



Revealed pathophysiological mechanisms of crosslinking interaction of affected vital organs in COVID-19

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Abstract

SARS-CoV-2 is one of the main serious challenges of human societies, which emerged in December 2019 from China and quickly extends to all parts of the world. The virus was previously believed to only affect the lungs and respiratory system, but subsequent research has revealed that it affects a variety of organs. For this reason, this disease is known as a multiorgan disease. Current article aimed to highlight latest information and updates about molecular studies regarding pathogenesis of SARS-CoV-2 in kidney, liver, and cardiovascular and respiratory systems, as well as the mechanisms of interaction of these organs with each other to cause clinical manifestations in patients.

Keywords SARS-CoV-2 · Multiorgan disease · Pathogenesis

Introduction

Coronaviruses are a family of RNA viruses causing many acute as well as chronic diseases in both humans and in animals. Of the six known human strains of the corona virus, four cause the common cold. However, two groups of these viruses SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) are the known roots for deadly respiratory disorders. Like SARS-CoV, SARS-CoV-2 is the deadliest virus in this family (Pedersen and Ho 2020). This new corona virus strain was initially reported early of December 2019 in Wuhan city of Hubei province in China. Since then, the virus quickly disseminated to all parts of the world and has had devastating effects on the global health system, while social and economic activities of the world have also deteriorates (Nishiga et al. 2020).

The virus is transmitted mainly through respiration, respiratory droplets, aerosols, and mucosal membranes. Certain recent studies showed that RNA of this virus has also been detected in human feces (Mokhtari et al. 2020). Patients with

this disease show different symptoms, but initial symptoms observed in COVID-19 patients include repetitive cycles of fevers, headache, dry cough, and eventually pneumonia. However, with the spread of this disease in different parts of the world, other symptoms of this disease has also been reported (da Rosa Mesquita et al. 2020).

Although, initially, it was thought that major reasons for causalities in COVID-19 patients are primarily because of respiratory disorders and damage to lungs, but advancements in knowledge through extensive recent studies shown that it may affect most of the body organs particularly lungs, liver, heart, and kidneys leading patient's mortality (Zaim et al. 2020). The aim of this article is to present the pathogenesis of SARS-CoV-2 in four vital organs. Lungs, liver, kidneys, and cardiovascular system. Furthermore, the study cross-link these organs with each other to elucidate clinical manifestations in patients affected with Covid-19.

Respiratory system in pathogenesis of COVID-19

The β -coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2) make their penetration into the human body via respiratory tract epithelium (Astuti 2020, Shereen et al. 2020). This functions as a barrier for any foreign particles or pathogens to provide protection against infections and tissue injuries via secreting mucus and mucociliary clearances

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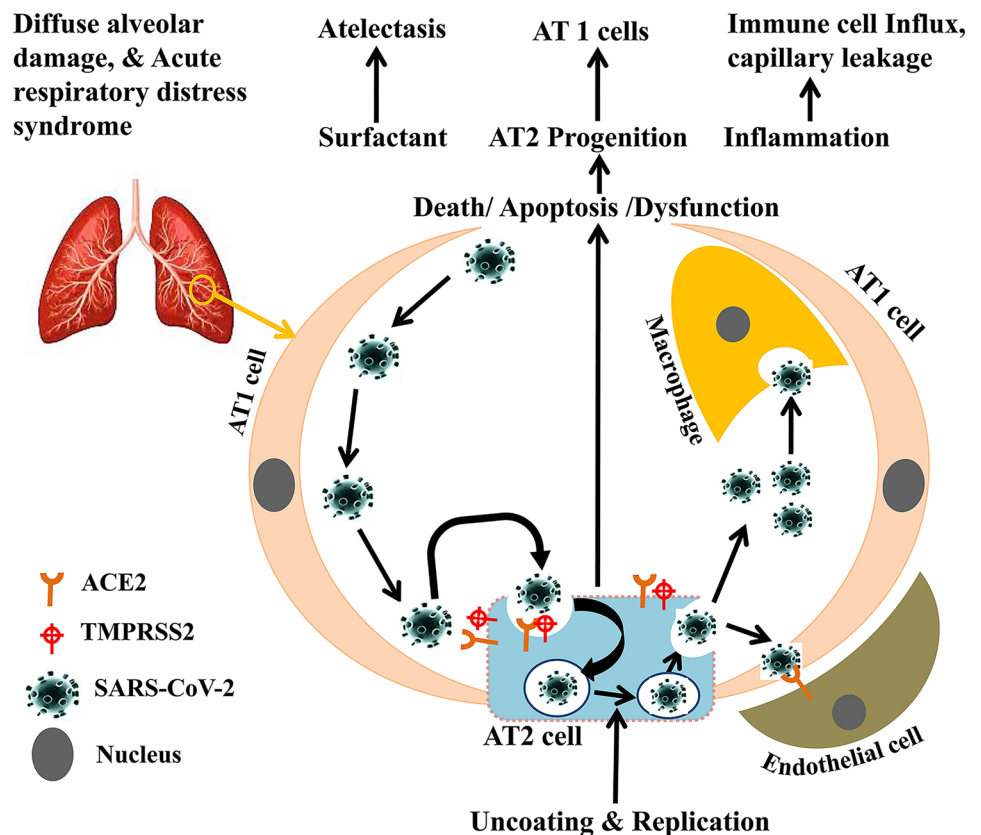
while keeping the original airflow in the lungs (Fig. 1). During inhalation, SARS-CoV-2 particles are supposed to infect various types of epithelial cells. The initial SARS-CoV-2 contact starts inside the nasal mucosal cavity when the viral S (spike) proteins binds with that of the angiotensin-converting enzyme-2 (ACE2) receptors, and later, these S proteins cleaved by transmembrane serine protease 2 (TMPRSS2) and the viral particles start replicating normally within these cells (Hoffmann et al. 2020b; Wan et al. 2020; Sungnak et al. 2020). In vitro studies suggested that the ciliated airway epithelium serves as a primary host for SARS-CoV-2 infection if the airway epithelium cells express sufficient ACE2 that allows virus entry (Reyfman et al. 2019). ACE2 is a type I transmembrane metalloproteinase that promotes conversion of angiotensin 2 into different metabolites that help exert vasodilator effects or either interfere with the renin–angiotensin–aldosterone system. Moreover, manipulating the levels of ACE2 or its activities could alter the chances for the onset of COVID-19.

After successful penetration and replication inside the nasal mucosal cells, SARS-CoV-2 starts traveling towards conducting airways to set off an immune modulatory and inflammatory response that results in apparent clinical signs and symptoms of COVID-19 (Mason 2020). After their entry inside the epithelial cells, pro-inflammatory C-X-C motif chemokine-10 (CXCL-10) is expressed along, while

type I and III interferons expressed and activated as the front line defensive molecules by recognizing SARS-CoV-2 attack (Hancock et al. 2018; Tang et al. 2005; Choi and Shin 2021). Initially, ACE2 expression increased inside small airways of smokers and people with chronic obstructive pulmonary disease (COPD), and may partly explain why individuals with underlying cardiopulmonary disease appear to be more likely to die from severe COVID-19 (Leung et al. 2020; Wu and McGoogan 2020). On the contrary, low expression lack of ACE2 in aged people and the one suffering either from diabetes mellitus or cardiovascular disease together with increased clearance of ACE2 from the cell surface with infection may result in over activity of the ACE-angiotensin 2-angiotensin 1 receptor axis, leading to increased inflammation and thrombosis (Verdecchia et al. 2020).

