MINI-REVIEW

Biochemical parameters and pathogenesis of SARS-CoV-2 infection in vital organs: COVID-19 outbreak in Iran

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Abstract

Since its emergence, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, and led to ever-increasing mortality. SARS-CoV-2 infection perturbs the function of the body's vital organs, making patients of all ages susceptible to the disease. Nevertheless, individuals developing critical illness with poor outcomes were mostly the elderly and people with co-morbid conditions, who constituted the vast majority of coronavirus disease 2019 (COVID-19) fatalities. Complications of COVID-19 mostly involve the respiratory, renal and cardiovascular systems, and in severe cases secondary infections leading to pneumonia and acute respiratory distress syndrome, which may precede the death of the patient. Multi-organ failure in individuals with COVID-19 could be a consequence of their co-morbidities. A patient's pre-existing conditions may affect the disease prognosis, requiring immediate attention to accurately detect and evaluate them in SARS-CoV-2-infected individuals. This review addresses several issues in relation to manifestations of the body's vital organs along with potential diagnostic blood factors in SARS-CoV-2 infection. It is hoped that the review will lead to more comprehensive understanding of this complex disease.

Keywords: Acute respiratory distress syndrome, angiotensin-converting enzyme 2, coronavirus, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2
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Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) outbreak, has disseminated throughout the world from Wuhan, China. The pandemic has become the greatest global public health crisis since the 1918 influenza outbreak [1]. Currently, the number of individuals with COVID-19 is still soaring worldwide. As of November 3, 2020, according to the WHO, confirmed COVID-19 patients exceeded 46 millions with over 1.2 million deaths worldwide [2,3]. In Iran, the first case of COVID-19 was reported on 19 February 2020 and although in early March the SARS-CoV-2 outbreak appeared to dwindle in China [4], the outbreak in Iran increased. This was largely caused by a relaxing of bans by people who were preparing for the annual Nowruz ceremony and an underestimation of the seriousness of COVID-19, according to local sources. At the time of preparing this manuscript, the number of confirmed SARS-CoV-2-infected individuals in Iran had reached 284 034, of whom 15 074 had died, based on WHO sources. In Asia and globally, Iran has the second and tenth rankings, respectively, in terms of

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COVID-19 mortality rate, according to its official statistics reported to WHO. In addition, Iran has the eighth highest number of SARS-CoV-2 cases in the world [5]. Total number of confirmed COVID-19 patients in Iran and worldwide along with their outcomes are compared and presented in Fig.1.

Upon exposure to SARS-CoV-2, symptoms develop within 2–14 days; patients initially manifest symptoms including fever, dry cough, fatigue and shortness of breath as well as some less frequent symptoms, such as diarrhoea and vomiting. Although most people with COVID-19 exhibit mild to moderate symptoms, the disease can lead to severe complications. The clinical phenotype can be worse in older adults and people with pre-existing chronic medical conditions, such as cardiovascular disease, diabetes and cancer; it has also been described in children [6,7]. Critically ill patients can die as the result of acute respiratory distress syndrome (ARDS) together with pneumonia in lungs and multi-organ failure [3,8]. According to proteome-wide data analysis, SARS-CoV-2 could impact several targets in diverse host tissues, making the treatment of COVID-19 patients a complex task [9]. Molecular pathogenesis shows that angiotensin-converting enzyme 2 (ACE2) acts as the receptor where the spike (S) proteins of both SARS-CoV and SARS-CoV-2 bind and so obtain entry to the host cell. New evidence unveiled another prerequisite for entry and infection of ACE2-expressing cells, namely, SARS-CoV-2 not only needs ACE2, but also requires cleaving of its S protein by host cell transmembrane protease serine 2 (TMPRSS2) [10]. ACE2-positive cells are not ubiquitous, but have been found in certain organs and tissues vulnerable to SARS-CoV-2 infection including oesophagus, type II alveolar cells (AT2) of the lung, myocardial cells, kidney, liver, brain and intestines [11,12]. Here we describe the pathophysiology and symptoms of SARS-CoV-2 infection in the pulmonary system and other vital organs, in addition to signs and blood factors employed for detecting inflammation or organ dysfunction.

