



Relation of ACE2 with co-morbidity factors in SARS-CoV-2 pathogenicity

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Abstract

In the last 3 years of the pandemic situation, SARS-CoV-2 caused a significant number of deaths. Infection rates for symptomatic and asymptomatic patients are higher than that for death. Eventually, researchers explored that the major deaths are attributed to several comorbidity factors. The confounding factors and gender-associated infection/death rate are observed globally. This suggests that SARS-CoV-2 selects the human system recognizing the internal comorbid environment. This article explored the influences of hypertension, diabetes, cardiovascular, and renovascular disorders in COVID-19 severity and mortality. Brief mechanistic layouts have been presented here, indicating some of the comorbidity as the critical determinant in the COVID-19 pathogenesis and related mortality.

Keywords SARS-CoV-2 · Infection and mortality · Hypertension and diabetes · Peripheral vascular disease · Comorbidity factors

Introduction

Coronavirus disease (COVID-19) is a worldwide pandemic that is brought on by the SARS-CoV-2 coronavirus, which first appeared in Wuhan, China, then spread incredibly swiftly to more than 180 other nations. SARS-CoV-2 is rapidly spreading all over the world, it is projected that patient characteristics, including age, sex, and comorbidity, might be more vulnerable to either an increased risk of infection or an increased death. According to certain reports, COVID-19 was higher in males than females (Huang et al. 2019; Chen et al. 2019), while patients who were somewhat older than 50 years had a higher rate of COVID-19 confirmed cases, according to some

studies (Yang et al. 2020; Zhang et al. 2020a). Comorbidities are defined in medicine as the simultaneous presence of multiple underlying illnesses in one individual. Each condition is considered comorbidity, and sometimes comorbidities could be present in the form of mental or physical conditions. The best examples of comorbidities are when a person is suffering from diabetes and asthma, or when the person is suffering from hypertension and clinical depression. Comorbidities are generally non-communicable and contribute to nearly two-thirds of the annual deaths around the world. The prevalence of comorbidities in patients with COVID-19 was also highly variable in many reports (Li et al. 2020). A recent study showed that among COVID-19 patients, fever (88.8%) was the most prevalent symptom, followed by fatigue (33%) and dry cough (68%) (Paudel 2020). Another symptom included productive shortness of breath, or SOB (17%), cough (28.5%), sore throat (11.4%), muscle pain (14%), and headache (10%) (Paudel 2020). The least common symptoms were nausea and vomiting (4.1%), diarrhea (4.4%), abdominal pain (0.16%), rhinorrhea (3.2%), and chest pain (0.11%) (Paudel 2020). The progression of the disease COVID-19 is linked to a number of comorbidities. Patients with COVID-19 who have diabetes, hypertension, HIV, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), malignancies, and other comorbidities may develop a condition that is life-threatening. Comorbidity is linked to severe medical conditions, higher medical expenses,

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and more difficult clinical management. SARS-CoV-2 enters into cells using ACE2 receptors that are present on the surface of the host cell. Certain comorbidities are associated with a strong ACE2 receptor expression and higher release of proprotein convertase that enhances the viral entry into the host cells. The comorbidities lead the COVID-19 patient into a violent infectious circle of life and are substantially associated with significant morbidity and mortality. COVID-19 infection is more likely in people with underlying serious medical disorders like high blood pressure, hyperglycemia, lung, kidney, and liver illness, smoking, cancer patients receiving chemotherapy, transplant recipients, and individuals taking steroids persistently (CDC. Coronavirus (COVID-19): symptoms of Coronavirus 2020). Cardiovascular and cerebrovascular conditions (11%), hypertension (15%), and diabetes (9%), among other conditions, were the most prevalent comorbidities found in these patients (Paudel 2020; Zhou et al. 2020). The less common comorbidities were coexisting infection with HIV and hepatitis B (1.5%), malignancy (1.5%), respiratory illnesses (1.4%), renal disorders (0.8%), and immunodeficiencies (0.01%) (Paudel 2020). Comorbidities may be a risk factor for COVID-19 infection given the high percentage of COVID-19 patients and other disorders among admitted ICU cases (Wang et al. 2020). Comorbidity may also relate to reduced immune function. For instance, in diabetic patients, natural immune function may be significantly diminished, which may restrict the body to produce respective antibodies against any infection (Berbudi et al. 2020). Also, polypharmacy and comorbidity are interrelated and dependable on each other. In order to better direct clinical therapy, there has not yet been a systematic review that thoroughly examines whether the presence of common comorbidities increases COVID-19 patients' risk, to guide clinical practice better. Therefore, this research was designed to review the association of different comorbidities with the risk of mortality by estimating aggregated risk in patients with COVID-19.

