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Harmful Effects of COVID-19 on Major Human Body Organs: A Review

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Abstract

The world experienced the outbreak of a new pandemic disease in 2019, known as coronavirus (CoV) disease 2019 (COVID-19), which is caused by the novel severe acute respiratory syndrome-CoV-2 (SARS-CoV-2). The respiratory system is the organ system most commonly affected by COVID-19; however, several other organ systems have been reported to be affected. The SARS-CoV-2 RNA found in infected stub samples can cause lung contagion by binding to the angiotensin-converting enzyme-2 (ACE-2) receptor of the alveolar epithelial cells. The gut microbiota (GM) promote immunity, indicating that the alignment of the microbiota and corresponding metabolic processes in COVID-19 can help to identify novel biomarkers and new therapeutic targets for this disease. The cause of kidney damage in COVID-19 patients is possibly multifactorial, involving a complex mechanism that involves complement dysregulation and thrombotic microangiopathy, as well as the occurrence of a "cytokine storm" syndrome, which are immune responses that are abandoned and dysfunctional with unfavorable prognosis in severe COVID-19 cases. Furthermore, COVID-19 involves a continuous proliferation and activation of macrophages and lymphocytes. SARS-CoV-2 can also bind to the ACE-2 receptor expressed in the cerebral capillary endothelial cells that can invade the blood-brain wall, to penetrate the brain parenchyma. However, in the ongoing pandemic, there has been a surge in studies on a wide range of topics, including causes of respiratory failure, asymptomatic patients, intensive care patients, and survivors. This review briefly describes the damaging effects of COVID-19 on vital human organs and the inhibitory function of the ACE-2 receptor on the GM, which causes gut dysbiosis, and thus, this review discusses topics that have an opportunity for further investigation.

Keywords: COVID-19, SARS-CoV-2, ACE-2, Gut microbiome, Body organs

INTRODUCTION

Currently, coronavirus (CoV) disease-2019 (COVID-19) is a public health concern due to its rapid spread and high mortality rate throughout the world, despite its discovery in late 2019 in Wuhan, the capital of the Hubei province of China[1]. The causative agent of COVID-19 is severe acute respiratory syndrome-CoV-2 (SARS-CoV-2)[2]. In January 2020, a study reported that RNA detected in COVID-19 patients was similar to the SARS-CoV-2 viral genome responsible for causing bilateral interstitial pneumonia[2]. This virus is included in the β-CoV cluster of viruses that causes SARS and Middle East respiratory syndrome (MERS), based on a report by the World Health Organization (WHO)[2-5]. The symptoms of COVID-19, including shortness of breath, fever, coughing, and pneumonia, typically appear between 2 and 14 days after the viral infection. Moreover, it can harm other organs in the body, such as the intestines, liver, and brain, as well as cause lung-related problems after hospitalization, which may ultimately lead to rapid death compared to those observed in previous cases of SARS- and MERS-CoV infections[6-8]. Recently, different research teams have been trying to develop novel SARS-CoV-2 therapies or vaccines and new solutions to prevent or halt the replication of the virus. In addition to the vaccine development efforts, multiple therapy options, including the use of drugs for blocking the ACE-2 receptor found in human cells, are currently being assessed[9-12]. Furthermore, ACE-2 also demonstrates anti-renin-angiotensin system (RAS) functions associated with the carriage of neutral amino acids and healthy homeostasis[13,14]. It is also associated with gastrointestinal (GI) symptoms such as diarrhoea and nausea[15]. Mounting evidence suggest that ACE-2 plays a vital role in the progression of gut dysbiosis in response to renal, metabolic, and cardiovascular distress associated with older age[16-19]. Moreover, there is an increased risk of multi-organ failure with an increasing death rate in the elderly COVID-19 patients with prevailing renal, metabolic, and cardiovascular conditions. Therefore, the disease incidences and mortality rates are much higher for the elderly population[20-22]. Acute kidney injury (AKI) is a condition where in the glomerular filtration rate unexpectedly decreases with nitrogen waste retention, along with affecting the fluid content, electrolytes, and homeostasis[23,24]. The WHO earlier declared that currently, there is

no specific treatment or vaccine for COVID-19[25]; however, human clinical trials with few vaccines have already been started in many countries. In this review, we aimed to describe the damaging effects of COVID-19 on vital body organs of individuals with age-related comorbidities, as well as to explore the interactive role of intestinal microbiota dysbiosis in individuals with mutant ACE-2 receptors.