Although SARS-CoV-2 infection starts at upper airway epithelium, but in certain patients, the virus infects deeply in the alveolar epithelium to impair gaseous exchange and finally respiratory failure occurs (Fig. 1). The SARS-CoV-2 infection initiated by interaction of the viral S protein with ACE2, leading to internalization of the virion into endosomes. Host proteases such as TMPRSS2 or either furin help cleave the S protein giving rise to a fusion protein which facilitate the cytoplasmic entry of the virus (Hoffmann et al. 2020b; Shang et al. 2020). Similar to SARS-CoV,

Fig. 1 Pathobiological consequences of alveolar epithelial injury by SARS-CoV-2 infection



SARS-CoV-2 shows alveolar type I (AT1) and AT2 cells which are equipped with increased ACE2 expression, but the prolific infections perhaps occurs primarily in surfactant-producing AT2 cells (Mossel et al. 2008). Few studies also claimed some alternative cellular-entry route for the SARS-CoV-2 such as Fc-receptor-mediated internalization of antibody-bound virions (Yip et al. 2014). The infected epithelial cells produce multiple virions which immediately invades adjacent endothelial cells and macrophages. Pathological examinations of late-stage cases depicted virus protein, while complete absence of prominent interstitial inflammation and vasculitis that suggest a persistent infection of alveolar epithelium occurs in severe disease.

Apoptosis is an ultimate fate of an infected alveolar epithelial cell, but some other types of cell deaths are still largely unknown. A wide expression of virus proteins has been observed in a rodent model of SARS-CoV-2 infection. The terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay confirmed that majority of the cells are apoptosed in this rodent model of SARS-CoV-2 (Chan et al. 2020). These virus proteins destabilize cellular physiology, induce apoptosis and release of interferon, and facilitate the production of virion (Lim et al. 2016). The infected epithelial cells fuse to create syncytia, a process mediated by the fusion machinery helping the virus entry, which promotes cell–cell spread of the SARS-CoV-2 and evasion of immune surveillance. The infected epithelial cells detach and leave behind a porous alveolar-capillary barrier. This alveolar epithelium offers majority of the barrier functions of the alveolar-capillary interface; hence, the loss of epithelium gets linked with the plasma exudation or hemorrhage, while the development of hyaline membranes full of factor VIII, cytokeratins and fibrin happens (Gorin and Stewart 1979). The epithelium infection not only results in the production of the virus but also the loss of the barrier function. The infected or strictly injured epithelium generates cytokine burst. In vitro studies of alveolar epithelial cells infected with coronavirus or either influenza virus showed production of a series of proinflammatory molecules, e.g., interleukins (ILs) (IL1 β , IL6, IL8, and IL29), CXCL9, CXCL10, CXCL11, and CCL5. The loss of AT2 cells declines the secretion of the surfactants and may facilitate alveolar collapse. In an in vitro study, influenza infection of AT2 cells down regulated the release of surfactant proteins A and D (Wang et al. 2011). Surfactant protein D is a lectin that bind with SARS-CoV S protein but not confirmed in case of SARS-CoV-2 S protein (Leth-Larsen et al. 2007). Alveolar epithelium regulates coagulation and fibrinolysis on the alveolar surface, mainly by producing urokinase and plasminogen activator inhibitor 1 (PAI1) (IDELL 2003). SARS-CoV-2 pathology includes both hemorrhage and fibrin deposition in the alveolar spaces and microvasculature, implying perturbations in coagulation

and fibrinolysis. A system biology analysis of experimental SARS-CoV infection demonstrated that urokinase-related pathways predict lung injury (Gralinski et al. 2013). Thus, alveolar epithelium as well as endothelium may promote coagulation disorders in COVID-19.

The biomarkers are of extreme importance especially in this time of COVID-19 pandemic to help diagnosis and developing novel drugs and treatment methods especially the vaccine formation. At clinical levels, biomarkers or biological indicators of the COVID-19 have gained much focus recently which depict the severity of the disease and its possible treatment options (Strimbu and Tavel 2010, Dobler 2019). The expressions of biomarkers especially IL-8, intracellular adhesion molecule 1 (ICAM-1), and NO that have already been reported in ARDS are linked with increased mortalities and modulation in survival respectively (Jain 2010) and give a general idea for their implementation in COVID-19 prognosis. The genome of SARS-CoV-2 comprised of an RNA molecule which may act as primary biomarker for straightforward diagnosis of COVID-19. Furthermore, SARS-CoV-2 RNA encodes multiple structural proteins. i.e., nucleocapsid (N), envelope (E), membrane (M), and spike (S) protein along with various other proteins that mediate the viral entry into the human cells and the subsequent replication in the host cells (Chen 2020; Schoeman and Fielding 2019) may also be used as alternative biomarkers using appropriate detection techniques such as enzyme linked immunosorbent assay (ELISA). But there are certain hurdles that limit the use of these proteins as the biomarkers for the detection of SARS-CoV-2 in particular organs. These hurdles include the complexity in structure of these proteins (N, E, M, and S) and require huge quantity of the sample from that particular organ. Majority of these virus proteins, however, could serve as potential targets for antiviral drugs or biomarkers of drug development for COVID-19 treatment.

Kidney in pathogenesis of COVID-19

The clinical picture of COVID-19 infection is a disease with systemic involvement of the body, especially dysfunction in vital organs (Ronco et al. 2020). Kidneys are mostly involved in COVID-19, and abnormal proteinuria is reported. Acute kidney injury (AKI) is thought as a key indicator for the severity of disease while a negative prognostic factor for survivorship (Qian et al. 2020). The term of AKI nearby ICU patients hangs on creatinine levels 3.1 mg/dl and urea level 145 mg/dl (Reference creatinine range 0.6–1.2 mg/dl) and (Urea Reference range 15–45 mg/dl) (Ghobadi et al. 2020). The AKI pathogenesis in COVID-19 is generally presumptive; it was mentioned that renal destruction is mainly assaulted by the SARS-CoV-2 via

efflux of cytokines along with immune system dysfunctions (Qian et al. 2020). A hormone released from kidneys transfers angiotensinogen proteins into angiotensin-I, which is being converted to angiotensin-II by the ACE present in lung capillaries. (Alebrahim-Dehkordi et al. 2020; Corvol et al. 2004; Pan et al. 2020; Wang et al. 2020c). ACE2 receptors mainly facilitate the entry of the coronavirus into the cell and hence become target cells susceptible to COVID-19 infection (Zou et al. 2020). It has been confirmed that ACE2 can be effectively bound to the S1 domain of the spike protein on SARS-CoV. So this protein is supposed to be essential receptor of SARS-CoV (Zhou et al. 2020c). This receptor is expressed at several parts of the kidney cells such as several types of epithelial cells of the glomerulus, distal tubular cells, also endothelium of interlobular arteries, and smooth muscle cells of the kidney (Asgharpour et al. 2020). The association between ACE2 and S protein in SARS-CoV depends on numerous variants of the ACE2 gene which may be determinative for outcome, symptoms, and sensitivity of SARS-CoV-2 infection in diverse tissues (Zhou et al. 2020c). The major coronavirus receptor ACE2 is expressed in human kidney cells primarily in the brush border of proximal tubules, afferent arterioles, collecting ducts, and the thick ascending loop of Henle, except in mesangial cells and glomerular endothelial (Santos et al. 2013; Ye et al. 2006). The presence of viral nucleic acid in the urine can also indicate the kidneys might be the target of this virus (Ling et al. 2020). Recently, it was demonstrated that SARS-CoV-2 by infecting kidney tubules can directly induce acute tubular necrosis (Qian et al. 2020). Immunohistochemistry findings demonstrated that renal failure happens before death (Diao et al. 2020). About inducing AKI in COVID-19 patients, these outcomes support that the SARS-CoV-2 virus can directly affect the podocytes and renal tubular epithelium (Su et al. 2020).