SARS-CoV-2 cell entry and infectivity

The initial step of virion entry to the host cell is facilitated by interactions between the S protein and its receptor. Different coronaviruses take advantage of different host receptors through different receptor binding domains. As such, ACE2 and dipeptidyl peptidase 4, also known as CD26, serve as the main receptors of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively. These specific interactions between S protein and its receptor are responsible for host-specific infection and also tissue tropism [13,14]. Accumulating evidence suggests that SARS-CoV-2 also uses ACE2 and no other coronavirus receptors. It is noteworthy that SARS-CoV exploits an alternative receptor, CD209L, expressed on type II alveolar cells and lung endothelial cells for cell entry; similarly, CD209L is the portal for cell entry and infecting by other enveloped viruses, like Ebola virus [15]. Importantly, computational methods have illustrated stronger affinity of the SARS-CoV-2 S protein receptor binding domains to ACE2 compared with that of SARS-CoV, nearly 10- to 20-fold, suggesting higher pathogenicity and easier human-to-human spread of SARS-CoV-2 [16]. Upon binding to ACE2, the S protein, consisting of S1 and S2 domains, undergoes acid-dependent proteolytic cleavage by TMPRSS2, followed by viral and cellular membrane fusion. For fusion, the S1-containing receptor binding domain is cleaved and S2, which is a fusion peptide, inserts into the membrane followed by joining of two heptad repeats in S2, which together form an antiparallel six-helix bundle. The bundle formation paves the way for the

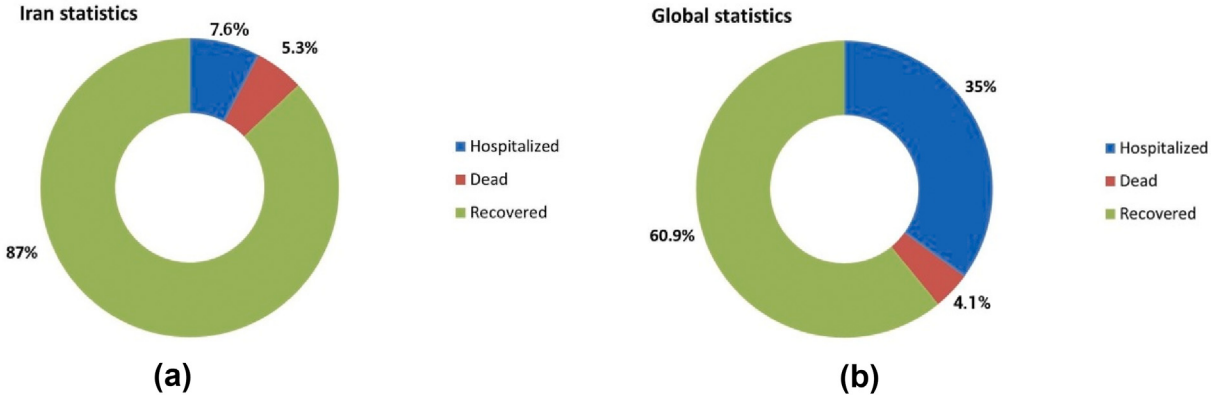

FIG. 1. Comparative statistics between Iran and the globe according to WHO reports (A) Iran's COVID-19 statistics, since the beginning until 2020/24/7, indicate the total number of confirmed SARS-CoV-2 infected patients and their outcomes in percentages. (B) At the same time span, world's total COVID-19 statistics and outcomes are also shown in percentages. **WHO:** World health organization; **COVID-19:** Coronavirus disease 2019.

fusion of viral and cellular membranes and eventual release of the viral genome into the cytoplasm [17].

Widespread distribution of ACE2 in human tissues

The earliest step of SARS-CoV-2 infection is its entrance into cells through ACE2, which has an uneven distribution on different tissue cell types. Single-cell RNA-sequencing technology has found those cells and tissues that express ACE2, to help pinpoint viral tropism and its likely routes of transmission [11]. Interestingly, different immune cells in the lung, such as neutrophils, monocytes, and B and T cells, express high levels of ACE2, as do alveolar type I and type II cells. In the digestive system, oesophagus, stomach, ileum and colon also possess ACE2-positive cells. The proximal tubule cells of kidney, hepatocytes of liver and various cells in the spleen demonstrate ACE2 expression. Eyes, as sensory organs and part of the nervous system with different cell types, plus bone marrow and blood cells including platelets, macrophages, erythrocytes, dendritic cells and natural killer cells were all ACE2 positive. Macrophages, as omnipresent cells in almost all organs and tissues, have constant cross-talk with ACE2-positive cells, suggesting their central role both at the start of and during SARS-CoV-2 infections [12].

