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REVIEW

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Effects of COVID-19 on vital organs in patients infected with SARS-CoV-2

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Abstract: The world is now facing one of the most devastating public health concern where the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is spreading all over the world initiating from Wuhan, China, started from December, 2019. The World Health Organization (WHO) already announced the situation as pandemic all over the world. According to the webpage of WHO, this SARS-CoV-2 has been spreading all over the world (223 countries, areas or territories) with 126,890,643 confirmed cases of coronavirus disease 2019 (COVID-19) and 2,778,619 confirmed deaths (as of March 30, 2021). Accumulated published documents indicate that the SARS-CoV-2 virus primarily affects the lungs causing hypoxia, which is the leading cause of death. There are many reports describing that with the progress of this disease, many other organs (such as heart, kidney, liver, brain) of the affected person start to malfunction. Though SARS-CoV-2 uses the cell surface receptor angiotensin-converting enzyme 2 (ACE-2) expressed by lungs, cardiovascular system, and kidneys but it is still not clear except for lungs that all these other organs are directly affected by this virus or not. Therefore, the aim of this review is to gather informations about affected/damaged organs or tissues and consequences of this damage in COVID-19 patients.

***Keywords*:** SARS-CoV-2, COVID-19, ACE-2, multi-organ failure, ARDS

Introduction

Coronaviruses are a family of related viruses that cause diseases, ranging from mild to lethal, in mammals and birds. In humans such types of coronavirus cause deadly pneumonia with other life threating diseases. The first coronavirus was reported in 1931 but the first human coronavirus (HCoV-229E) was isolated from humans in 1965 (*1*). However, five coronaviruses have been reported at different times during this century: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 (*2,3*), human coronavirus (HCoV-NL63) in 2003 (*4*), coronavirus HKU1 (CoV-HKU1) in 2004 (*5*), Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012 (*6*) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019 (*7,8*). Among them SARS-CoV-2 (also called the 2019 novel coronavirus, 2019-nCoV) is the coronavirus strain that causes the deadly respiratory illness, severe pneumonia, along with other severe health problems and is known as coronavirus disease 2019 (COVID-19).

Since December 2019 starting from Wuhan, China, this SARS-CoV-2 has been spreading all over the world (223 countries, areas or territories) with 126,890,643 confirmed cases and 2,778,619 confirmed deaths (as of March 30, 2021) (*9*). This situation in the current World is declared as the most serious crisis situation since World War 2 by World Health Organization (WHO). Though currently some vaccines are approved by WHO and these vaccines are used in different countries all over the world, in many countries where vaccines are inadequate, treatment of COVID-19 largely depends on the usual treatment of pneumonia and the experience of the clinicians (*10*).

Therefore, the aim of this current review is to gather information about the complications of patients infected with this novel virus, SARS-CoV-2.

Clinical features

Persons infected with SARS-CoV-2 showed similar symptoms of normal flu. But the most important clinical feature is the occurrence of severe pneumonia. Within February 2020, three major case studies reported pneumonia as a major clinical feature of patients infected with SARS-CoV-2 in Wuhan, China (*7,11,12*). One study about the clinical manifestations of COVID-19 patients infected with SARS-CoV-2 had been reported. The study reported about 278 COVID-19 patients where all of them were suffering from severe pneumonia. All the patients were older than 18 years and about 61.9% (n = 172) were males.

Fever was the most common symptom (92.8%; *n* = 258), followed by cough (69.8%; *n* = 194), dyspnoea (34.5%; *n* = 96), myalgia (27.7%; *n* = 77), headache (7.2%; *n* = 20) and diarrhoea (6.1%; *n* = 17) (*13*). However, symptoms of COVID-19 can vary from mild features to a critical state. In addition to those that were mentioned earlier, the patients may show muscle aches, confusion, headache, sore throat, rhinorrhoea, chest pain, sputum production, nausea and vomiting and many others (*7,11,12*). Following such types of symptoms acute respiratory distress syndrome (ARDS) and multiple-organ failure occurred rapidly, resulting in death within a short period of time (*14*). Patients with underlying conditions like hypertension, cancer, kidney disease, diabetes and many other comorbidities are more prone to severe respiratory conditions and death than normal patients (*11,12,14*). However, as the virus is spreading all over the world, newer symptoms might occur depending on the changed nature of this virus, physiological status of patients as well as the region of the world.