Although earlier studies offered a lower incidence (3–9%) of AKI in patient with COVID-19, but currently, it has been recognized as one of the fatal side effects of this infection. As said by previous studies on SARS-CoV and MERS-CoV infections, AKI has a high mortality rate (60–90%) (Alebrahim-Dehkordi et al. 2020; Gagliardi et al. 2020).

New prognostic glomerular filtration biomarkers are β -trace protein (BTP) and β 2-microglobulin (B2M) which comparisons to creatinine and cystatin C are limited by the absence of carefully developed GFR assessing stabilities for the unique biomarkers (Inker et al. 2016). In the general population and high-risk groups, these factors are autonomously associated with outcome of renal function such as end-stage renal disease (ESRD) and mortality (Foster et al. 2016).

Prognosis factors of AKI are creatinine (sCr), urea, and cystatin C. Recognition cystatin C, alone or in association with sCr, could be reflected a strong tool for the prediction of kidney action (Bongiovanni et al. 2015). Also, in

the early detection of renal dysfunction, especially to detect mild reductions in GFR, in different types of renal diseases, assessment of cystatin C level may be helpful to estimate GFR (Coll et al. 2000). Nevertheless, it has also been used to estimate level of mortality; higher cystatin C levels are an independent forecaster of death in COVID-19 patients and can be used as an indicator of poor prognosis (Gagliardi et al. 2020). It was shown that COVID-19 patients with elevated urinary β 2-microglobulin (β 2MG) and α 1-microglobulin (α 1MG) levels had pointedly lower amounts of hospital discharge equated to those with normal urinary β 2MG and α 1MG levels (Sun et al. 2020).

With a better understanding of the physiopathology of AKI in COVID-19 disease, be possible to achieve early diagnosis, optimize treatment plans, and promote life expectancy in these patients.

The critical point in this infection is interaction between lung and kidney damage. Acute respiratory distress syndrome (ARDS) causes acute hypoxia and may contribute to the development of acute kidney injury through systemic processes such as altered kidney function, increased renal vascular resistance, venous congestion, and decreased cardiac output, all of which may contribute to renal hypoperfusion and acute tubular necrosis (Fogagnolo et al. 2021). Acute kidney injury, on the other hand, has been demonstrated to promote lung injury by increasing lung capillary permeability, local inflammation, and fluid overload in various conditions (Legrand et al. 2021). According to several pathways that are caused to COVID-19 infections, the main factors are revealed in Table 1 that occur in the acute phase of patients admitted to the intensive care unit so can reach the good concepts of the pathogenesis of COVID-19 disease.

Cardiovascular system in pathogenesis of COVID-19

One of the main involved organs in patients with COVID-19 is cardiovascular system. The evidence and studies suggest that about 20–40% of the patients referring to hospitals report complications such as myocardial injury, acute myocardial infarction, myocarditis, acute coronary syndrome (ACS), venous thromboembolic even, cardiac chest pain, fulminant heart failure, cardiac arrhythmias, and cardiac death. However, chest pain and heartbeat are the most common symptoms in cardiac patients (Fig. 2) (Guzik et al. 2020; Long et al. 2020; Nishiga et al. 2020).

The hospital evidence suggests that some of the patients without any typical symptoms of COVID-19 report cardiac symptoms as the primary clinical manifestations (Nishiga et al. 2020). Cardiac symptoms are not the specific symptoms of COVID-19; rather, other diseases may be also

Table 1 The signaling pathway of pathophysiological mechanisms of AKI in COVID-19

Signaling pathway	Mediator and axis	Pathophysiological mechanisms	Reference
ACE2 or Angiotensin II	ACE2 receptor and TMPRSS and KIM1	Co-expression of interactions factors in podocytes and cells in proximal straight tubules, direct viral invasion and Ang II activation and myeloid cell activation → <i>cytokine storm</i>	Izzedine and Jhaveri (2020a), Ichimura et al. (2020), Pan et al. (2020), Li et al. (2020b), Batlle et al. (2020)
	Imbalanced RAAS activation and ACE2 (membrane-bound ACE2) and CD147, in proximal tubule cells	Promotes glomerular dysfunction, fibrosis, vasoconstriction, and inflammation	Gabarre et al. (2020)
Apoptotic, and mitochondrial pathways	Sepsis procedure	Hypovolemia, increasing kidney hypo perfusion	Bellomo et al. (2017)
Pro-inflammatory systems	TGF β 1, TNF α , IL-1 β and IL-6, IP-10, GCSF, MCP-1, MIP-1 α , and TNF- α and ACE2 proteins	Decrease the survival	Zhang et al. (2020d), Zhou et al. (2020b), Asgharpour et al. (2020)
Cytokine storm	TNF α , IL-6, IL-8, and IL-10	Endothelial dysfunction, lymphopenia, DAMPS and IL-6 cause organ crosstalk and lung–kidney interactions	Ronco and Reis (2020), Legrand et al. (2021)
Hypercoagulability		Endothelial damage, microthrombin, rhabdomyolysis, microembolism, kidney infarction, myocardial dysfunction	Zhang et al. (2020e)
<i>Organ crosstalk</i>			
	Lung–kidney axis	Overproduction of cytokines, acute respiratory distress \uparrow → renal medullary hypoxia \uparrow	Ronco and Reis (2020)
	Heart–kidney axis	Cardiomyopathy and/or acute viral myocarditis → developed AKI	Ronco and Reis (2020), Izzedine and Jhaveri (2020b)

TMPRSS transmembrane serine proteases, *KIM1* cell immunoglobulin mucin domain 1, *RAAS* renin–angiotensin–aldosterone system, *TGF β 1* transforming growth factor beta, *TNF α* tumor necrosis factors alpha, *DAMPS* damage-associated molecular patterns.

manifested by the symptoms similar to the ones reported by COVID-19 patients. In 2009, studies on SARS-CoV patients showed that this virus can cause myocardial injury and systolic dysfunction by interacting with ACE2. In 2016, the symptoms of cardiovascular disorders in MERS-CoV patients were evaluated by cardiac MRI (Babapoor-Farrokhran et al. 2020). For example, Stefanini et al. reported that patients with COVID-19 who showed high levels of hs-TnI and BNP had a significant mortality rate than patients without elevated hs-TnI and BNP. The group also showed that concomitant increases in hs-TnI and BNP could be considered as an independent and reliable predictor of all-cause mortality (Stefanini et al. 2020). A meta-analysis included 23 studies and 4631 patients revealed that patients with high levels of TnI were more likely to have severe disease, ICU hospitalization, and mortality. Patients with raised CK, CK-MB, LDH, and IL-6 levels, as well as arrhythmia, are associated to the development of severe disease and the requirement for ICU admission, and patients with elevated LDH and IL-6 levels have a higher mortality rate (Li et al. 2020a) In 2954 COVID-19 patients showed

that patients with pre-existing coronary artery disease showed high levels of cardiac biomarkers and high rates of ICU hospitalization and mortality. High levels of hs-TnI, -HBDH, CK-MB, and LDH, regardless of the presence or absence of coronary artery disease, are also prognostic biomarkers in COVID-19 patients (Li et al. 2021).