ACE2

A lot of researchers are interested in a particular protein that allows SARS CoV-2 to infect human cells. This specific protein is called “angiotensin-converting enzyme 2 or ACE2 receptor”. ACE2 receptor serves cellular entry point for COVID-19 to hook into and infect a wide range of human cells. ACE2 is a protein widely expressed at the surface of many cells and also acts as a cellular doorway for the SARS-CoV2 virus, which causes COVID-19. The 805 amino acids in ACE2 are organized into a single extracellular catalytic domain. ACE2 is a type I zinc trans-membrane metallo-carboxypeptidase with variable homology to ACE and an enzyme that cut larger protein angiotensinogen into small proteins that then go on to regulate functions in the other cells. ACE2 can offset the renin-angiotensin system's (RAS) detrimental effects in a variety of illnesses (Donoghue et al.

2000). ACE2 is present in many cell types and tissue, such as the blood vessels, lungs, kidneys, heart, gastrointestinal tract, testes, and liver. It is present in all tissues' endothelial cells from small and large arteries and veins, as well as in epithelium in the lungs, nose, and mouth, which create protective barriers. In the lungs, ACE2 is highly rich with type 2 pneumocytes, an important cell type present in chambers within the alveoli, where oxygen is absorbed and waste carbon dioxide is released. ACE2 serves as a co-receptor for nutrient absorption, particularly for amino acid resorption from meals, on the surface of intestinal epithelial cells in the kidney (Hashimoto et al. 2012). In the nasopharynx and nasal and oral mucosa, we discovered ACE2 expression in the basal layer of the non-keratinizing squamous epithelium. The basal cell layer of the epidermis and the basal cell layer of the hair follicles in the skin both contained ACE2. Although ACE2 has similarities with ACE, its function is different from ACE; ACE2 releases a single amino acid (monocarboxypeptidase), whereas ACE cleaves a C-terminal dipeptide from its substrate (dipeptidylpeptidase) (Donoghue et al. 2000; Tipnis et al. 2000). Angiotensin I (Ang I) is converted by ACE into strong vasoconstrictor Ang II and ACE2 then uses its carboxypeptidase activity to cleave Ang II and hydrolyzes it into heptapeptide called Ang (1–7) (Turner et al. 2004). ACE2 also cleaves Ang I to the inactive peptide Ang (1–9), which is then converted into vasodilator peptide Ang (1–7) by ACE, competing with Ang I and decreasing Ang II (Arendse et al. 2019). Additionally, ACE2 directly breaks down Ang II to generate Ang 1–7 with much higher efficiency than converting Ang I to Ang 1–9. Ang 1–7 then binds to the MasR receptor, which was initially thought to be an orphan receptor due to the suppression of Ang 1–7 effects caused by the application of a MasR antagonist (Alenina et al. 2008). ACE2 also hydrolyzes a number of other peptides, including apelin-13, bradykinin, neurotensin- (1–11), β -casomorphin-(1–7), dynorphin A-(1–13), and ghrelin (Vickers et al. 2002). In addition to serving as an amino transporter, ACE2 acts as a functional receptor for severe acute respiratory syndrome coronaviruses (SARS-CoV). The physiological purpose of ACE2 is to act as a counterbalance to ACE. ACE cleaves the angiotensin I hormone into the vasoconstricting angiotensin II. ACE2, in turn, cleaves the carboxyl-terminal amino acid phenylalanine from angiotensin II and converts it into the vasodilator angiotensin (1–7). Other peptides that ACE2 can break down include neurotensin, [des-Arg9]-bradykinin, apelin, dynorphin A, and ghrelin (Turner 2015). Multiple mechanisms control ACE2, including transcriptional, posttranscriptional (miRNA and epigenetic), and posttranslational through its shedding from the cell surface. The stronger binding of SARS CoV-2 with ACE2 than SARS-CoV may help to explain why SARS CoV2 infection has a more widespread effect than SARS CoV (Shang et al. 2020; Yan et al. 2020).