Organs affected by COVID-19

SARS-CoV-2 infection impacts different parts of the human body, including the gut microbiota (GM), heart, lungs, liver, brain, and kidneys, causing acute to severe damage. Table 1 presents the list of different body parts affected by COVID-19 and its deleterious effects on them; major effects of COVID-19 on the human body are depicted in Fig. 1.

Gut microbiota

The number of resident microorganisms in the human GM approximately exceeds 10^{14} and includes fungi, viruses, archaea, and bacteria[5]. Zuo et al. found significant alterations in fecal microbiomes of COVID-19 patients compared to those of healthy and pneumonia controls, after adjusting for age, gender, antibiotic use, and comorbidities[26]. The GM plays an important role in human health through its metabolic, nutritional, and defensive functions. Firmicutes and Bacteroidetes cause gut dysbiosis, while Firmicutes, Proteobacteria, and Bacteroidetes dominate throughout the lungs[27]. Previous studies have suggested variations in GM due to respiratory infections[28]. Pneumonia is a severe clinical symptom of COVID-19, which can cause acute respiratory distress syndrome (ARDS), specifically in elderly immune-compromised patients[29].

GM and coronavirus infection

The GM plays a major role in host immunity by interacting with antigen-presenting cells. However, SARS-CoV-2 possibly interacts with the GM and infects enterocytes to induce GI symptoms. COVID-19 may interact with the microbiome and affect cytokine production, leading to the over-production of pro-inflammatory cytokines[30]. Previous studies, particularly on MERS- and SARS-CoV infections, have revealed that the resulting immune system "cytokine storm" was complimented by an impaired acute inflammatory reaction and the high expression of TNFα, IL-2, IL-6, IL-1β, MCP-1, IFNα, IFNβ, and IFNγ[31,32]. These findings are consistent with the high levels of pro-inflammatory cytokines (G-CSF, MIP-1A, IL-1, IL-2, IL-7, IP-10, TNFα, and MCP-1) in COVID-19 cases[33]. Based on these findings, new biomarkers are under investigation for the long-term improvement of the COVID-19 pandemic, considering the prevention of respiratory SARS-CoV-2 infections by age-linked pathways[34]. GM dysbiosis is characterized by a decrease in the levels of probiotic bacteria in COVID-19 patients due to imbalances in intestinal microflora[35,36],

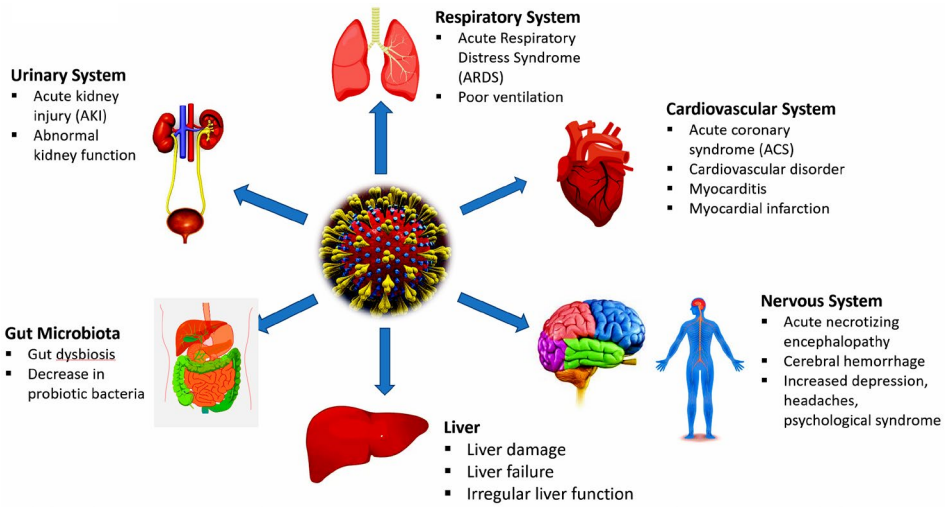

Fig. 1. Effects of COVID-19 on major parts of the human body.