The molecular pathogenesis of the effect of COVID-19 on cardiovascular system

Studies about the molecular mechanism of COVID-19 in myocardial injury suggest that this virus can probably cause myocardial injury in different ways such as the ACE2 receptor (the direct way), hypoxia induction, systemic inflammation, and production of inflammatory cytokines (indirect way) (Zhu et al. 2020). As we know, ACE2 and serine protease (TMPRSS2) are necessary for intrusion of COVID-19 into the cell. First, S protein is priming by TMPRSS2, and in the following, it binds to ACE2 to enter into the cell. Therefore, simultaneous expression of TMPRSS2 and ACE2

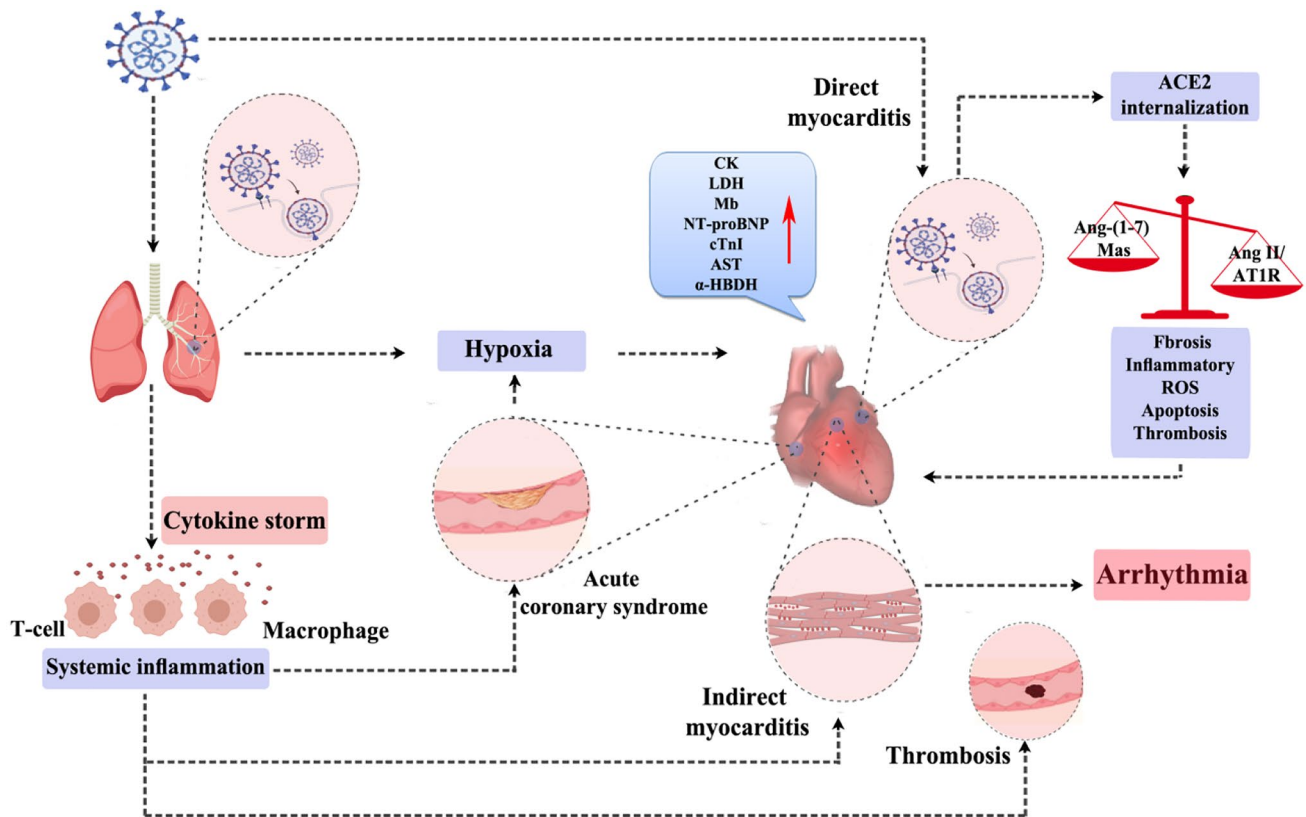


Fig. 2 Schematic of the effect of COVID-19 on the cardiovascular system. COVID-19 affects the cardiovascular system through a variety of pathways. (1) COVID-19 affects the cardiovascular system through the production of large amounts of inflammatory cytokines. Large amounts of inflammatory factors released cause acute coronary

syndrome, thrombosis, and myocarditis. (2) This virus also has an impact on the cardiovascular system by inducing hypoxia as a result of respiratory system disruptions or acute coronary syndrome. (3) In addition to the indirect effects, COVID-19 causes cardiomyocytes through its direct effect on cardiomyocytes

is the main requisite for COVID-19 infection (Tajbakhsh et al. 2020).

ACE2 is a protein with a high expression in many tissues such as testicle, kidney, lung, and heart. Studies on expression of this protein in different cardiovascular cells suggest that ACE2 has a high expression in cardiomyocyte, fibroblast, smooth muscle cells, and pericytes (Unudurthi et al. 2020). According to the recent studies about the molecular mechanism of cardiovascular disorders in COVID-19 patients, there is a high level of ACE2 in pericytes that can be the cause of cardiovascular failure in this virus. On the other hand, expression of ACE2 increases in patients with failing human hearts, and it can be the cause of vulnerability of failing human hearts patients to COVID-19 (Guzik et al. 2020). In addition to the direct damage of COVID-19 to myocardial cells by ACE2, the other mechanism through which COVID-19 leads to myocardial injury is hypoxia and ischemia.

Researchers assume that this ischemia may be caused by the acute respiratory distress syndrome (ARDS) or the direct effects of the virus on macro- or micro-vascular system. It has been reported that ACE2 arteries are expressed on the

surface of endothelial cells, and COVID-19 can probably disturb the arterial function and induce ischemia by binding to these receptors. On the other hand, local inflammation in these arteries leads to production of procoagulant factors that can cause thrombosis and ischemia in COVID-19 patients (Zhu et al. 2020). The other mechanism through which COVID-19 induces ischemia and myocardial injury is coagulopathy. One of the main indications of these patients is the increased production of coagulant factors and disseminated intravascular coagulation (DIC) which increases the probability of thrombosis and ischemia in these patients (Tang et al. 2020, LILLICRAP 2020).

The other mechanism through which COVID-19 causes cardiovascular diseases is systemic inflammatory response and immune response dysfunction which leads to production of large amounts of inflammatory cytokines, i.e., cytokine storm (Tajbakhsh et al. 2020). Inflammatory factors are among the factors involved in electrical disorders and cardiac arrhythmia. For example, IL-6 is one of the inflammatory factors that are significantly increased in the systemic inflammation caused by COVID-19 (Grifoni et al. 2020).