A higher level of soluble ACE2 expression in the blood may result from increased ACE2 expression on the cell surface, which may actually bind to most SARS-CoV-2 and prevent it from interacting with the membrane-bound receptor (Fig. 1). Tissue ACE2 downregulation and RAS imbalance might contribute to the advancement of multi-organ damage attributed to SARS-CoV-2 infections (Wang et al. 2020). A decreased level of ACE2 secondary to SARS-CoV-2 infection followed by an increase in Ang II can exacerbate cardiovascular disease symptoms or promote further disease complications (Oudit et al. 2009; Aksoy et al. 2020).

Obesity, hypertension, and diabetes are among the most prevalent comorbidities that are frequently linked to catastrophic outcomes brought on by due to SARS-CoV-2 infections (Obukhov et al. 2020; Richardson et al. 2020). The level of ACE2 expression in the liver and kidney has been shown to increase when patients take ARB and ACEi medications, but these patients do not appear to have an increased risk of developing SARS-CoV-2 infection or suffering from severe disease. Instead, it appears that reduced ACE2 activity may be

a key role in increased disease severity rather than the initial high levels of ACE2 expression leading to worsened prognosis.

ACE2 in renin angiotensin system

The complex hormonal axis known as RAAS, which plays a role in blood pressure control, sodium reabsorption, fibrosis, and inflammation, is made up of renin, aldosterone, and angiotensin (Ghazi and Drawz 2017). RAAS imbalance or modification can cause numerous disorders, including heart failure, hypotension, atherosclerosis, and diabetes, respectively (Tikellis and Thomas 2012). The renin-angiotensin system (RAS) is a peptidergic system that maintains the homeostatic control of the cardiovascular and renal systems and controls extracellular fluid volume. Inhibition of the RAS plays a central role in alleviating the increased mortality and morbidity of patients with heart failure (HF) (Givertz 2001; Zaman et al. 2002). Angiotensin II (Ang) is produced by a series of enzyme activities within the RAS. Renin, an