Clinical manifestations

Upon infection, COVID-19 has an incubation period ranging from 2 to 14 days, with a median time of 4–5 days from exposure to onset of symptoms. Early reports suggest that the majority of patients with COVID-19 present fever (82%–99%), cough (59%–81%), fatigue (44%–70%), anorexia (40%–84%), shortness of breath (31%–40%), sputum production (28%–33%) and myalgia (11%–35%), although symptoms at the onset of disease may vary among individuals. Most COVID-19 patients (81%) show mild symptoms with no pneumonia or mild pneumonia, whereas those with severe symptoms (14%) experienced complications like dyspnoea. Symptoms including headache, confusion, rhinorrhoea, sore throat, haemoptysis, vomiting and diarrhoea were reported as less frequent manifestations [3,8,18]. The case fatality rate (CFR) has varied significantly around the world. Early reports suggested a CFR of 2.3% but later studies reported the symptomatic case fatality risk (the probability of dying after developing symptoms) was lower, at 1.4%, which contrasts with influenza (0.1%), MERS (34%) and SARS (10%) [19,20]. The CFR in COVID-19 rises rapidly with increasing age; the CFR is <1% for those under 50 years of age, rising to 1.3% for 50-year-olds and 3.6% for 60-year-olds. Likewise, the CFR increases with the disease severity, as there were no deaths reported among the mildly symptomatic cases; however, CFR was 49% among critically ill patients [19].

Pathophysiology of organs in COVID-19

Lung

The respiratory tract is composed of upper and lower respiratory systems, which terminate in alveoli, where the critical process of gas exchange occurs. The fine structure of alveoli constitutes a compartment lined with a thin alveolar–capillary barrier. This barrier in turn comprises three parts: an epithelial cell layer having both type I and type II cells, a microvascular endothelial cell layer, and an interstitial airspace between the epithelial and endothelial surfaces. In addition, the alveolar macrophages located within the alveoli have a scavenging function against cell debris and foreign pathogens [21]. Several studies show that when a lung injury occurs, which is common in pulmonary infections, it may stimulate ARDS, wherein loss of the alveolar–capillary barrier arises. Pneumonia caused by viral infections or joint viral and bacterial infections that activate a substantial innate immune response in alveolar cells and macrophages may result in ARDS [22]. Furthermore, patients with COVID-19 pneumonia are at risk of acute pulmonary embolism so CT pulmonary angiography and appropriate therapy are required [23]. In this context, Grillet *et al.* [24] proposed that the use of contrast-enhanced CT rather than routine non-contrast CT may be important for patients with severe clinical features of COVID-19. According to the comparative replication capacity of SARS-CoV-2 and SARS-CoV in the infected lung tissues, within the 48-hour interval, SARS-CoV-2 produced 3.2-fold more infectious virus particles than did SARS-CoV [25]. Growing evidence supports the central role of alveolar macrophages as they secrete chemokines that induce neutrophils and polymorphonuclear cells to migrate from the bloodstream into the airspaces and alveoli. As a result of neutrophil influx and subsequent activation, these cells release toxic mediators such as reactive oxygen species, and pro-inflammatory mediators, such as tumour necrosis factor, interleukin-1β and interleukin-6, proteases and neutrophil extracellular traps, which fight invading pathogens. However, it may give rise to epithelial and endothelial injury; this weakens the alveolar–capillary barrier integrity leading to more neutrophil infiltration and surfactant dysfunction, and thereby the development of protein-rich alveolar oedema that typically causes dyspnoea or difficult breathing (Fig. 2) [26]. COVID-19