This pre-inflammatory factor increases the level of L-type Ca²⁺ current (ICaL) and decreases the expression of Ca²⁺-ATPase (SERCA2) and junction proteins in myocardial cells and so, it causes cardiac arrhythmia (Wang et al. 2020e; Unudurthi et al. 2020).

The other probable mechanism proposed for myocardial injury in COVID-19 patients is the decreased level of ACE2 on the cell surface that results from its binding and internalization with the virus in the process of viral transmission into the cell. It can increase the expression of Ang II and decrease the expression of Ang-(1–7). The evidence and studies suggest that Ang-(1–7) activates the protective signaling pathway from the myocardium by Mas receptor and it inhibits the effects of Ang II (Wang et al. 2020e; Patel et al. 2016). However, several clinical studies have reported that with the increase of Ang II, this factor can induce atherosclerosis, fibrosis, hypertrophy, and consequently cardiovascular disorders by AT1 receptor (Billet et al. 2008; De Mello and Danser 2000; Chakafana et al. 2020).

Liver in pathogenesis of COVID-19

Previous reports have revealed that some SARS-CoV-2 patients have gastrointestinal symptoms such as diarrhea, abdominal pain, loss of appetite, vomiting, and nausea (Zhou et al. 2020d; Guan et al. 2020b). In addition, concomitant injury of liver has recently been published in COVID-19 patients (Zhang et al. 2020a). The abnormality of function tests of liver were seen in some patients with COVID-19 upon admission (Xiao et al. 2020). A group of liver function tests was performed, and the results revealed that some COVID-19 patients had liver dysfunction. Alteration of liver cells damages biomarkers, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, and bilirubin, is a common laboratory finding in patients with SARS-CoV-2 (Lei et al. 2020a; Bangash et al. 2020; Han et al. 2020; Hu et al. 2020). Furthermore, pathological examination of COVID-19 patients showed that hepatocyte destruction was linked with moderate steatosis, focal necrosis, leukocyte infiltration into the lobular and portal area, and sinusoidal congestion (Chang et al. 2020). Therefore, all of these showed liver involvement in COVID-19 patients. However, the underlying mechanism is not completely discovered, especially in the case of hepatobiliary involvement of the disease (Kovalic et al. 2021). In these patients, as in the case of previous infections seen with SARS-CoV, the binding and uptake through the cholangiocyte receptor of the angiotensin converting enzyme (ACE2) causes liver injury (Chai et al. 2020b). Not only does the increase degree in ALT or AST appear to be related to the severity of SARS-CoV-2 infection, but also suggests that this mechanism is mediated by liver damage through ACE2 up-regulation also among liver cells in a mouse model (Guan et al. 2020a).

Although hepatocytes and bile duct epithelial cells express ACE2 receptor (Chai et al. 2020b), but no significant changed histopathological properties have been tested in such cells from SARS-CoV-2 infected patients (Xu et al. 2020). In addition, glutamyl transpeptidase (GGT) is a biomarker for the diagnosis of cholangiocyte damage. Some COVID-19 patients have GGT enhanced during hospitalization (Chai et al. 2020a). Preliminary reports revealed that ACE2 receptor expression is enriched in cholangiocytes (Hoffmann et al. 2020a), and SARS-CoV-2 enters the target cell via ACE2 receptor (Hoffmann et al. 2020a), which results in serum abnormality. A direct cause of liver damage in SARS-CoV-2-infected patients may be that the virus infects liver cells. Approximately 2–10% of COVID-19 patients developed diarrhea symptoms, and SARS-CoV-2 nucleic acids were detected in their feces and blood specimens (Yeo et al. 2020), which suggests that the virus may invade the liver through blood circulation or digestive tract. On the other hand, hypoalbuminemia and abnormal PT were seen in some patients with COVID-19 (Lei et al. 2020a). Abnormal PT can be due to liver damage or coagulopathy. Hypoalbuminemia is reported via liver damage, kidney injury, heart failure, malnutrition, and protein-losing enteropathy. Hypoalbuminemia and elevated AST levels were frequently seen in severe patients, and correlation analysis revealed a correlation between AST and albumin levels with gradation of severity. Therefore, biomarkers of liver function including albumin and AST should be evaluated in COVID-19 patients (Lei et al. 2020b).

Due to clinical evaluation and biochemical experiments on COVID-19 patients, enhanced levels of liver function abnormality biomarkers have been linked with severe COVID-19 and worse prognosis (Lippi and Plebani, 2020). Severe patients with COVID-19 frequently induce hypercoagulability with both microangiopathy and local thrombus formation, while abnormality in prothrombin time, in disease onset, is relatively uncommon (Connors and Levy 2020; Iba et al. 2020). Evaluation of several COVID-19 studies reveals that laboratory chemistries were collected from patients following their hospitalization. More comprehensive trends in liver chemistries may be considered in the future due to test; the peak value of this biochemical composition results and compares them based on clinical results. For instance, the peak AST and ALT levels noted were 1445 U/L and 7590 U/L, respectively, in severe COVID-19 (Chen et al. 2020; Fan et al. 2020). Literatures revealed that 14–53% of patients with advanced COVID-19 had elevated AST and ALT levels. The alkaline phosphatase (ALP) level increased in 1.8% of COVID-19 patients during hospitalization. There is a higher liver dysfunction incidence in severe patients with COVID-19 (Zhang et al. 2020b). The prothrombin test (PT), D-dimers, fibrinogen, and the platelet count are significant predictors of severity of disease illness as detection

alterations herald the onset of disseminated intravascular coagulopathy (DIC) (O'Shea et al. 2020).

In addition, the description of “chronic liver disease” is not yet defined in these reports and requires further study. Many of these laboratory results, such as abnormal liver parameters, reduced albumin, low platelet count, or prolonged PT, can be attributed to acute SARS-CoV-2 infection, but can also be associated with underlying viral hepatitis or cirrhosis that is obviously not observed between these studies. An Italian study reported chronic liver injuries in only 28 of 1591 ICU patients (Grasselli et al. 2020).

Another study from the USA found that of 5700 hospitalized patients, only 11 (0.2%) had HBV or HCV and only 19 (0.4%) had cirrhosis (Richardson et al. 2020). A large readiness study found that individuals with chronic liver disease and COVID-19 were three times more likely to die than patients without liver problems (Singh and Khan 2020). In contrast, two other meta-analyses have recently failed to show an association between chronic liver disease and the severity or mortality from SARS-CoV-2 infection (Wang et al. 2020d; Lippi et al. 2021).

Other causes of liver damage include underlying liver injury, medication including experimental drugs, and in severe patients, a cytokine storm via tumor necrosis factor α (TNF- α), interleukin [IL] -6 or IL-18), and the ischemic hypoxia-reperfusion that associated with COVID 19 infection with more severity (Hu et al. 2020).

Therefore, SARS-CoV-2 infection-related liver damage should be the result of secondary liver damage due to the systemic inflammatory response, underlying liver diseases, respiratory distress syndrome-induced hypoxia, hypoxic hepatitis, MOF, and administration of hepatotoxic drugs (Feng et al. 2020; Bangash et al. 2020; Han et al. 2020; Hu et al. 2020). The characterization of liver dysfunction among patients with SARS-CoV-2-infected remains paramount with respect to potential therapeutic methods. Regarding to treatment effect on liver function of patients with COVID-19, Xu et al. (Hu et al. 2020) showed the medications applied for SARS-CoV-2 patients probably induced liver injury, such as antibiotics, antiviral agents, etc.