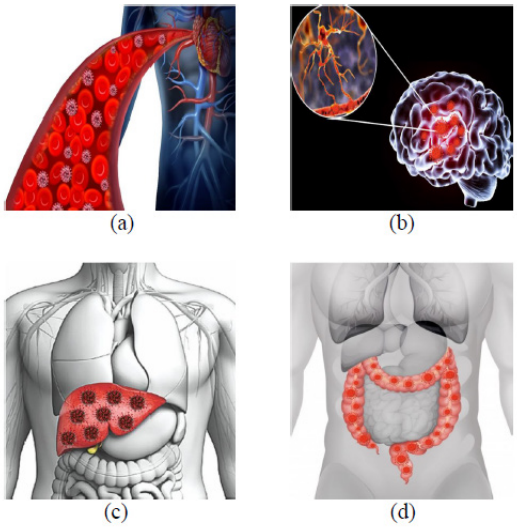

Figure 1. Distribution of SARS-CoV-2 in the COVID-19 patients. In COVID-19 patients, the SARS-CoV-2 is mainly found in the lungs. Beside lungs, so far reported, this virus is found in the cardiovascular system **(a)**, in the brain **(b)**, in the liver but at low levels **(c)** and in the gastrointestinal system **(d)**.

The reason behind the occurrence of severe pneumonia (inflammation of the air sacs of lungs) in the SARS-CoV-2 infected persons is that the virus uses the surface protein called angiotensin-converting enzyme 2 (ACE-2) (*15*) and cells of the lungs express ACE-2 surface receptors (*16*). This ACE-2 cell surface receptor is also expressed by some other cell types such as cells of the gastrointestinal system (*17*), arterial and venous endothelial cells, smooth muscle cells (*16*), cells of heart, kidney and testes (*18*). Structural studies showed that the SARS-CoV-2 binds 10 to 20 times more strongly with the human ACE-2 than the SARS-CoV predecessor (*19*). This might be the reason why this new SARS-CoV-2 is more infectious or contagious than its 2002 predecessor, SARS-CoV. Since a variety of tissues express ACE-2 in their cells, these tissues or organs might be affected first and due to the malfunctions of one organ others are affected and as a result the person dies (Figure 1). In the following section, we will try to summarize information found in different articles affecting various vital organs of COVID-19 patients (Table 1).

Lungs

As the name suggests, SARS-CoV-2, this virus primarily/mainly affects the respiratory system with severe infection in the lungs. There are a large number of reports of severe pneumonia in COVID-19 patients (*7,8,20,21*). Although much is known about the rate of mortality in COVID-19 patients, less is known about the pathophysiology of this virus. However, accumulating evidences suggest a general mechanism causing pneumonia (*22*) (Figure 2). According to this article the mechanism starts with binding of virus to epithelial cells in the nasal cavity and starts replicating. This virus uses the cell surface receptor ACE-2 to bind to the cell (*23*). In the next few days, the virus starts to migrate down the respiratory tract. During this time the body responds by activating the innate immune response by producing interferons. One of the interferons that is produced during early phase of infection of SARS is interferon-inducible protein-10, CXCL-10. For this reason CXCL-10 has been reported

Table 1. Summary of the effects of organs/tissues with their corresponding symptoms in the COVID-19 patients all over the Globe

