addition, MERS-COV was transmitted through dromedary camels.[12] Therefore, human COVs are a major threat to public health by causing morbidity and mortality in all ages of human beings.

SARS-COV-2, ACE2 and RASS

A key to stop SARS-COV-2 (COVID-19) is to recognize its entry to human cells and the mechanism of infection. The SARS-COV-2 is composed of mainly four structural proteins, namely, spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein. In general, COVs make entry to the host cell via binding to a receptor on the cell surface via surface-anchored spike protein (S) followed by endosome insertion and finally fused viral and lysosomal membranes.[14,15] S is composed of two functional subunits, S1 and S2. S1 facilitates binding to the host cell receptor, while S2 is responsible for the fusion of the viral and cellular membranes.[16,17] SARS-COV-2 has a specific furin cleavage site that is not located in the cleavage site of other SARS-COV.[18] It is suggested that SARS-COV recognizes angiotensin-converting enzyme 2 (ACE2) as its receptor through the receptor-binding domain (S1).[19] Moreover, the SARS-COV spike needs to be proteolytically activated at the S1/S2 boundary to fuse membranes.[20] In this regard, the transmembrane protease serine 2 (TMPRSS2), an androgen-dependent enzyme acts to reinforce the ACE-2 receptor activity in facilitating entry to a cell as adopted by a number of viral pathogens as well as to SARS-COV-2.[21] SARS-COV and SARS-COV-2 have many resemblances. For instance, spike proteins of SARS-COV and SARS-COV-2 are 76.5% identical in amino acid sequences.[22] Therefore, like SARS-COV, SARS-COV-2 also uses ACE2 as its receptor to enter a cell and subsequent viral replication.[23,24] However, the binding affinity of SARS-COV-2 to ACE2 is significantly higher than SARS-COV does.[25] Therefore, SARS-COV-2 is considered more contagious.

To understand the physiological role of ACE2, here we briefly recall the renin-angiotensin-aldosterone system (RAAS) for the readers. As shown in Figure 1, RAAS is a key body mechanism to regulate and balance blood pressure, inflammation, and fibrosis. Moreover, RAAS has a crucial role in the pathophysiology of cardiovascular disease, hypertension, and chronic kidney disorders.[26]

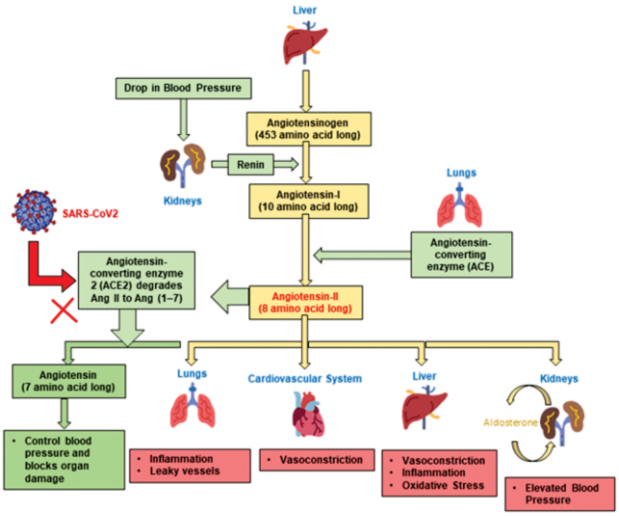

Fig 1: The physiological role of ACE2 and RAAS Mechanism[27]

In the typical RAAS, the circulating precursor angiotensinogen is converted to angiotensin (Ang) I by the protease renin, secreted from the kidney. Angiotensin-converting enzyme (ACE) is released by the lungs, which converts Ang I to Ang II, which causes vasoconstriction, inflammation, and fibrosis

properties. ACE2 enzyme in lungs cleaves Ang I into Ang (1–9), which can be converted to Ang (1–7) by ACE. Furthermore, ACE2 degrades Ang II to Ang (1–7). Ang (1–7) has the properties of vasodilatation, anti-proliferation, and apoptosis and thereby counteract the adverse effects of Ang II.[28]

The key player of RAAS, ACE, and ACE2 is highly expressed in lungs. A balance between ACE and ACE2 is crucial for the normal physiology of the lungs. Indeed, an increased level of ACE might cause multiple pulmonary disorders such as pulmonary hypertension, sarcoidosis, idiopathic pulmonary fibrosis, and acute respiratory distress syndrome. Therefore, a good ACE2 as a counter-regulatory mechanism of bad ACE is crucial in the lung.