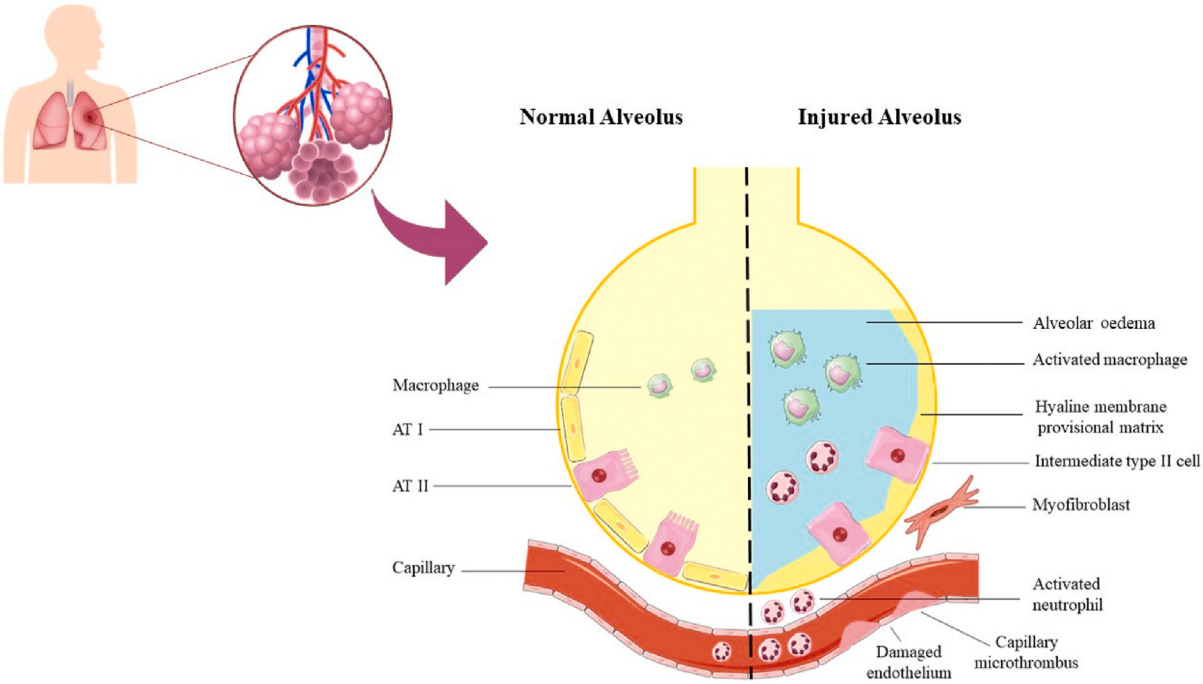

FIG. 2. Schematic of a normal and an injured alveolus. In normal state, the alveoli facilitate gas exchange and provide a medium for dispersal of surfactant and alveolar macrophages, which are necessary for maintaining alveolar stability and host defenses. When injured, e.g. in ARDS, the alveoli loss of epithelial and endothelial barrier integrity and loss of function result in increased permeability and pulmonary edema. Increased fluid accumulation together with the presence of pro-inflammatory mediators and activated macrophages make difficulty breathing. ARDS happen in severe cases of COVID-19 with fatal outcomes, if not managed properly. **ARDS:** Acute respiratory distress syndrome; **COVID-19:** Coronavirus disease 2019. **AT I:** Pulmonary alveolar type I; **AT II:** Pulmonary alveolar type II.

and the earlier beta-coronavirus infections SARS and MERS largely share clinical characteristics. Importantly, the pulmonary system is by far the organ most affected by SARS-CoV-2 infection, and in severe cases the infection may develop into a serious lung injury and ARDS with eventual death [3,8].