Name of the organ/tissue	Expression of ACE-2	Symptoms of COVID-19 patients	*Ref.*
Lungs (alveolus)	yes, high	ARDS, pneumonia	(*7,8,16,20,21*)
Gastrointestinal system (intestine)	yes, high	diarrhea	(*17,20,34*)
Blood vessels (endothelial cells)	yes, high	blood coagulation	(*16,40,41,42*)
Heart (myocardium)	yes, high	arrhythmia, myocardial damage	(*7,18,44,45*)
Kidney (nephron)	yes, high	chronic kidney disease	(*18,48,49*)
Liver (hepatocytes)	no (yes* low)	liver injury, abnormal functions	(*51,52*)
Brain (neuron, glia)	no (yes**)	anosmia, ageusia	(*62-64*)

Footnote: * non-conclusive; ** highly non-conclusive.

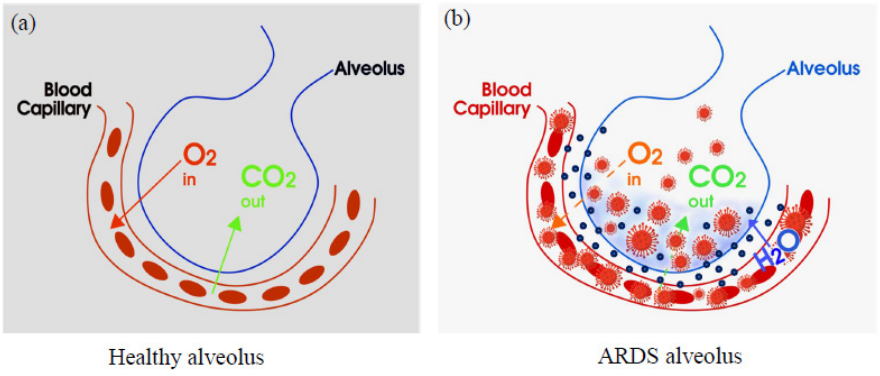

Figure 2. Probable mechanism of the formation of ARDS in COVID-19 patients. (a) The alveolus of a healthy person shows frequent exchange of gases between O_2 and CO_2 (O_2 goes into the blood for use by different types of cells and CO_2 goes into alveolus to be expelled out from the body). **(b)** The alveolus of COVID-19 patient shows due to infection by SARS-CoV-2, the infected alveolus secreted various cytokines and chemokines (shown as blue dots) causing damage of pulmonary microvascular and alveolar epithelial cell barriers. As a result H_2O enters into the alveolus from blood capillaries causing pulmonary edema or ARDS. Therefore exchange of gases is hampered causing breathing difficulties.

as a disease marker for SARS patients (*24*). Within the next few days, the virus reaches the basic structure of the lungs, the alveolus. With the help of this basic structure, the lungs perform its main function, which is the exchange of gases (O_2 and CO_2). Probably, like SARS-CoV, SARS-CoV-2 infects type-II alveolar cells (*25*). Influenza virus also infects the same alveolar cells of the lungs (*26*). Type-II alveolar cells constitute 60% of lung alveolar cells and produce phospholipid rich materials known as surfactant, which reduces the surface tension between the two wet surfaces of the alveolus (*27*). As a result the alveolus fails to reinflate causing ARDS with the body's excessive defense mechanism. One of the major causes of ARDS and multiple-organ failure is the cytokine storm (*28*).

The cytokine storm contains a large number of different types of soluble mediators like pro-inflammatory cytokines (IL-1β, IL-6, IL-8, granulocyte-macrophage colony stimulating factor and ROS) and chemokines (CCL2, CCL3, CCL5, IFNγ-induced protein 10) that all contribute to the occurrence of ARDS (*29,30*). Viral replication into the cell causes these pro-inflammatory cytokines or chemokines to release and as a response to this there is induction of apoptosis in lung epithelial and endothelial cells involving mechanisms like Fas-Fas ligand (FasL) or TRAIL-death receptor 5 (DR5) (*31,32*). Death of lung epithelial cells and endothelial cells causes damage to pulmonary microvascular and alveolar epithelial cell barriers leading to formation of alveolar edema ultimately causing hypoxia in the body. Therefore, probably, the cytokine storm is the cause of ARDS in COVID-19 patients infected with SARS-CoV-2.