Cytokine storm

SARS-COV-2 viral infection mediates both innate and adaptive immune systems. The enhanced level of the group of differentiation 4 (CD4+) and differentiation 8 (CD8+) T-cells can be seen during the anti-viral response. This T-cell response induces a pro-inflammatory response through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling. SARS-COV-2 induces cytokines and pro-inflammatory cytokines along with high interferons (IFN) levels.[29] There is a high rise of IFN chemokines such as tumor necrosis factor-alpha (TNF-α), IFN-γ, IFN-α, interleukin 6 (IL-6), interleukin 1β (IL-1β), interleukin 18 (IL-18), interleukin 12 (IL-12), transforming growth factor-beta (TGFβ), interleukin 33 (IL-33) and C—C Motif Chemokine Ligands (CCL-5, CCL-2, and CCL-3), C-X-C Motif Chemokine Ligands (CXCL9, CXCL8, CXXL10), interferon-induced protein with tetratricopeptide repeat 1 (IFIT1), radical S-adenosyl methionine domain containing 2 (RSAD2) and toll-like receptors 3 (TLR3). These interleukins and chemokines over-production cause complications in hemostasis, T-cells growth, motility, and differentiation. The cytokine storm has a violent impact on the body by causing multiple organ failures.[30,31]

The cytokine storm also led to the wet lung condition known as acute respiratory distress syndrome (ARDS). Presence of lung edema, due to cytokine storm, eventually cause lung injury. Lung injury promotes hypoxemia condition and eventually can cause ARDS. Patients with ARDS have a high mortality rate of COVID-19.[32]

Pathogenesis of COVID-19: Multiple Organs Involvement

SARS-COV-2 infection in humans can cause respiratory complications, ranging from mild symptoms of the upper airway to progressive fatal pneumonia.[3] COVID-19 patients with a severe infection need mechanical ventilator support due to the difficulty in breathing and progressive hypoxemia. An important question raised is why the lungs are the most susceptible target organ of SARS-COV-2. First, alveolar epithelial type II cells represent 83% of ACE2-expressing cells and an ideal home for SARS-COV-2 invasion.[33] A second possible reason could be the increased surface area of the lung, which provides a suitable environment for the inhaled virus.

Most COVID-19 patients suffer from mild symptoms and recover. However, some patients lead to severe medical complications and need intensive medical care and treatment. ACE2 receptor is also expressed in many extrapulmonary tissues, including the intestine, heart, endothelium, and kidney.[34,35] Therefore, in some cases of COVID-19, the virus can cause multi-organ complications that express ACE-2 receptors, including cardiovascular, kidney, gastrointestinal tract, liver, and brain. The pathogenesis of COVID-19 is still not very clear; however, direct cellular damage by SARS-COV-2 and hyperinflammatory response (cytokines storms) are strongly believed to be the causative mechanisms.[36] In this part, we will briefly summarize the possible mechanisms of the pathophysiology of vitals body organs, and systems of COVID-19 patients reported in recent literature.