Heart

Cardiovascular diseases were common co-morbidities in SARS and MERS. In SARS, the prevalences of cardiovascular disease and diabetes mellitus were 8% and 11%, respectively; and having either one increased the risk of death 12-fold. Hypertension was reported to be common in about 50% of MERS cases, and cardiovascular disease was reported to be present in almost 30% of the patients [27,28]. Similarly, increasing evidence links COVID-19 to higher rates of cardiovascular complications and subsequent mortalities, most notably among those with more severe disease. Wang *et al.* reported, among 138 confirmed cases of COVID-19, that co-morbidities were prevalent, 46% overall and 72% in those requiring admission to an intensive care unit (ICU), as were cardiovascular co-morbidities, namely, hypertension in 31% (58% in those requiring ICU), cardiovascular disease in 15% (25% in patients requiring ICU) and diabetes mellitus in 10% (22% in those requiring ICU) [8]. Another cohort study with 1099 individuals with confirmed COVID-19 documented that 24% overall had any co-morbidity with 58% among those critically ill or deceased, with 15% having hypertension (36% among those critically ill or deceased), 7.4% with diabetes mellitus (27% among those critically ill or deceased), as well as 2.5% with coronary heart disease (9% among those critically ill or deceased) [18]. Importantly, in a meta-analysis involving six studies and covering a total of 1527 people, Li *et al.* found that there was a three-fold increase of cardio-cerebrovascular diseases in ICU/severe COVID-19 cases (relative risk 3.30, 95% CI 2.03–5.36, $p < 0.00001$). The researchers also reported that in comparison to the non-ICU/severe patients, the incidence of acute cardiac injury was approximately 13-fold higher in ICU/severe patients [29]. Myocardial injury, exhibited by elevated cardiac troponin I above the 99th centile upper reference limit, was recognized among early cases of COVID-19 with 7.2% of patients overall, and 22% that required ICU surveillance [8]. In a separate study, higher cTnI was also reported in 46% of non-survivors, in contrast to 1% of survivors [30]. Furthermore, in a meta-analysis conducted on four studies in China comprising 341

individuals (123 with severe disease; 36%), Lippi *et al.* [31] found that the levels of cTnI significantly increased in COVID-19 patients with severe disease compared with those without (95% CI 6.8–44.5 ng/L). The value of creatine kinase isoenzyme MB (CK-MB) as a biomarker of myocardial injury was increased in patients with COVID-19 and was associated with severity of disease [8,32,33]. Yang *et al.* [32] found that CK-MB was significantly higher in the group of patients who died among individuals with COVID-19 compared with the group of patients who survived. Mean CK-MB was significantly higher in individuals with severe COVID-19, compared with those with less severe disease [33]. In addition to cTnI and CK-MB, increased lactate dehydrogenase (LDH) has been presented as a common laboratory abnormality in COVID-19 patients [34]. The haematological findings by Fan *et al.* showed that individuals requiring ICU care had a higher LDH: LDH levels for four ICU patients were raised with a median value of 1684 U/L (reference range 270–550 U/L). Only five out of 26 non-ICU patients indicated an increased LDH above 550 U/L. Moreover, values of LDH were observed to decrease as the clinical condition of patients improved [35]. In a systematic review and meta-analysis of all published studies up to 15 March 2020 (45 studies with 4203 patients) by Zhang *et al.* [36], LDH was among factors that predict ICU admission. More importantly, ARDS was predicted by increased LDH. The exact mechanism of cardiac involvement in COVID-19 remains to be elucidated; but, direct myocardial involvement, possibly mediated by ACE2, is a likely explanation. In contrast, however, a case report study by Tavazzi *et al.* described an in-detail observation on possible SARS-CoV-2 pathobiology involving myocardial localization. They detected viral particles in interstitial cytopathic macrophages and their surroundings but not in cardiac myocytes, which rejects viral cardiotropism. The researchers also reported non-specific damage to cardiac myocytes mainly characterized by focal myofibrillar lysis. The study suggests that the cardiac complications are the result of either a transient viraemia or migration of infected alveolar macrophages from the respiratory tract—the latter seems to be common in many other extrapulmonary tissues [37]; similar pathological studies are needed to confirm these observations. Another explanation could be the likelihood of cytokine storm induced by SARS-CoV-2 infection, which possibly results from a hyper-inflammatory innate immune response and subsequent imbalanced immune response among subtypes of T helper cells [30].