Gastrointestinal system

Initially diarrhea or gastrointestinal problems was considered as a minor symptom of this virus compared with pneumonia or problems with respiratory systems but with the increasing number of infection cases the incidence of diarrhea is also increasing (*33*). Now, diarrhea is one of the frequent symptoms in COVID-19 infection as it was detected in up to 30% of patients with MERS-CoV and 10.6% of patients with SARS-CoV-2 (*20,34*). In addition to use the receptor protein ACE-2 expressed on the cell surface, SARS-CoV also uses cellular serine proteases (TMPRSS2) to get entry inside the cell. The entry process into the cell involves priming by TMPRSS2, which allows spike protein cleavage and regulation of the entire mechanism (*23*). But the major role of entry is by the surface protein ACE-2, which first mediates the attachment of the virus with the host cell membrane and then TMPRSS2 favors the fusion of the two (one is the virus and other one is the host cell) cell membranes (*23*). Therefore, the virus entry into the host cell or infectivity mainly depends on binding with the ACE-2 surface receptor (*35*) and the ACE-2 surface receptor is also greatly expressed by gastrointestinal epithelial cells (*17,36*). Analyses of COVID-19 patients also confirmed the presence of SARS-CoV-2 RNA in anal or rectal swabs (*37,38*) as well as in stool specimens (*39*). Even after clearance of the virus in the upper respiratory system, SARS-CoV-2 RNA is still found in anal or rectal swabs (*37,38*). All of this evidence indicates that diarrhea or gastrointestinal abnormalities should be considered as a major symptom of SARS-CoV-2 infections and absence of SARS-CoV-2 RNA in anal or rectal swabs or in stool specimens should be taken into account before declaring an infected person to be a healthy person.

Blood endothelial cells

ACE-2 surface receptors are expressed in the endothelial cells of blood vessels (*16*). Therefore, the consequences of infected endothelial cells of blood

vessels have not yet been addressed. However, there is evidence that some COVID-19 patients have prominent changes in blood coagulation (*40*). For example, the values of D-dimer, fibrin/fibrinogen degradation products (FDP), and fibrinogen (FIB) in all SARS-CoV-2 cases are substantially higher than those in healthy controls and values of D-dimer and FDP are higher in severe COVID-19 patients than milder patients. And the prothrombin time activity (PT-act) is lower in SARS-CoV-2 patients (*40*). In another article, it was also reported that in the late stages of pneumonia caused by SARS-CoV-2, fibrin-related markers (*e.g.* D-dimer) are markedly elevated suggesting coagulation activation and start of secondary hyperfibrinolysis, which may be induced following severe COVID-19 infection (*41*). When some (n = 99) severe COVID-19 patients, who had markedly elevated D-dimer, received heparin as anticoagulant therapy for 7 days or longer they had better prognosis of the disease with a decreased rate of mortality of about 20% (*42*). Therefore, changes in blood coagulation is a prominent feature of severe infection with SARS-CoV-2 and it was suggested that monitoring D-dimer and FDP values may be helpful for early identification of severe cases (*40*).