Hydroxychloroquine has been used as a potential option for COVID-19 treatment (Gautret et al. 2020), and although hepatotoxicity is relatively rare, it is metabolized in the liver and has been revealed to cause acute liver damage in some individuals (Hydroxychloroquine 2012). Preliminary reports of the IL-6 inhibitor tosilizumab in COVID-19 patients also suggest that tosilizumab may be linked with unusual hepatotoxicity (Zhang et al. 2020c).

In addition, the use of antiviral therapy has been further investigated. Remdesivir, a new antiviral agent that acts as an RNA-strand terminator, has been shown to be effective in vitro, and in early clinical trials, the results of remdesivir

showed liver dysfunction among other side effects (Grein et al. 2020; Beigel et al. 2020; Goldman et al. 2020). Among the baseline data from a study of the first cases of SARS-CoV-2 infected admitted to the hospital, all patients receiving remdesivir experienced transaminase during their clinical course (Kujawski et al. 2020). However, an increase in ALT or AST levels more than five times the normal range is still an exclusion criterion for starting remdesivir in patients with SARS-CoV-2 infected, and this may exclude many cases with liver damage from taking remdesivir (Grein et al. 2020; Beigel et al. 2020; Goldman et al. 2020; Kujawski et al. 2020).

Thus, further characterization and identification of liver damage are very important among SARS-CoV-2-infected patients with severe/critical infections, especially if one of the few treatment options for underlying liver chemical conditions is expected. To overcome this difficulty, in one study, functional liver chemistries were collected within 2 days of hospitalization to prevent drug-induced liver injury (DILI). In addition, liver function abnormalities were observed in patients with chronic liver disease, so these types of cases were excluded. Therefore, the possibility of liver injury in COVID-19 patients may be associated with viral infection of liver cells, inflammatory reactions, and hypoxic hepatitis (Lei et al. 2020b).

As the COVID-19 epidemics continue to affect more people around the world, case studies and the clinical implications of liver damage among this patient population will go a long way.

In addition to coronary artery disease, cerebrovascular disease, leukocytosis, COPD, neutrophilia, elevated creatinine kinase, lymphopenia, elevated LDH, and elevated PT, it appears to be correlation significantly with severe or critical COVID-19 cases. Extensive long-term studies are required to describe the cause and extent of liver damage in patients with COVID-19. The impact of COVID-19 on chronic liver disease needs to be carefully studied and further research is needed in this area (Jothimani et al. 2020).

Finally, the experience from researchers and doctors around the world suggests that liver function should be considered in all SARS-CoV-2-infected patients, but mild to moderate abnormalities may be of secondary importance. However, during illness, one of the most important points to consider is the use of medications that can cause DILI in COVID-19 patients. Also, more careful monitoring of liver enzymes in serum is required, especially in hospitalized patients or patients with liver disease (Papadopoulos et al. 2020). Current knowledge about contributing factors such as liver failure or concomitant drug use remains largely unknown. To continue prospective studies, it is necessary to assess the various factor roles in the pathogenesis of liver damage in infection with SARS-CoV-2.

Cross-link of SARS-CoV-2 with various body organs

The entry of the SARS-CoV-2 inside the host cells is considered important milestone for viral infection and pathogenesis (Li 2016, Perlman and Netland 2009) and remains a key target for immune surveillance in the host cells (Du et al. 2009, 2017). In-depth understanding of underlying mechanism that shows SARS-CoV-2 make its interaction with the lungs epithelial cells is crucial for advancing the knowledge of SARS pathogenesis. Most of coronaviruses initially bind with specialized cell surface receptors for proper attachment, through its surface-anchored spike proteins, enter into the cell by forming an endosome, and finally, the virus and lysosome membranes get fused (Li 2016, Perlman and Netland 2009). The extracellular vehicles (EVs) (30–120 nm) encircled by lipid bilayer are secreted from almost all kind of cells, even the cells of the linings of respiratory tract and are assigned to perform specialized functions by providing immunity to the lung cells, and pathogenesis of multiple disorders of the lungs especially the viral infections (Pocsfalvi et al. 2020). Cells infected with SARS-CoV-2 discharge exosomes, which are linked with infections primarily by transporting various constituents of the viruses particularly virus-derived micro RNAs (miRNAs) multiple proteins, also contain ACE2 receptors making the recipient cells highly susceptible and make an easy for viral entry (Hassanpour et al. 2020). Some studies showed the presence of SARS-CoV-2 RNA-containing exosomal bodies shows an alternative route for cellular entry especially in cardiomyocytes which results in quick

cardiac dysfunction and no more direct coronavirus infection is needed in this case. Moreover, the examinations of the exosomal bodies filled with coronavirus genes may upregulate inflammatory factors at transcriptional levels in pluripotent stem-cell-derived cardiomyocytes (Kwon et al. 2020). (Fig. 3).

In pursuance to give an effective reaction against COVID-19 disease, a deep understanding of the mechanism of infection along with identified and authentic biomarkers facilitates the availability, precision, and efficacy of COVID-19 testing. The respiratory system of the people who have developed clinical illness due to SARS-CoV-2, remained highly vulnerable. The virus may have a potential to affect any organ of the body and even in severe patient’s multiple organs get severely affected (Fig. 4). It is postulated that cellular responses to SARS-CoV are uncertain, and COVID-19 disease is divided in three stages, and corresponds to multiple clinical phases based on infected cells (Wu and McGoogan 2020). Just after the entry into the nasal cavity via inhalation SARS-CoV-2 potentially binds and begins to replicate inside epithelial cells (Fig. 3). SARS-CoV-2 have higher reproduction number (R0) of 2.2–5.7 that gives rise to its exponential spread (Patil et al. 2020).

ACE2 receptor facilitates SARS-CoV-2 attachment on the cell surface (Wan et al. 2020; Hoffmann et al. 2020c), and lung ciliated cells are the main destination in the contaminated airways (Sims et al. 2005). ACE2 receptors are present in the membranes of vascular endothelial cells, lung cells, cardiomyocytes, brain cells, kidney cells, intestinal cells, hepatocytes, pharynx, and lot more to count (Meredith

Fig. 3 The extracellular vesicle (EV) formation in SARS-CoV-2 entry into the cell, replication, and exocytosis to approach other cells/organs of the body