relative abundance of pathogens (for example, *Rothia, Actinomyces*, and *Streptococcus* spp.), as well as interactions among pathogens[37]. These GM changes mainly occur following the resolution of respiratory symptoms and are correlated with the severity of COVID-19[38]. In general, these findings provide fundamental details of the research initiatives involving mammalian host immune interactions with the intestinal microbiota following SARS-CoV-2 infection[39]. Immunity against SARS-CoV-2 must be accurately evaluated under these circumstances, considering the effects of intestinal and lung microorganisms, as the host microbiome plays an essential role in infection.

GM permeability and dysbiosis in COVID-19 patients

A wide variety of age-related vascular and cardiac problems have been linked to GM, including heart failure, hypertension, coronary artery disease, myocardial infarction, and stroke[18]. The primary sign of specific strokes is a persistent inflammatory condition, which has also been linked to GM dysbiosis[18,40]. In kidney disease, immune deregulation and inflammation are both a cause and consequence of microbial dysbiosis[41]. Dysbiosis causes chronic inflammation and leads to renal disease, which ultimately modifies the GM, leading to dysbiosis[42]. Most medical conditions with a high mortality rate, caused due to SARS-CoV-2 infection, are related to increased intestinal dysbiosis, diabetes, obesity, lung inflammatory conditions, and cardiovascular disorders (CVDs)[43]. Furthermore, increased intestinal permeability is critical for viral infections because it is caused by initial inflammation (cytokine storm), thereby strengthening the previous fever[44]. As most viruses initially contact the host surfaces through bacteria, the interactions between bacteria and viruses are a long-standing element of viral pathophysiology[45]. Additionally, increased intestinal permeability contributes to higher TLR4 and lipopolysaccharide (LPS) levels[46].

Crosstalk between GM and SARS-CoV-2

Robust biochemical and epidemiological findings during the COVID-19 pandemic indicate that older individuals with pre-existing lung, metabolic, cardiovascular, or renal infections are at a higher risk of severe sickness and death, upon SARS-CoV-2 infection[47,48]. The number of COVID-19 patients with diabetes, hypertension, or CVDs, receiving care at intensive care units (ICUs), is approximately two- to three-folds higher than that in a non-ICU treatment unit[47]. LPS-induced lung injury in rats decreases the expression of ACE-2, alleviating inflammation-related diseases and initiating the upregulation of Ras1[49]. Notably,

Table 1. List of body parts affected by COVID-19 and its deleterious effects

Body organs/parts	Acts on/ Type of cell affected	Damage/ Consequences	References
Gut Microbiota	Decrease probiotic microorganisms	Gut dysbiosis	30, 31
	Small intestine, enterocytes, colon	Inflammation and diarrhoea	32
Kidney	Podocytes and proximally straight tubular cells	Acute Kidney Injury (AKI)	33
	Glomerular cells, tubular epithelium, and podocytes	Rhabdomyolysis, hypoxemia, and coagulopathy	34
Liver	Cells of the bile duct	Irregular liver function	35, 36
Heart	Pericytes	Microvascular disorders	36
	Myocardium	Myocarditis	37
	Endothelial cells	Acute Coronary Syndrome	38
Lungs	Alveolar cell	Alveolar damage, hypoxemia	39
	Hyper fusion of alveolar cells	Acute Respiratory Distress Syndrome	40
Brain	ACE-2 receptor affected due to amplified blood pressure	Cerebral hemorrhage	41
	Neuronal destruction and nerve tissue lesions	Encephalitis	42
	Cerebral capillary endothelial cells	Puzzlement, loss of awareness, coma	43

increasing of Ang II levels affects microbial gut metabolomics[50]. The gain and loss of ACE-2 function is associated with the improvement and deterioration of leaky intestinal conditions, respectively[51]. Enteric SARS-COV-2 infection and ACE2 imbalance, causing gastroenteritis-like symptoms, intestinal homeostasis disruption, and GM dysbiosis, are observed in COVID-19 patients[52].