Heart and cardiovascular system

Since myocardium or cardiac muscle cells express ACE-2 surface receptor (*18*), SARS-CoV-2 might attack the heart as well though there is no report about the presence of virus in the heart (*43*). In a case study of 138 COVID-19 patients admitted into the hospital, 16.7% developed arrhythmia and 7.2% presented acute cardiac injury (*12*). In another report, acute cardiac injury was reported in 5 among the first 41 humans infected with SARS-CoV-2 in Wuhan, China, with an increased level of high-sensitivity cardiac troponin I, cTnI (*7*). Another acute cardiac injury marker brain-type natriuretic peptide (BNP) was also found to be elevated among patients admitted into a hospital ICU in Washington (*44*). There is a report of 150 COVID-19 patients from Wuhan, China, where 68 (45%) died. Among the 68 patients, 29 (40%) patients died exclusively due to myocardial damage or in combination with myocardial damage and circulatory failure (*45*). COVID-19 patients with these comorbidities are more likely to die than regular patients. According to the New York State Health Department, among these comorbidities hypertension is number one in terms of patient's severity. Because hypertensive patients have to use ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and usage of these drugs can increase ACE-2 expression. Since ACE-2 surface receptors are used by SARS-CoV-2, usage of these anti-hypertensive drugs can be life threatening for a person who has both hypertension and COVID-19 (*46*). However, Tignanelli *et al.* claimed that no evidence is available to support routine discontinuation of ACEIs or ARBs in COVID-19 patients since the role of renin-angiotensin system (RAS) inhibition in COVID-19 is controversial (*47*). Therefore, they suggest an urgent investigation in multicenter trials to test this hypothesis in patients with COVID-19 before the medical community makes recommendations for patients to withhold potentially life-saving drugs (*47*).

All of these data indicate that myocardium of infected persons is somehow involved in the mortality rate of COVID-19 patients. Though the mechanisms of such acute cardiac injury in COVID-19 patients are not well understood, however, Akhmerov and Marban proposed one mechanism which likely involves increased cardiac stress due to respiratory failure and hypoxemia, direct myocardial infection by SARS-CoV-2, indirect injury from the systemic inflammatory response, or a combination of all three factors (*43*).

Kidneys

Though kidneys express ACE-2, there are no reports yet about the presence of SARS-CoV-2 into the kidney like heart. Chronic kidney disease (CKD) is a frequently encountered disease in the general population of a country. During the first two months of the current outbreak in China, CKD was re-ported in 4.3% of the Chinese patients infected with COVID-19 who had severe presentation (*48,49*). End-stage kidney disease patients are a highly susceptible group with an infection rate of 16%, which exceeds that observed in other populations (*49*). Persons infected with SARS-CoV-2 with this co-morbidity are at high risk of mortality. And various kidney diseases are a vital candidate of this comorbidity. One article concludes that the prevalence of kidney disease on admission and the development of acute kidney disease (AKI) during hospitalization in patients with COVID-19 is high and is associated with in-hospital mortality (*50*). Hence, clinicians should increase their awareness of kidney disease in patients with severe COVID-19 (*50*).

Liver

There are few reports concerning liver dysfunction in COVID-19 patients. Though there are no reports yet that hepatocytes express ACE-2 surface receptors, although one article reported that bile duct epithelial cells may express ACE-2 receptors more than hepatocytes (*51*). In a study of 417 COVID-19 patients, 318 (76.3%) had abnormal liver test results and 90 (21.5%) had liver injury during hospitalization. These abnormal liver tests became more pronounced in the next 2 weeks where all the essential liver enzymes (ALT, AST, total bilirubin and γ-GT) were elevated to more than 3 times of the upper limits indicating abnormal liver tests had higher risks of progressing to severe

disease in SARS-CoV-2 infection (*52*). In another study of 99 COVID-19 patients in China, 43% of patients had differing degrees of liver function abnormalities with ALT and AST with an upper range of ALT 7,590 U/L and AST 1,445 U/L (*55*). An opposing state of arguments was also reported concerning liver damage in COVID-19 patients. According to the report the derangement of liver function is mild and when liver function tests for patients with different durations of symptoms are examined, there is no evidence that later presentation is associated with greater liver function derangement (*53*).

Therefore, whether SARS-CoV-2 has direct adverse effects on liver function is currently not known due to unavailable data on the expression of viral receptor ACE-2 in hepatocytes. But according to Guan *et al.* hepatocytes do express ACE-2 receptors but at very low concentrations. They also proposed a mechanism of how hepatocytes are infected by SARS-CoV-2. They reported that upon SARS-CoV-2 infection, the upregulation of ACE-2 in liver tissue is caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells, which express ACE-2 at higher levels than hepatocytes and this might play a role in liver damage in COVID-19 patients (*51*).