Central nervous system

The main target organ in SARS-CoV-2 is widely believed to be the lung; however, patients may display evidence of other organ dysfunction including the nervous system. Several respiratory viral infections, known to be neurotropic and neuroinvasive, such as measles virus and herpes virus, as well as influenza virus and coronaviruses are capable of spreading throughout the body once in the lungs, and eventually infect the central nervous system (CNS) [38]. Many individuals with COVID-19 may have non-specific neurological symptoms like dizziness, nausea, vomiting and headache, even though laboratory findings could not identify clinical symptoms of nervous system involvement. However, based on recent clinical observations, reports of sudden loss of smell (anosmia) and/or taste (ageusia) suggest nervous system involvement in SARS-CoV-2 infection [39]. Human and animal studies report that the coronavirus enters the CNS through the olfactory bulb, wherein it causes inflammation and demyelination, which is most probably behind the temporary loss of smell and/or taste in SARS-CoV-2 infection [40]. Moreover, severe hypoxia often occurs in patients with COVID-19, which may lead to subsequent nervous system damage [41]. It is noteworthy that the neuroinvasive tendency of coronaviruses was described in post-mortem studies of 18 SARS patients who had died days after infection. In addition to lungs and various immune cells, SARS-CoV viral particles and genomic sequences were found in neurons in the brain. Although neurological manifestations of COVID-19 have not been studied fully in humans, it is likely that some of these patients, particularly those with severe illness, have CNS involvement and neurological manifestations [42]. According to genome sequencing, the presence of SARS-CoV-2 in cerebrospinal fluid has been confirmed, which may be an indication of viral encephalitis [41]. Emerging evidence concerning the CNS suggests that clinicians dealing with COVID-19 patients should consider olfactory and other sensory changes, or any other suspected neurological symptoms, because they may help detect and isolate infected individuals in the early stages of disease without conducting specimen-based procedures.

Gastrointestinal tract

Despite being infrequent in COVID-19, gastrointestinal tract symptoms, predominantly diarrhoea, should not be ignored as in confirmed COVID-19 cases its incidence would be underestimated. Similarly, early reports may have unknowingly missed diarrhoea in these patients because of prioritizing respiratory symptoms, such as ARDS, as the main sign in COVID-19 [14]. Importantly, several studies identified SARS-CoV-2 RNA in anal/rectal swabs [43,44] and stool specimens from individuals with COVID-19 using RT-PCR [45,46]. Nonetheless, regardless of diarrhoea, SARS-CoV-2 RNA may not be detected in all COVID-19 patients [47]. In a study on 1099 individuals with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces of China, nausea or vomiting was found in 5.0% and diarrhoea in 3.8% of patients [18]. Gastrointestinal complications were reported to be more frequent in other studies.

According to a cohort study of 140 hospitalized COVID-19 patients in Wuhan, gastrointestinal symptoms (39.6%) were among the most common clinical manifestations, including nausea in 17.3%, diarrhoea in 12.9% and vomiting in 5.0% [48]. Moreover, in a cohort of 171 paediatric patients with COVID-19, the frequencies of diarrhoea and vomiting were found to be 8.8% and 6.4%, respectively [49]. With ACE2-positive cells in the stomach, intestine and colon tissues, the digestive system could be susceptible to COVID-19 complications and also could act as a route of SARS-CoV-2 entry. Intriguingly, small intestine cells have paralleled expression of dipeptidyl peptidase-4 (a cell surface enzyme that acts as a MERS-CoV receptor) and ACE2, making them highly susceptible to betacoronavirus infections. Overall, the presence of SARS-CoV-2 RNA in stool samples from individuals with COVID-19 suggests potential faecal–oral transmission as an alternative infection route, so it would seem wise to take measures to minimize the spread [50]. Gastrointestinal symptoms of COVID-19 can also be important for clinicians, notably because they may manifest before the onset of pyrexia and respiratory symptoms [51].