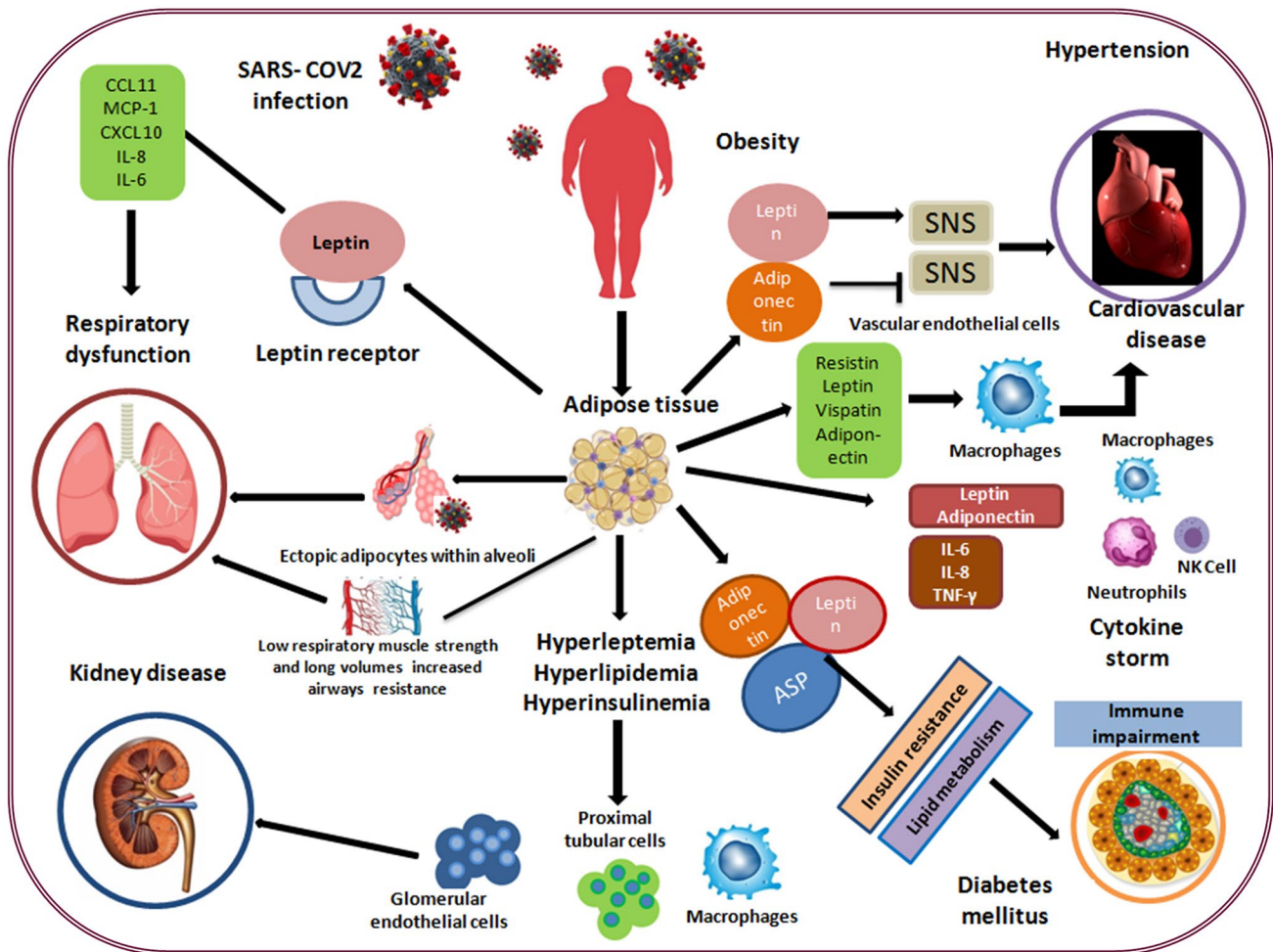


Fig. 1 Brief representations of the major organ and tissue targets of COVID-19-associated damages

aspartyl proteinase secreted by the kidney into the bloodstream, produces Ang I in the first phase by cleaving hepatic peptide angiotensinogen in the blood. Ang I is then hydrolyzed by angiotensin-converting enzyme (ACE) in the second stage, resulting in the octapeptide Ang II (Fig. 1). This biologically active peptide acts on both Ang II type 1 and type 2 receptors (AT₁R and AT₂R) (Bader and Ganten 2008 Jun). Ang II promotes inflammation, vasoconstriction, oxidative stress, and salt and water reabsorption via the activation of AT₁R. RAS blockers increase angiotensin II, which is a substrate for ACE2. By regulating vasoconstriction, ACE2 is a component of RAS, which maintains blood pressure, fluid and electrolyte balance, and reabsorption of sodium in the kidney (Song et al. 2019). The interaction between ACE2 and angiotensin II could induce a conformational change in the RBD domain of ACE2 (Towler et al. 2004). The human body contains two functional forms of ACE2: the tissue-bound or membranous form and the soluble or circulating form (Vaduganathan et al. 2020; Batlle et al. 2020). The extracellular domain of membranous ACE2 has a receptor for attachment with spike (S) protein of SARS-CoV-2, allowing for viral entry (Fig. 1). Since the soluble form of ACE2 lacks the transmembrane anchor and it can freely circulate in the blood. According to Monteil et al. (Monteil et al. 2020), the SARS-CoV-2-ACE2 complex first binds to the host cells' cellular membrane through the spike protein of the virus before entering the cells themselves. The virus would release into host cells upon membrane fusion. The ACE2 on the cellular membrane of the host cells showed a decline, and RAS showed an imbalance, which triggered the inflammatory reactions. Following the initial entry of SARS-CoV-2 into the cells through ACE2, the virus further controls ACE2 expression, reducing the protective properties of the enzyme Ang II is transformed into Ang (1–7) and Ang-I into inactive Ang by ACE2 (1–9). The unopposed action of Ang-II through its AT₁ receptor is caused downregulation of ACE2. As a result, local RAS activation is caused by increased Ang II activity, which in turn causes organ damage seen with COVID-19 (Vaduganathan et al. 2020). By preventing its manufacture and receptor, respectively, ACEi and ARB work to counteract the Ang effects. Additionally, ACE-I/ARB may increase the amount of the soluble form of ACE2 and prevent the virus from entering the host cell. ARBs and ACE-Is both have differing effects on Ang-II, with the latter blocking its receptor while the former prevents its production (reduction in Ang-II levels) (no effect on levels of Ang-II). ACE-I/ARB will protect against this organ damage by (1) possible upregulation of ACE2 activity, (2) reduced levels of Ang-II (by ACE-Is), and (3) inhibiting the AT₁ receptor of Ang-II. ACE-I/ARB will guard against this organ harm (by ARBs). Increased levels of ACE2, with the theoretical chance that elevated the levels of ACE2 generated by ACEi/ARB, could facilitate SARS-CoV-2 invasion

and amplify the amount of organ damage brought on by this unique coronavirus.