Lungs and COVID-19

The pathogenesis of COVID- 19 is still being interpreted, but it includes deteriorating effects on the lungs by the virus and injury from a cytokines storm response. The following steps, as shown in Figure 2 may explain the lung manifestation in a COVID-19 patient.[37]

1. When SARS-COV-2 enters a human lung, first it infects pneumocytes type II cells (alveolar cells) and replicates there.
2. Initially, the infected cells release pro-inflammatory cytokines, and immune system response is initiated. In this early stage of infection, the patients may present mild

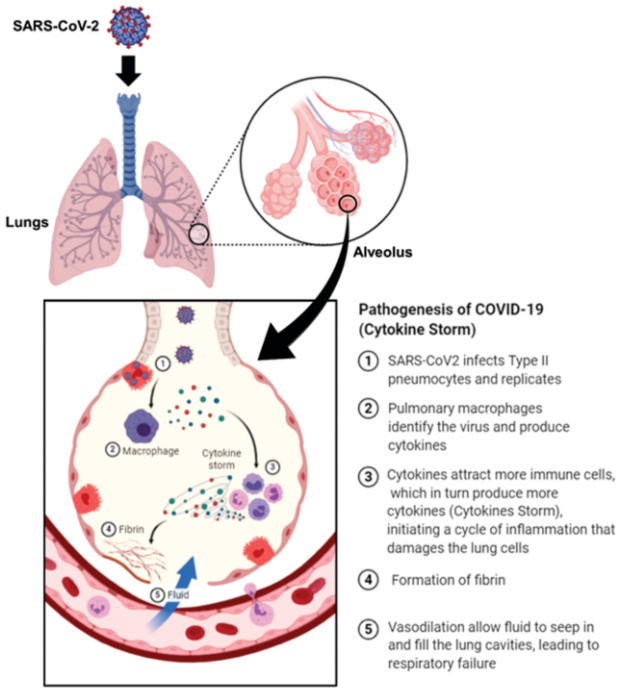

Fig 2: Lungs and COVID-19: Pathogenesis[38]

symptoms such as cough, fever, and body pain.

3. The pulmonary macrophages are patrolling and comes with the contact of virus and infected cells and release IL-1, IL-6, and TNF-α. These pro-inflammatory cytokines cause vasodilation and increase capillary permeability, allowing leakage of more immune cells and plasma to the alveolus.
4. Neutrophils are also employed, which kills infected cells by releasing reactive oxygen species and proteinases.
5. In this stage, shortness of breath and pneumonia develops due to the accumulation of protein-rich fluid in the alveolus. The accumulation of fluid will lead to the dilution of surfactant lining the alveolus that will cause alveolar collapse and decrease gas exchanges (CO_2 and O_2). In this stage, hypoxemia and acute respiratory distress syndrome (ARDS) will develop.
6. If the immune system goes over-responsive, the inflammatory cytokines can spread throughout the bodily fluids, resulting in systemic inflammatory response syndrome, also known as a cytokine storm. In this stage, the patients can go into septic shock (low blood pressure and hypoperfusion) due to systemic inflammation and can lead to multi-organ failure and death of the COVID-19 patient.

The histological study of peripheral lungs of COVID-19 dead patients due to respiratory failure showed alveolar damage with infiltration of perivascular T-cells. Severe endothelial injury associated with the infection of intracellular virus and disrupted cell membranes were observed in the lungs from dead patients of COVID-19. Pulmonary vessels also exhibited widespread thrombosis and disrupted cell membranes.[39] Multi-organ failure can be linked with diffuse intravascular coagulation and large-vessel thrombosis.[40]

The ACE2 is not only expressed on type II alveolar cells: indeed, it has been detected on the oral mucosa, kidney, myocardium, ileum, colon, esophagus, and urothelial cells. This may partially explain the multiple organs' viral presentations and cytokine storms of COVID-19. The following section will discuss the extrapulmonary, multiple organs involvement, and clinical manifestation in COVID-19 patients (Figure 3).