GM dysbiosis, altered intestinal permeability, and inefficient initiation of local and systemic immune responses can lead to severe symptoms because ACE-2 protective functions are lost upon SARS-CoV-2 infection[53]. For COVID-19 patients, GI impairment (for example, diarrhoea and GI discomfort) sustains until respiratory issues are mitigated[15], which is similar to that observed in patients infected with other CoVs[54]. Abdominal pain is more prevalent in ICU-admitted patients than non-ICU admitted patients[1]. A pulmonary axis associated with phenotypic intestinal dysbiosis and permeable intestines, which corresponds to stimulation of the ACE/Ang II/AT1R axis, results from ACE-2 deficiency occurring at the onset of pulmonary hypertension[55-57]. The GM particularly causes pulmonary distress in a crucial cross-talk between itself and the lungs, called the "gut-lung axis"[5]. Some COVID-19 patients present with intestinal microbial dysbiosis, which supports this frame of logic[35].

Effects of COVID-19 on the kidneys

It is essential to analyze the pathogenesis of COVID-19 to determine why renal failure can be a contributing factor in patients with SARS-CoV-2 infection. The development of an acute disease can be categorized into 3 distinct phases: an early infection phase, a pulmonary phase, and a severe hyper-inflammatory phase[65,66,32]. The ACE-2 receptor is expressed in various organs, including the kidneys[53]. ACE-2 and dipeptidyl peptidase-4, which can bind to SARS- and MERS-CoV, are expressed in renal tubular cells[58,59]. In both infections, viral RNA can be isolated via extraction from the kidneys and by collecting urine samples of the patients[60]. ACE-2 assists in viral entry by making the target cells vulnerable to some CoV, including SARS-CoV-2[61,62]. A positive correlation exists between the expression of ACE-2 and SARS-CoV-2 *in vitro*. Thus, the expression of the human ACE-2 gene in various tissues may cause immune sensitization to SARS-CoV-2 infection[21]. Only 6% of SARS-CoV-2-infected subjects suffer from AKI[63]. Although AKI is a rare feature of SARS viral infection, it is a fatal complication; a high mortality rate has been observed in 5-15% of cases with AKI (60-90%). Expression of the ACE-2 and TMPRSS genes has been reported in cellular components of the kidney. In contrast, proximally straight tubular cells are potential SARS-CoV-2 hosts, with infections resulting in the development of AKI. In fatal pneumonia, synergistic cytopathic and systemic inflammatory attacks can affect AKI patients, particularly in serious and critical instances with positive viral RNA in blood and proteinuria[64].

Renal impairment in COVID-19 patients

Researchers have analyzed the renal post-mortem viral nuclear capsid protein in situ and found that SARS-CoV-2 antigens aggregate in the kidney tubules, indicating that it specifically infects the human kidneys and causes AKI[65]. Alberici et al. identified 20 patients with kidney transplants and SARS-CoV-2-mediated pneumonia[66]. All the patients had fever, but only one had trouble breathing. With a median of 15 days post-symptom initiation, 5 kidney transplant recipients died, indicating rapid clinical deterioration and increased oxygen requirement in renal transplant patients with SARS-CoV-2 pneumonia. SARS-CoV-2-induced pneumonia had a high progression risk and a high mortality rate in this small cohort of long-term kidney transplant patients.

Uribarri et al. studied 758 patients, out of which 90.8% of the SARS-CoV-2-infected patients were identified through the nasopharyngeal PCR screening method[67]. Of these patients, 317 (48.9%) were diagnosed with hypertension, 290 (38.7%) with dyslipidemia, 138 (21.9%) with type-2 diabetes mellitus, 149 (19.5%) with pulmonary disorders, and 199 (26.0%) with cardiac disorders. However, only 8.5% of patients with a history of CKD showed kidney impairment, which was determined by measuring eGFR glomerular filtration rate after hospital admission. The patients received intensive COVID-19 medication. Systemic immunosuppression results in a poorer prognosis in organ transplantation patients with COVID-19 infection[68]. An intensive study by Wang et al. described the epidemiological and clinical characteristics of 138 patients with confirmed COVID-19-mediated pneumonia. The death

rate was higher in patients with comorbidities, including ARDS[1]. Multisystem inflammatory syndrome in children (MIS-C) is a post-viral disease associated with COVID-19. However, it is still not known whether the AKI etiologies in MIS-C correlate with acute infections or whether the mechanisms are different for patients with a post-viral inflammatory condition.