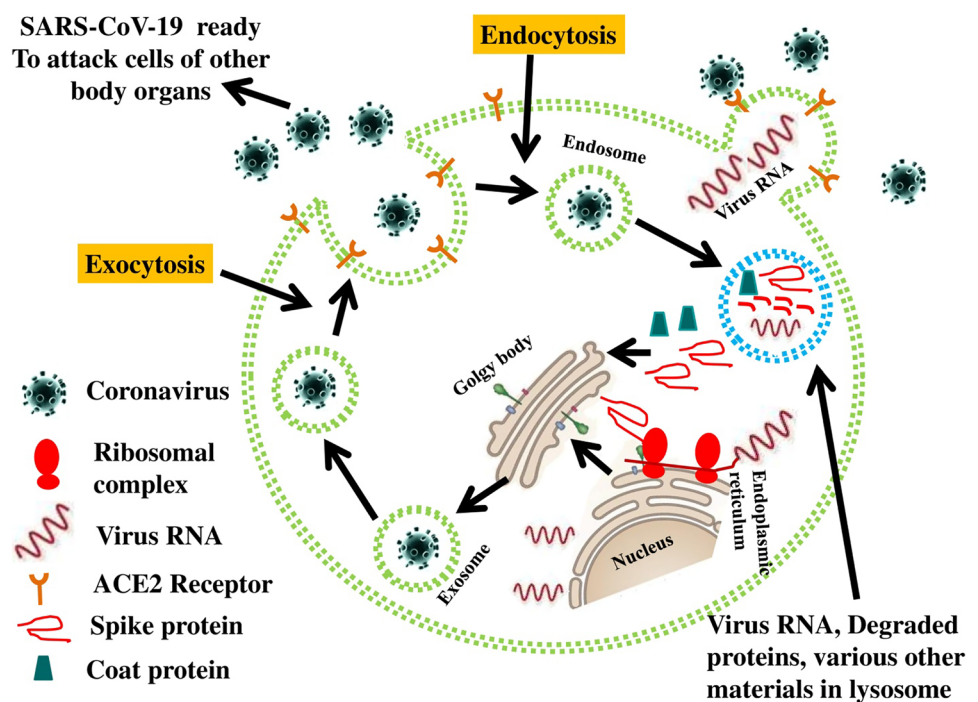
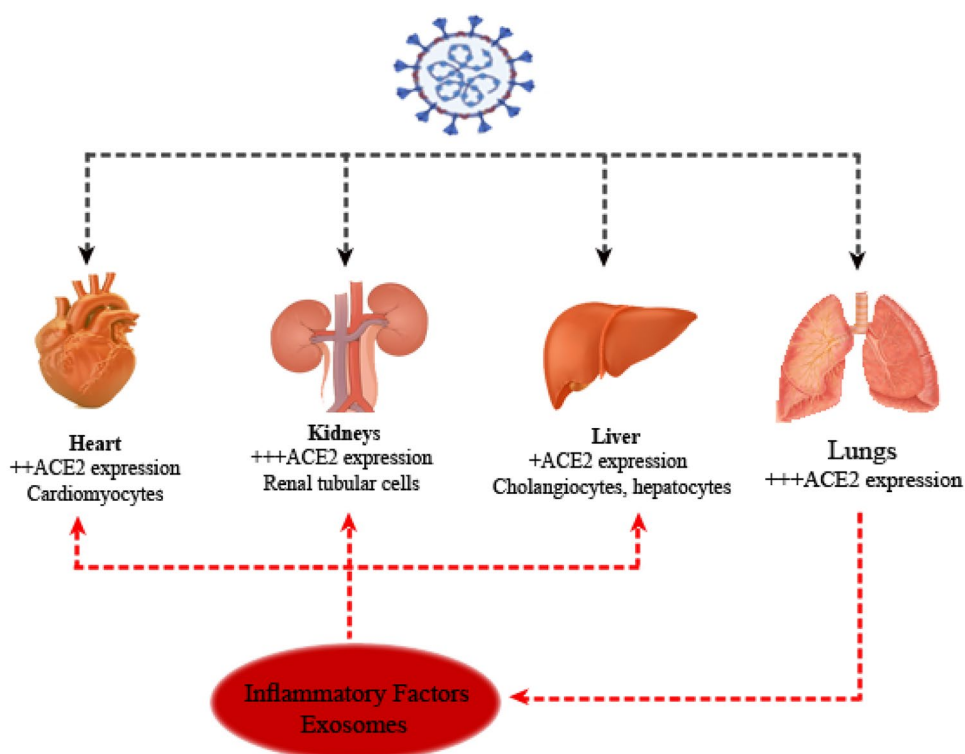


Fig. 4 A cross-talk of SARS-CoV-2 spread to different body organs



Wadman et al. 2020). but less in the airway cell membranes (Reyffman et al. 2019), ACE cleaves angiotensin (Ang)-I and converts into Ang-II, that may help in inflammations and vasoconstriction, while ACE2 help process Ang-II further into Ang(I-VII) that produce vasodilation, anti-inflammatory, antioxidant, and anti-apoptotic effects. Moreover, ACE2 in addition to the cellular receptors for SARS-CoV-2 gets down-regulated following binding by SARS-CoV-2 particles, and the Ang-II levels increased, which promote vasoconstriction, inflammation, oxidative stress, and cell apoptosis (Chen and Subbarao 2007).

Initially, systemic influx of inflammatory cytokine may result in cytokine release syndrome (CRS), is the key underlying mechanism for creating severe complications, and increased mortalities in COVID-19. Inflammations started in lung tissues because of SARS-CoV-2 mediated damage to the alveolar epithelial cells, triggering an immense infiltration of the immune cells (Li and Ma 2020). These micro inflammatory responses mediate the systemic discharge of proinflammatory factors (cytokines), that results in the hyperinflammations of numerous body organs, and subsequently, tissues are damaged and the patients dies (Ye et al. 2020). Various pathophysiological mechanisms particularly endotheliosis, dysregulation of RAAS (Renin–Angiotensin–Aldosterone System), thrombosis, lymphocytopenia, and T cell energy are the contributing factors for enhanced morbidities (Amraei and Rahimi 2020; Jesenak et al. 2020).

It is crucial to find the risk linked with the mortalities in COVID-19 patients especially the vulnerable ones. The SARS-CoV-2 is known to develop serious conditions in different body organs such as inflammation, endothelitis, vasoconstriction, hyper-coagulability, and edema (Jain 2020). Furthermore, lymphocytopenia, increasing levels of D-dimers and FDPs (fibrin degradation products), and disseminated intravascular coagulation (DIC) are observed in COVID-19. Many diseases such as venous thromboembolism, pulmonary embolism (PE), systemic and pulmonary arterial thrombosis or embolism, deep vein thrombosis (DVT), ischemic strokes, and myocardial infarctions (MI) have been studied extensively (Jain 2020). Attempts are being made for the development of novel COVID-19 biomarkers; herein, the cross talks between various body organs, the diagnostic, and prognostics to shield against the COVID-19 are discussed. The COVID-19 patients primarily depict respiratory disease symptoms being treated for pneumonia. It is crucial to focus the cardiovascular system specifically to identify prior symptoms of acute myocardial injuries. ACE2 receptors are present on cardiomyocytes and endothelial cells but not on the cell membranes lining of liver sinusoids, lungs, bile ducts, intestines, or kidney cells (Hamming et al. 2004).

About one quarter of COVID-19 patients showed an unusual prevalence of cardiovascular disease (CVD) remained in ICU (intensive care unit) along with hypertension patients (58%) (Wang et al. 2020a). During myocardial injuries, an

increased level in serum cardiac troponin-I (cTn-I) is seen, and same has also been seen in COVID-19 patients which might be the reason of half of deaths (Zhou et al. 2020a).

Several recent reports examined that abnormal liver functions is linked with enhanced disease-mediated deaths. SARS-CoV-2 may cause hepatic injury even in initial medication started, suggesting the primary threshold is un-related to medical management but rather due to either direct effect of the coronavirus or might be consequence of any systemic disease. The hepatologists are continuously facing a great job of looking after COVID-19 patients suffering liver diseases or liver transplant patients who have been SARS-CoV-2 positive, and also patients on routine surveillance without COVID-19 (Sahin et al. 2020).