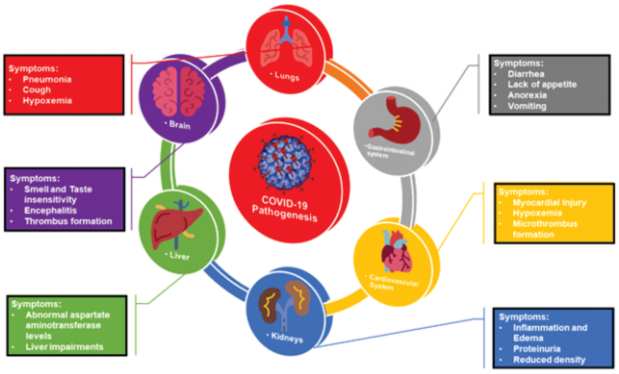

Fig 3: Extrapulmonary manifestations in COVID-19 patients[41]

Gastrointestinal system and COVID-19

The well-established symptoms of COVID-19 patients include fever along with dyspnea and cough, indicating an infected respiratory system.[42,43] However, extrapulmonary symptoms, particularly those arising from the gastrointestinal tract, are very important in the early diagnosis of COVID-19 patients. Most importantly, some COVID-19 patients in the early phase of infection complained of gastrointestinal disorders such as vomiting, anorexia, and diarrhea without respiratory symptoms.[44] The detection of COVID-19 in stool was a breakthrough that suggested that SARS-COV-2 also replicates and spreads in the digestive tract. A study

reported that the first case of COVID-19 in the United States also mentioned abdominal discomfort and loose stool symptoms. On examination of stool, SARS-COV-2 was positive.[45] A descriptive, cross-sectional study from Hubei, China, enrolled 204 confirmed COVID-19 patients from 18 Jan, 2020, to 28 Feb, 2020. The average age of patients was 52.9 years, including 107 men and 97 women. Out of 204 patients, 103 patients (50.5%) showed gastrointestinal symptom, including lack of appetite (81 [78.6%] cases), diarrhea (35 [34%] cases), vomiting (4 [3.9%] cases), and abdominal pain (2 [1.9%] cases). The study reported that 6 cases showed gastrointestinal symptoms, but no symptom of respiratory infection.[46]

The possible pathogenesis through which the COVID-19 causes gastrointestinal symptoms are: (i). ACE2 receptors are highly expressed on differentiated enterocytes, which suggests that the gastrointestinal system is the target organ for SARS-COV-2.[47] Several studies reported the presence of SARS-COV-2 nucleic acid in a stool sample of COVID-19 patients.[48,49] This data indicates that SARS-COV-2 directly or indirectly harms the patients' gastrointestinal tract through inflammatory reactions. The malabsorption by enterocytes due to viral infection may lead to enteric symptoms of COVID-19, such as diarrhea.[50] (ii). The SARS-COV-2 may cause dysregulation of the intestinal flora, which could lead to gastrointestinal symptoms of COVID-19. The intestinal flora is essential for the antimicrobial effects, body's nutritional metabolism and regulation, and the development and maturation of the body's immune system.[51]

The extra pulmonary symptoms such as those appearing in the gastrointestinal system are significant in the early diagnosis of COVID-19 cases, and clinicians should pay attention to it. Otherwise, they may miss the COVID-19 case with only digestive symptoms until respiratory symptoms appear. This may be a cause for the unnoticed transmission of the COVID-19 inside the family or the other close contacts.

Cardiovascular system and COVID-19

Along with respiratory symptoms, some COVID-19 patients presented severe cardiovascular injuries. Furthermore, there might have a higher risk of death of COVID-19 patients with pre-existing cardiovascular disease (CVD) such as hypertension, coronary heart disease, and cardiomyopathy.[52] To evaluate the involvement of the cardiovascular system in the fatal outcomes of COVID-19, a retrospective single-center case series investigated 187 COVID-19 patients at the Seventh Hospital of Wuhan City, China.[53] The study was conducted from 23 Jan, 2020 to 23 Feb, 2020. The average age of COVID-19 patients was 58.50 years. Out of 187 patients, 144 patients (77%) were discharged, while 43 patients (23%) died. Among 187 patients, 66 (35.3%) had pre-existing CVD, and 52 (27.8%) showed myocardial injury as evaluated by higher troponin T (TnT) levels. Furthermore, patients with pre-existing CVD exhibited a higher level of TnT compared with the patients without CVD. Hence, higher mortality, 69.44% (25 of 36), was observed for patients with pre-existing CVD and elevated TnTs compared to patients without pre-existing CVD but elevated TnT levels which showed 37.50% (6 of 16) mortality.