Effects of COVID-19 on the liver

ACE2 has higher expression levels in the colon, liver, and biliary system[35]. ACE2 receptors are expressed in the gastrointestinal tract, vascular endothelium, and cholangiocytes of the liver. Therefore, cases of acute liver injury, having higher mortality associated with the effects of COVID-19, have been reported[69]. Previous studies have also reported that the subclinical features and laboratory test results of patients with COVID-19 infection are associated with liver dysfunction[70]. SARS-CoV-2 cannot cause viral hepatitis because of the low levels or a total lack of ACE-2 in hepatocytes. Generally, COVID-19 is correlated with mild-to-moderate levels of aspartate aminotransferase, and to a lesser degree, alanine aminotransferase elevations, with elevated aminotransferase levels more common in patients with mild disease than in those with very mild disease[33].

Alterations in the biochemistry of the liver upon COVID-19 infection include elevated levels of aminotransferase expression, with rare severe liver injuries and abnormalities in more severe cases of COVID-19[33]. Fever, dry cough, weakness, and troubled breathing are the primary signs of SARS-CoV-2 infection. Studies on liver function abnormalities have been previously reported[46,48] and have identified ACE-2 receptor as the SARS-CoV-2 cell entrance receptor[71]. SARS-CoV-2 infection severity is correlated with the expression levels of IL-6[72]. The use of various drugs such as antibiotics, antivirals, analgesics, and conventional Chinese medicine can cause liver damage in COVID-19 patients[33]. Currently, there is no robust evidence that liver damage during hospitalization of severe COVID-19 patients is fully drug-induced. A patient who died with COVID-19 after a liver operation displayed higher liver enzyme expression levels, possibly due to the fractional properties of the drugs, and liver dysfunction due to sepsis[33]. Hepatotoxicity in COVID-19 patients, caused due to viral hepatocyte-associated infection or drug toxicity, has also been reported. SARS-CoV-2 fixes cholangiocytes positive for ACE-2 and causes dysfunction[73]. COVID-19 causes a severe inflammatory reaction, which results in immune-mediated injury[74]. Significantly elevated levels of infection biomarkers such as CRP, LDH, D-dimer, serum ferritin, IL-6, and IL-2 were observed in acute COVID-19[75]. Patients with stable liver disease may be more susceptible to SARS-CoV-2-mediated liver injury[76].

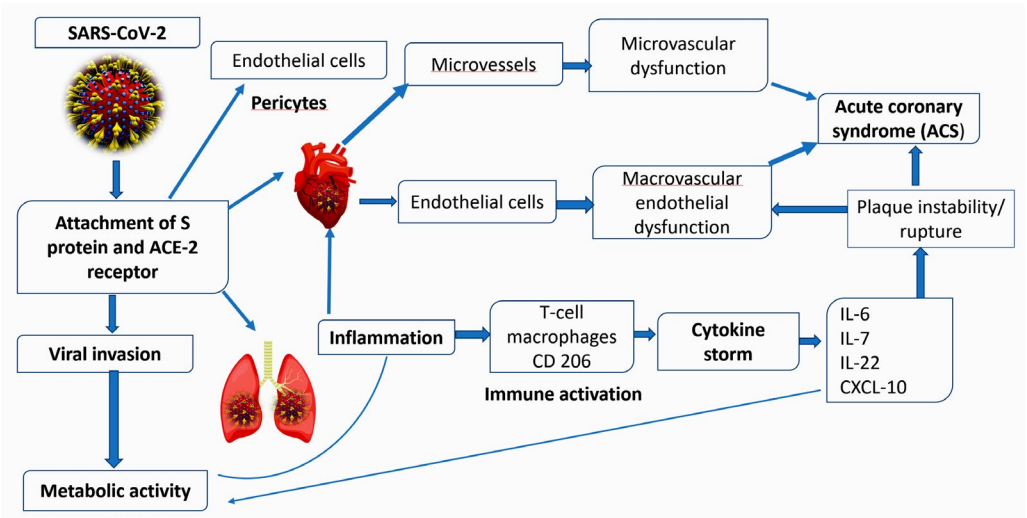

Fig. 2. Effects of SARS-CoV-2 on the heart and lungs, which result in acute coronary syndrome (ACS).