Brain

Though the invasions of molecules or particles are strictly regulated into the brain by the blood-brain barrier (BBB), many viruses (from human immunodeficiency virus type 1 to togaviruses) can escape the BBB by different mechanisms and enter into the brain (*54*). The neuroinvasive nature of coronaviruses has been documented for different members of the betacoronaviruses such as SARS-CoV (*55*), MERS-CoV (*56*), HCoV-229E (*57*), HCoV-OC43 (*58*), and mouse hepatitis virus (MHV) (*59*). Since coronaviruses use the cell surface receptor protein ACE-2, now the question arises do cells of the brain express the ACE-2 receptor? Well, the answer is not known clearly yet but mice transgenic (Tg) for the expression of human ACE-2 (hACE-2), called K18-*hACE2* mice, were shown to be extremely susceptible to SARS-CoV with infection of the lungs and brain in all the experimental mice which were infected with intranasal inoculation (*60*). Later it was reported that SARS-CoV causes neural death in the brain of K18-*hACE2* mice even in the absence of encephalitis (*61*). There is another report shown to have SARS-CoV RNA polymerase gene in neurons of an infected person (*62*) indicating neurons might have the viral receptor ACE-2 but more studies are required to make sure of the existence of SARS-CoV in neurons.

Several other recent reports described COVID-19 patients experienced anosmia and ageusia, which might be due to an invasion of this virus into the brain causing olfactory and gustatory dysfunction (*63-65*). In one study of 417 mild to moderate COVID-19 patients with general symptoms like cough, myalgia and loss of appetite, about 85.6% and 88% of patients suffered from olfactory and gustatory dysfunctions, respectively (*63*). In another study of 72 COVID-19 patients in Italy, 60 cases had a variable degree of hyposmia with 2 cases of anosmia and 33 cases of hypogeusia and 1 case of ageusia (*66*) suggesting anosmia and ageusia as initial or unique symptoms after SARS-COV-2 virus infection (*64,65*). Since neither the olfactory neurons nor the other brain cells express the surface receptor ACE-2 for viral entry, further research is urgently needed to solve this issue of how the olfactory or gustatory related neurons are affected due to SARS-COV-2 virus infection.

There is an alternative way of SARS-CoV-2 invasion into the brain of COVID-19 patients described by Kabbani and Olds (*67*). According to them, if brain is susceptible to SARS-CoV-2 infection then persons will be at high risk if they have a habit of smoking. Functional interactions between nicotine exposure and ACE2 expression in lungs and other organ systems such as heart and kidneys, as well as nicotine and other components of the renin-angiotensin system (RAS) suggest that smoking can promote COVID-19 cellular entry through nicotinic acetylcholine receptor (nAChR) signaling. Kabbani and Olds suggest that regions, which are known to express various types of nAChRs, are putative sites for primary infection with COVID-19 in the human brain. Interactions between nAChRs and ACE2 have been studied in several of these regions including the ventrolateral medulla and smoking may lead to enhanced viral infection through the ability of nicotine to upregulate nAChRs in regions such as the lungs. In this case, upregulation of nAChRs in either/both neurons and astrocytes could promote greater viral entry and replication through augmented ACE2 expression in the cell (*67*). Supporting the notion that smokers are at high risk for SARS-CoV infection, there is another report which demonstrated that ACE-2 expression are increased in the small airway epithelia of smokers (*68*). Dealing with all of these, SARS-CoV might infect brain tissue and smokers are at high risk.

Conclusion

In conclusion, we may say COVID-19 patients might die due to lack of oxygen as lungs are suffering from ARDS. But as the infection progresses within the body, various other organs are being affected. But it is not yet known, whether other organs are affected due to the direct attack of this virus or as a consequence of lack of oxygen since lungs are not working properly or any other unknown underlying reasons. More extensive research is required to further rule out these possibilities.

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