Based on the above reports, it is very important to know the mechanisms of cardiovascular system damage in COVID-19 patients so that early and timely treatment can reduce mortality and complication. It is suggested that the myocardial injury reported in COVID-19 patients might be linked with ACE2. Since ACE2 is also highly expressed in the cardiovascular system, and hence ACE2 related signaling pathways have a key role in heart damage.[54] Patients with pre-existing CVD expressed higher ACE2 levels compared with healthy people. It might be due to the use of RAAS inhibitors. Higher expression of ACE2 in patients with pre-existing CVD can be linked with the severity of COVID-19.[55] It is also proposed that cytokine storm initiated in critical cases of COVID-19 might cause myocardial injury.[52] In addition, respiratory dysfunction in COVID-19 patients leads to hypoxemia, resulting in injury to the myocardial cells.[55] Moreover, endothelial cells express TMPRSS2 together with ACE2. These receptors can be targeted by SARS-COV-2 and can lead to the microthrombus formation, which can lead to disseminated intravascular coagulation and multi-organ failure.[21]

Kidney and COVID-19

Acute kidney injury was reported in previous pandemics of SARS-COV and MERS-COV.[56] A study

from China evaluated 59 COVID-19 patients for kidney manifestations.[57] They found massive albuminuria in 34% of patients on the first day of hospitalization, and later, 63% of patients suffered from proteinuria. Plasma creatinine levels were elevated in 19% of patients, while 27% of patients exhibited elevated levels of blood urea nitrogen level. Furthermore, a computed tomography scan (CT scan) of the kidneys was conducted, which exhibited reduced density, indicating inflammation and edema.[58] A systematic review and meta-analysis of 40 studies and 24,527 patients concluded that acute kidney injury in COVID-19 patients is associated with fatality and severe infections.[59] These results indicated impairment of kidney functions that may occur due to COVID-19.

The exact pathogenesis of kidney injury in COVID-19 is unknown. ACE2 is expressed on renal tubular cells and can be a direct target of viral infection. In previous SARS-COV, viral RNA was detected in kidney tissues and urine.[60] Therefore, renal ACE2 was believed to be a binding site for viral infection.[19] Recently, SARS-COV-2 was diagnosed in a urine sample of a COVID-19 patient, indicating the kidney as the target organ. The likely mechanism of kidney injury in COVID-19 patients could be the direct viral injury or sepsis leading to the cytokine storm.[61]

Overall, the above reports showed evidence that kidney function impairment is common in COVID-19 patients, which may exaggerate the illness and can lead to fatal consequences. Therefore, clinicians and other health professionals should consider the renal clinical manifestations of COVID-19 patients. Early diagnosis of kidney injury in COVID-19 patients will make it possible to apply potential therapeutic strategies to protect kidney functions and prevent complications. Furthermore, ACE2 is also expressed on Leydig cells and seminiferous ducts cells in the testis, along with renal tubular cells.[62] Therefore, the COVID-19 patients could suffer from virus testicular tissue injury. The clinicians should observe the risk of testicular lesions in patients during hospitalization and later clinical follow-up of COVID-19 patients to avoid any fertility problems.