In one-third of COVID-19 patients, cardiomyopathy is frequent condition in SARS-CoV-2-positive patients in USA (Arentz et al. 2020). It is emphasized that both cardiac dysfunction along with hepatic congestion contributes to hepatic injury in COVID-19 infection and is mainly linked with an elevated levels of amino-transferases and gamma-glutamyl transferase (GGT) (Weisberg and Jacobson, 2011; Van Deursen et al. 2010). Severe ischemic hepatitis is a condition characterized by severe AST-predominant hepatitis (Tapper et al. 2015) and may be observed in critically ill patients with COVID-19. The infrequently observed alkaline phosphatase elevation occurs late in COVID-19 disease progression and could reflect the cholestasis of sepsis, critical illness, or medication effect (Fuchs and Sanyal 2008).

In the heart, SARS-CoV-2 may develop acute coronary syndrome, myocarditis, congestive heart failure, and arrhythmias. Many young's face stroke and cardiac complications can lead and occur in lack of pulmonary and other complications (Madjid et al. 2020; Akhmerov and Marbán 2020). Many of the patients faced ischemic cardiac injury who have developed coronary artery disease (CAD), latent CAD and without CAD, where former remained vulnerable due to attack of SARS-CoV-2 which alters the pulmonary system to cause acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage, and the failure of the lungs (Yang et al. 2020).

The primary cause of the former two is plaque rupture and thrombosis. The last one is due to inadequate oxygen supply and mimics a myocardial infarction (MI). For acute coronary syndrome due to plaque rupture, antiplatelet and anticoagulation therapy may be beneficial. Fibrinolytic therapy and percutaneous coronary intervention may be considered. However, the reported incidence of acute MI has declined in the COVID-19 period (Solomon et al. 2020). The SARS-CoV-2 invades myocytes to generate a cytokine burst to produce a systemic inflammatory response to cause myocarditis without direct viral infiltration. Moreover, it may lead heart failure and arrhythmias even at the acute phase of the viral infection has resolved without any damage to the

lung. Almost 50% of non survivors of COVID-19 reported having acute cardiac injury and heart failure.

During early stages of the COVID-19, respiratory failure occurs while cardiac injury is more obvious and severe in the later stages of the disease. Various risk factors associated with severity and deaths, diabetes, obesity, age, and hypertension than does respiratory disease alone. Failure of the heart and elevated brain-type natriuretic peptide (BNP) are also observed, along with increased troponin are linked with mortalities (Akhmerov and Marbán 2020). In older patients with existing CAD or hypertension, heart failure is mainly due to poor demand–supply relationship, while in younger patients, myocarditis is the major reason. The hike in cardiac issues is reported due to inflammatory stress, myocarditis, hypoxemia, metabolic abnormalities, or medications. Cardiovascular issues (dyslipidemia, pulmonary fibrosis, and a vascular necrosis) appear long after virus clearance and even after recovery in survivors, while evolution and persistence of inflammations are silent (Solomon et al. 2020; Akhmerov and Marbán 2020). In such cases, frequently applied medicines include ACE inhibitors and angiotensin II receptor blockers, which have not been explained for increased risks of COVID-19 infection or its associated complications (Vaduganathan et al. 2020).

These observations led to define theories surrounding the interplay between the pathophysiology of COVID-19 and the cardiovascular system (Clerkin et al. 2020; Zheng et al. 2020). Moreover, COVID-19 may exacerbate cardiovascular risk factors and pre-existing CVD or may increase susceptibility for the development of new cardiovascular complications. Alternatively, CVD or myocardial injury may predispose to worse outcomes in COVID-19 patients, reflected in huge literature, whereby established CVD is linked with severe COVID-19, leading to higher morbidity and mortality.

The injuries to the kidney remained secondary to systemic abnormalities in COVID-19. Many of the studies indicate that ACE2 is highly expressed in renal tubular cells, Sertoli cells, Leydig cells, and cells in seminiferous ducts in testis (Fan et al. 2021). Moreover, recombinant SARS-CoV-2 spike protein (RBD) domain and ACE2 of RPTEC/SerC cell-binding assays also confirmed that SARS-CoV-2 can bind to ACE2 on the surface of these cells (Fan et al. 2021). Multiple factors may cause the renal injuries following SARS-CoV-2 infection. Various kidney cells (glomerular cells, tubular epithelium, and podocytes) also have got the ACE2 receptors on cell membranes and reported the existence of the SARS-CoV-2 virus (Puelles et al. 2020). Through highly expressed ACE2 in renal tissue, SARS-CoV-2 infection fundamentally initiates a mechanism of renal injury. Systemic effects such as host immune clearance and immune tolerance disorders, endothelial cell injury, thrombus formation, glucose and lipid metabolism

disorder, and hypoxia aggravate this renal injury (Wang et al. 2020b). Due to severe but huge number of COVID-19 patients and the associated complications make it hard to manage patients on dialysis and during kidney transplantation (Alberici et al. 2020). About 15% patients expired in the UK were reported suffering chronic kidney disease. The inflammatory bursts especially the cytokines play a role in severe hypo-perfusion and acute kidney injury (AKI) and are usually secondary to systemic abnormalities such as diabetes, hypertension, chronic kidney disease, hypoxemia, and coagulopathy (Braun et al. 2020). AKI may also be caused by the rhabdomyolysis mainly by hyperventilation or antiviral medicines especially remdesivir. In addition, over 90% patients suffering mechanical ventilation in New York city had been developed AKI in temporal association with respiratory failures (Braun et al. 2020; Hirsch et al. 2020). The lack of the renal replacement therapy system and related hemodialysis machines and supplies and peritoneal dialysis were used extensively especially for unstable patients. On the other hand, the patients of kidney transplant, initially fever, is present in 50% and diarrhea was reported in every fourth patient, and such patients have a faster progression of COVID-19 and higher death rates (Hirsch et al. 2020; Akalin et al. 2020; Boyarsky et al. 2020). The SARS-CoV-2-induced kidney damage is expected to be multifactorial, i.e., directly it can infect the kidney podocytes and proximal tubular cells and based on an ACE2-pathway may lead to acute tubular necrosis, protein leakage in Bowman's capsule, collapsing glomerulopathy and mitochondrial impairment (Ahmadian et al. 2020). The SARS-CoV-2-driven dysregulation of the immune responses including cytokine storm, macrophage activation syndrome, and lymphopenia can be other causes of the AKI. Lack of oxygen delivery to kidney may cause an ischemic injury.

Conclusion

Global pandemic COVID-19 caused by SARS-CoV-2 is being unraveling to open an array of effects through an extensive research spans on mild respiratory tract illness through brutal ARDS (acute respiratory distress syndrome) distinguished by acute interstitial and alveolar pneumonia, then failure of multiple organs (kidneys, heart, digestive tract, and blood circulatory system), and death. This study revealed the mechanism of pathogenesis in vital organs affected with COVID-19. The main common way is binding the virus to ACE2 receptor, overexpressed in the cells of all mentioned organs, then inducing the inflammatory and coagulant factors and leading disease to severe phase with cytokine storm and DIC, finally increasing risk of mortality. Overall, it is highly recommended that physicians may check the critical biomarkers and carefully

perform follow up the molecular signaling pathways to crosslink different organs to make an early diagnostic and good prognostics prior to start irreversible complication picture for infected patients with COVID-19 all over the world.

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Declarations

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Informed consent None.

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