Liver

Individuals with severe COVID-19 seem to have a higher incidence of liver impairment. Most COVID-19-associated liver injuries are mild and transient, but severe liver damage can be seen [18,51]. It seems that liver damage is related to gender and age so that the proportion of infected patients is higher in adults than in children and in men than in women [52]. The incidence of liver injury can reach up to 58% or even 78% in fatal cases. The ACE2 expression in bile duct cells is much higher compared with liver cells. Bile cells are involved in liver regeneration and the immune response, so liver injury in individuals with COVID-19 may be caused by damage to bile duct cells, but not liver cells [53]. Although the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) indicating abnormal liver function are not generally high on admission, a multi-centre study on 1099 individuals documented increased levels of AST and ALT in 22.2% and 21.3% of COVID-19 patients, respectively. Despite the elevated levels of ALT and AST observed in separate studies—ranging from 3.7% to 23.5% for ALT and from 3.7% to 37% for AST—it appears that liver damage is more common in patients with severe pneumonia, which is supposed to be associated with cytokine storm and abnormal innate immune response, but it cannot explain the fact that there is also liver dysfunction in patients with mild symptoms [18]. Unlike other biochemical parameters, albumin levels appear to be reduced in COVID-19, particularly in severe disease [53,54]. Moreover, according to the findings by Wang *et al.* [54], patients who had increased transaminase levels presented higher concentrations of γ-glutamyl transferase. It is worth noting that drug-induced liver injury and pre-existing chronic infections are possible contributing factors for the observed abnormalities in liver blood tests [3,8]. Antivirals, antibiotics and steroids, which are widely used for the treatment of SARS-CoV-2 infection, could potentially play a role in liver injury. It was recently reported that lopinavir/ritonavir may contribute to liver injury in individuals with COVID-19 [53]. Based on a report from 417 individuals with laboratory-confirmed COVID-19 in China [55], the use of lopinavir/ritonavir may increase the odds of liver injury up to four-fold (OR 4.44–5.03).

Kidney

Following lung infection with SARS-CoV-2, the virus may enter the blood circulation and, in turn, could accumulate in the kidneys resulting in renal dysfunction and its complications such as acute kidney injury [20]. In a single-cell RNA-sequencing analysis, Pan *et al.* [56] concluded that the cytopathic effects of SARS-CoV-2 on podocytes and proximal straight tubule cells may lead to acute kidney injury in individuals with COVID-19, particularly in those with SARS-CoV-2 infection in blood samples. Furthermore, according to a meta-analysis by Henry and Lippi, chronic kidney disease appears to be associated with increased risk of severe COVID-19. The authors suggested that the presence of chronic kidney disease should be considered as an important factor in future risk stratification models for COVID-19 [57]. Blood tests for assessing renal function mainly include proteinuria, urea and creatinine. Early reports of kidney dysfunction indicated acute kidney injury incidence ranging from 3% to 9% in those with SARS-CoV-2 infection [8,20]. A recent study also reported that among 710 hospitalized patients with COVID-19, 44% had proteinuria, and 15.5% and 14.1% had elevated serum creatinine and blood urea nitrogen, respectively [58]. Overall, acute kidney injury incidence in recently published data was shown to fluctuate between 2.9% and 23% in severe cases of COVID-19 [8,18]. In a prospective cohort study of 701 individuals with COVID-19, it was reported that increased baseline blood urea nitrogen, increased baseline serum creatinine, proteinuria and haematuria could be independent risk factors for in-hospital death after adjusting for age, sex, disease severity, co-morbidity and leucocyte count [59] Potential mechanisms responsible for kidney injury remain to be elucidated, but sepsis and inflammation leading to cytokine storm complications and/or direct cellular injury by virus are supposed to be the case in renal impairment. Accordingly, based on electron microscope analysis in 26 autopsies of patients with COVID-19 in China, there were clusters of coronavirus-like particles with distinctive spikes in the tubular epithelium and podocytes [60].

Eye

In spite of previous studies indicating ocular signs and symptoms in SARS patients, there are few investigations reporting ocular abnormalities in individuals with COVID-19. In a study by Wu et al. 12 out of 38 patients (31.6%) had ocular symptoms: typically conjunctivitis, inflammation in the eye mucus and epiphora, excessive watering of the eye, without any blurred vision. Most patients who developed ocular signs were among patients with more severe symptoms or with abnormal findings on blood tests. Also, despite being SARS-CoV-2-positive on nasopharyngeal swabs, only 5.2% of the cases were SARS-CoV-2-positive in conjunctival specimens, which is in line with previous studies on SARS [61]. Based on a cross-sectional study, out of 72 COVID-19 patients, only two had conjunctivitis [62]. Other research on a confirmed COVID-19 patient provided evidence consistent with former studies. Viral RNA was detected in a patient's conjunctival sacs for the last few days of infection with lower viral load. Although the SARS-CoV-2 in tear specimens may represent a potential source of viral transmission, commonly with higher viral loads in severe ocular cases, it appears that it is not an early detection source for COVID-19 [63]. Although ACE2 was found in the aqueous humor, its expression in more anterior tissues, such as the conjunctiva or cornea, is not yet known [64].