In COVID-19 patients, liver enzyme expression levels frequently increase, thereby indicating liver damage. Therefore, liver function is regularly and carefully monitored in COVID-19 patients, so that hepatitis, liver damage, and liver failure can be detected at early stages[77]. However, further investigation on the relationship between COVID-19 assessment and liver injury is required, as the liver damage mechanism for COVID-19 infection is still unknown and tends to be multifactorial[78].

Effects of COVID-19 on the cardiovascular system

Acute infections of the respiratory system, including influenza, respiratory syncytial virus, and bacterial pneumonia, are the major causes of CVDs[79]. Some individuals develop extreme acute respiratory disorders as a result of SARS-CoV, MERS-CoV, or SARS-CoV-2[48]. Cardiovascular problems may develop due to SARS-CoV infection, and myocardial infarction and acute coronary syndrome can occur after SARS[80]. SARS-CoV-2 appears to act on the middle region of the heart and cause myocarditis[81]. Myocardial injury is possibly associated with myocarditis and ischemia-related infections and is an important prognostic factor in COVID-19 cases[82]. Troponin, myoglobin, C-reactive protein, serum ferritin, and IL-6 expression levels were higher in patients who had died from COVID-19 than in those who had died of other reasons. COVID-19 patients have a high inflammatory load, which causes a spike in cardiac myocarditis-related diseases[83]. In a previous study, a novel CoV that uses ACE-2 inside cells, SARS-CoV, was detected in the heart. The study showed that SARS-CoV was capable of infecting the myocardium through the ACE-2 receptor in 35% of the subjects[84]. The liver synthesizes angiotensinogen, and the kidneys secrete renin; angiotensinogen and renin then produce angiotensin 1, which is secreted by the lungs. The direct invasion of cardiomyocytes by SARS-CoV-2 indicates malfunction in the cardiac tissue and appears symptom like minor inflammation in the heart and that it affects COVID-19 patients without significant myocardial injury[45]. COVID-19 infected death in hospital was significantly associated with age, inflammatory response, and cardiovascular comorbidities[85]. Patients who died from COVID-19 had a more significant proportion of both myocardial damage and related coronary comorbidities, indicating that heart complications typically coexist and evolve into permanent outcomes of underlying coronary diseases or risks[86]. Alternatively, pneumonia might increase the impact of inflammation in coronary atherosclerotic plaques through a systemic inflammatory reaction, rendering them unstable and vulnerable to rupturing[82]. Severe myocardial damage has been identified in COVID-19 patients. Interstitial mononuclear inflammatory infiltrates diffuse into the heart tissue in COVID-19 patients[81], suggesting that COVID-19 is not explicitly involved in heart damage.

Effects of COVID-19 on the respiratory system

COVID-19 is mainly associated with the respiratory system. A genome-wide association study analyzed 8,582,968 single nucleotide polymorphisms in 1,980 patients from Italy and Spain and conducted a meta-analysis of the two case-control panels[87]. A gene cluster, 3p21.31, was identified as a susceptible locus in COVID-19 patients. In the meta-analysis, associations between rs11385942 at locus 3p21.31 and rs657152 at locus 9q34.2 were detected[87]. The study also confirmed the involvement of the ABO blood types. It was found that population with blood group A had a higher risk of COVID-19 infection than the other blood types, whereas blood group O provided a protective function compared to the other blood types[87,88].

Majority of the COVID-19 patients in intensive care are hypoxemic, have characteristics of ARDS, and receive invasive mechanical ventilation[89]. Endotracheal intubation is avoided in severely hypoxemic patients[90]. Different COVID-19 symptoms are associated with ARDS. In a previous study, 8 patients showed hyperfusion in certain lung regions, particularly poorly ventilated ones. Blood gas analyses and CT scans revealed fractions of large shunts and minor gasless tissues[91]. The effects of SARS-CoV-2 on the heart and lungs are shown in Fig. 2.