Liver and COVID-19

Up to 60% of patients with SARS-COV infection were suffered from liver impairments and had also been exhibited in MERS-COV infected patients.[63,64] Since SARS-COV-2 shares 82% genome sequence similarity to SARS-COV and 50% to MERS-COV[65], there is a possibility of liver injury in COVID-19 patients. Some case studies reported clinical manifestations of liver involvement in COVID-19 infection. Critical cases of COVID-19 seem to have higher risks of liver impairments. For instance, in a study, 62% (8/13) of COVID-19 patients hospitalized in the intensive care unit (ICU) showed an elevated level of aspartate aminotransferase (AST) compared to 25% (7/28) non-ICU patients.[52] A large cohort study from mainland China, comprising 1099 COVID-19 patients from 552 hospitals in 31 provinces or provincial municipalities, reported that severe COVID-19 patients exhibited abnormal liver aminotransferase levels compared to non-severe patients.[66]

Currently, the pathogenesis of COVID-19-associated liver injury/dysfunction is not certain. The possible mechanism of liver injury in COVID-19 may include direct damage by SARS-COV-2. Based on the similarities of SARS-COV-2 to SARS-COV, it might enter the liver through ACE2 receptors and can cause injury and result in liver dysfunctions.[67] In addition, cytokines storm and hypoxia due to pneumonia in critical COVID-19 patients are expected to cause liver injury. Furthermore, hepatotoxic drugs can also be the possible cause of liver dysfunction. Some studies suggest that since ACE2 is also expressed on bile duct epithelial cells, which is 20 times higher than in hepatocytes, bile duct epithelial cells injury might also occur in COVID-19 patients.[68]

Brain and COVID-19

Nearly 30% to 50% of COVID-19 patients are associated with a range of neurological complications due to deterioration of the central and peripheral nervous system via direct damage of SARS-COV-2 or molecular mimicry, blood clotting, and cytokine storm.[69] COVID-19 shares these symptoms with the early coronaviruses. The 2003 SARS-COV outbreak and the 2012 MERS outbreak have evidence of neurological complications and nervous system damage.[70,71] The common symptoms that occur due to COVID-19 to the brain are the loss of smell and taste, encephalitis (inflammation of the brain), confusion, and immune system attack on body nerves also, termed as Guillain-Barre Syndrome as reported by Mark Ellul et al. and his colleagues.[72] In the early stage of SARS-COV-2, it

causes damage to epithelial cells in the nose and mouth, leading to dysfunction of smell and taste sensitivity. Mercante et al. study found that insensitivity in smell was reduced in 41.7% of people with COVID-19, while 55.4% faced insensitivity in taste.[73] SARS-COV-2 is found to cause thrombus formation with clotting of blood that can lead to brain stroke. Although COVID-19 patients of all ages are endangered to stroke, these incidents in COVID-19 patients are also reported in underage 50 adults with a mild respiratory system.[74] The severe state of the COVID-19 patient can lead to cytokine storm at the blood-brain barrier, the entry of immune cells to the brain may develop seizure, coma, and encephalopathy.[69,75]

Conclusion

The over-stimulation of pro-inflammatory cytokines and high interferon levels termed cytokine storms can lead to multiple-organs injury. Lungs are primary damaged organs in COVID-19 patients because of the higher expression of ACE2 receptors in epithelial cells. In addition, the cardiovascular risk with COVID-19 patients is due to dysregulation of ACE2, which induces hypertension and vasodilation. Moreover, COVID-19 patients can also face high creatinine levels, proteinuria, and edema due to pathogenesis in the kidney. SARS-COV-2 presence in stool also confirms its pathogenesis in the gut. The gastrointestinal complications usually include vomiting, diarrhea, and nausea in COVID-19 patients. The pathogenesis of SARS-COV-2 in liver is still unknown, however high levels of AST, ALT, GGT, and bilirubin in COVID-19 patients can also cause liver injury. Neurological complications were also reported in COVID-19 patients. SARS-COV-2 can cause damage to the central and peripheral nervous system, thrombus formation, and stroke. More data is still needed to evaluate other factors associated with multi-organ failure in COVID-19 patients. The clinicians should consider multi-organs manifestation in COVID-19 patients, which could be helpful in diagnosis and therapy in the future.

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