Conclusion

In addition to pneumonia and damage to the whole immune system, COVID-19 may also result in injury to the vital organs such as heart, liver, kidney and even eye, as well as in the CNS and gastrointestinal tract (Fig. 3). Particular attention should be given to the co-morbidities of patients with COVID-19, particularly in older patients with severe symptoms. Increased attention to these co-morbidities will help to better protect and manage COVID-19 patients and to decrease mortality. Variations in the extent of symptoms and varied incubation times, together with having polymorphic severity, could relate to both the existence of evolving mutant strains of SARS-CoV-2 and also host genetic factors blended with environmental factors. In addition, given the heightened vulnerability of elderly patients with co-morbid conditions and immunosuppressed individuals, studies should invest a focused effort in addressing these challenges. To date, in spite of intensive research, no effective

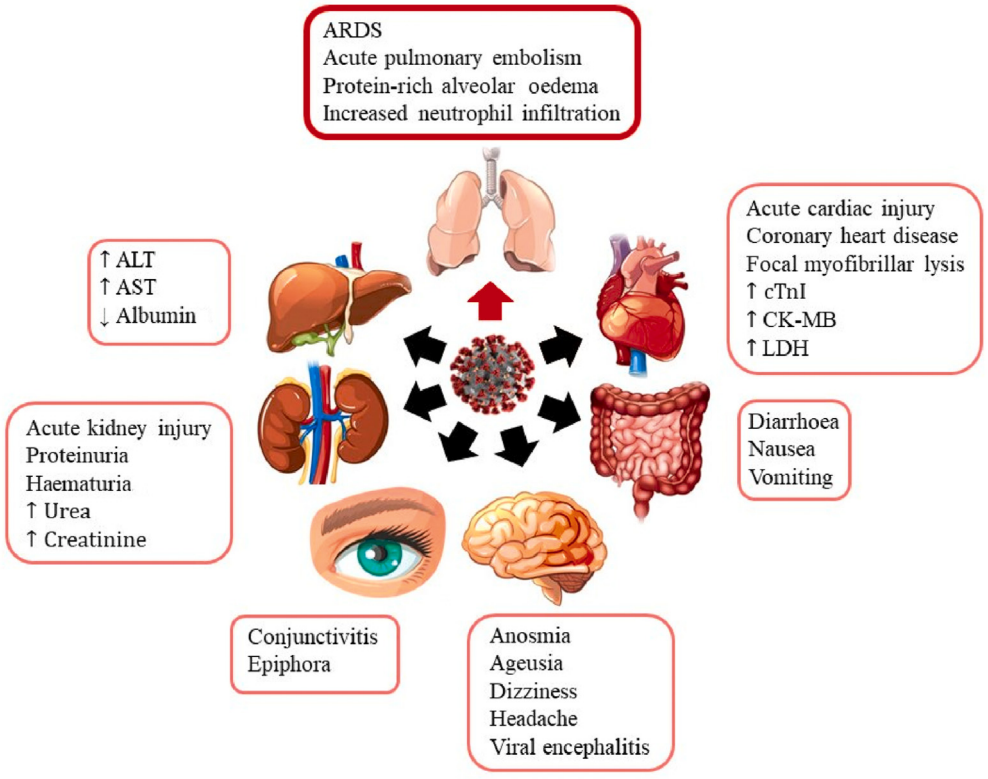

FIG. 3. Vital organs affected by SARS-CoV-2 infection and their complications and symptoms. Blood biochemical parameters which may associate with multiple organ dysfunction and severity of COVID-19 can be used for its diagnosis and prognosis as well as monitoring of treatment effects. **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **ARDS:** Acute respiratory distress syndrome; **cTnI:** Cardiac troponin I; **CK-MB:** Creatine kinase isoenzyme MB; **LDH:** lactate dehydrogenase.

antiviral drug or vaccine for COVID-19 is available; so symptomatic and supportive treatments are crucial.

Conflict of interest

The authors have stated that there are no conflicts of interest related to this article.

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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