The spike protein of SARS-CoV-2 first binds to the ACE-2 transmembrane receptor to enter the host cells, including endothelial cells and pericytes, leading to inflammation, and finally, to organ failure. The infection of endothelial cells or pericytes leads to severe microvascular and macrovascular dysfunction. In addition, it may effectively disrupt or rupture thrombotic plaques

to develop acute coronary syndrome. SARS-CoV-2 infects the respiratory tract, particularly pneumocytes, and is characterized by the progression of systemic inflammation and overactivation of immune cells, resulting in a "cytokine storm," i.e., an increased level of cytokines[61].

Effects of COVID-19 on the brain

Initially, COVID-19 was thought to have influenza-like respiratory symptoms[37]. However, few neurological symptoms have been reported in patients with respiratory severities. SARS-CoV-2 infection is characterized by various signs and symptoms such as headaches, hemoptysis, diarrhoea, dyspnea, lymphopenia, and pneumonia with abnormalities in the chest CTs[33], as well as cerebral hemorrhage, peripheral neuropathy, meningoencephalitis[92], and cerebral infarction[35]. A recent study reported that more than one-third of 241 COVID-19 patients suffered several neurological disorders, including severe cerebrovascular disorders, skeletal muscle damage, and reduced consciousness[92]. Another study reported acute necrotizing encephalopathy from the brain MRIs of COVID-19 patients. Cerebral hemorrhage indicates that the ACE-2 receptors are affected by COVID-19 due to high blood pressure[93].

Patients with severe infections may experience puzzlement, loss of awareness, and enter into a coma[94,95]. Nearly 40% of COVID-19 patients report increased depression, disturbed awareness, and other brain dysfunctions[92]. Additionally, an autopsy report showed brain tissue edema in a COVID-19 patient[35].

ACE-2 expression is a brain-cardiac defense response in a variety of organs and organ systems, including the skeletal muscles and nervous system, and it plays a central role in regulating blood density and mechanisms of anti-atherosclerosis[96]. The brain expresses ACE-2 receptors in neurons and glial cells, making them a possible target of COVID-19. Previous studies have shown that SARS-CoV-2 can cause neuronal cell death in mice by penetrating the brain behind the nose near the olfactory epithelium[97]. A recent study by Mao et al. identified neurologic manifestations occurring in COVID-19 patients, indicating a prospective viral tropism in COVID-19 patients[92]. This indicates the prospective viral tropism of SARS-CoV-2.

A study published before the SARS-CoV-2 outbreak in the USA and Europe attempted to screen for ACE-2 mutants that could resist S-protein attachment. A recent study showed that the spike exterior glycoprotein (Ala930Val) in the Indian SARS-CoV-2 strain is different from that found in other strains[98]. Although cerebral damage in SARS-CoV-2-infected patients may be correlated with age and is predisposed in older patients, clinical trials have demonstrated that CoVs have tropism in the central nervous system[99]. Severe neurological disorders such as hemorrhages and acute necrotizing encephalopathy occur in COVID-19 patients because of the direct viral incursion into the nerve structure[100,101].

CONCLUSIONS AND FUTURE PROSPECTS

In COVID-19 pathophysiology, ACE-2 has a series of functions that directly affect both disease treatment and outcome. The development of atherosclerosis and increased risk of death in patients with CVDs, obesity, diabetes, or chronic renal diseases, are strongly linked to microbiota dysbiosis and a compromised intestinal-blood barrier. In addition, gut dysbiosis in COVID-19 patients might be caused by AKI. Therefore, COVID-19 patients should undertake neurological examinations at an early stage, particularly for cerebrovascular infections, awareness, and paresthesia. However, there is still no specific cure for CoV infection. Therefore, primary intensive care is needed, which includes identifying critical signs, controlling blood pressure and oxygen, and treating and controlling other complications such as secondary infections and organ failure. Finally, analyzing the GM from the perspective of COVID-19 and exploring its modulation through probiotics, diet, and fecal transplants will provide insights into the interaction between the GM and SARS-CoV-2.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

MRC, MAM, MRA, MF, MFH, MNM developed the concept, involved in literature study and wrote the draft manuscript. MRA, MAI, ASS, MFH, MAH, MH and MMI revised the manuscript and assisted with literature search. MNM, MFH supervised the work and approved the manuscript for submission. All the authors carefully read the manuscript.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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