Effect of ACE2 on salt balance

It is believed that angiotensin-converting enzyme 2 (ACE2) balances off ACE by the breakdown of Ang II and producing Ang (1–7). Although the kidney contains substantial levels of these enzymes, accounts of how they are controlled vary. In order to better understand how renin–angiotensin–aldosterone–aldosterone system (RAAS) pharmacological changes (ACE inhibition) in activity and physiological changes (ACE inhibition) affect renal ACE and ACE2 expression, renal ACE and ACE2 expression were both examined. Those high in salt, glucose, and fat have the potential to quickly modify the activity and expression of ACE2. In mice, a high salt diet raised ACE2 activity in the urine, but a low salt diet lowered it (Wysocki et al. 2013). In fact, a high-salt diet was observed to raise the ratio of ACE/ACE2 in the glomeruli, which led to renal dysfunction by causing oxidative stress (Bernardi et al. 2012). Additionally, ACE2 was linked to the pathophysiology of hypertension, which was closely related to a high-salt diet. Consuming excessive amounts of salt made hypertension more common in people with the ACE2 rs2285666 TT and rs714205 GG genes (He et al. 2017). According to studies (Crackower et al. 2002; Raizada and Ferreira 2007; Tikellis et al. 2011), the ratio ACE/ACE2 determines the tissue levels of Ang II, and deficiency in ACE2 leads to an increase in Ang II levels (Crackower et al. 2002).

ACE2 appears to counteract the effects of Ang II and produce beneficial Ang 1–7. In both experimental and human renal illnesses, Ang II levels are elevated in injured tubules, making it a potential mediator of renal damage. There is strong evidence that renin is the rate-limiting step for the activation of Ang II via its control of Ang I formation (Hollenberg 2010). For instance, variations in salt intake alter Ang II activity largely via changes in renin release and plasma renin activity. Little is known regarding ACE2 activity changes brought on by physiological disturbances such as dietary salt intake. Since Ang II is controlled by the enzyme ACE2, changes in ACE2 would be anticipated anytime ACE or Ang II levels fluctuate. To maintain the Ang II level at a steady state, the production driven by ACE and the degradation caused by ACE2 need to be coordinated in many comorbid conditions (Fig. 1). When Ang II formation increases as a result of Ang I formation, an increase in ACE would also be expected. Because Ang II would otherwise increase without a checkpoint in this situation, ACE2 would eventually rise to encourage its degradation. It is likely that the rise in ACE2 levels is delayed or does not coincide with the rise in ACE activity, maintaining transiently high Ang

II levels similar to those seen in participants after a low-salt diet. On the other hand, one would anticipate a decrease in ACE, followed by a fall in ACE2, if Ang II production reduces, as in a high-salt diet.

Effect of ACE2 on hypertension

The protein ACE2 is widely known for its role in hypertension. In three strains of genetically hypertensive rats, the ACE2 gene maps to a quantitative trait locus on the X chromosome, suggesting that ACE2 may be the gene that causes hypertension. It is theorized that an imbalance between the tissue's ACE and ACE2 proteins causes enhanced ACE2 expression to guard against increased blood pressure and ACE2 deficiency to exacerbate hypertension. Through negatively regulating the renin-angiotensin system, which includes the pressor-hypertrophic route of ANG II and the depressor-antiproliferative effects of Ang-(1–7) (Li et al. 2019; Ferrario et al. 2005), ACE2 adjusts blood pressure and maintains blood pressure homeostasis. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) are two commonly administered common antihypertensive medicines that target RAS. Hypertension may be the primary co-morbidity and a potential risk factor for more severe clinical outcomes of COVID-19 (Grasselli et al. 2020). Additionally, ACEi and ARBs are used to treat hypertension which upregulates the amount of ACE2 level (Li et al. 2017). It was once believed that aberrant blood pressure management would come from the disruption of the delicate balance between ACE and ACE2 (Brunner 2001). The effects of the renin-angiotensin system on cardiac remodeling, vasoconstriction, vasopressin synthesis and release, and sympathetic outflow plays a significant role in the regulation of blood pressure and volume homeostasis (Allen et al. 2000). The primary physiologically active effector peptide of the RAS, Ang II, works primarily by interacting with the angiotensin II type-1 receptor (AT1R), helping to control blood pressure (Ferrario 1998). Ang II is transformed by ACE2 into Ang (1–7), which works at the Mas receptor to lower blood pressure and lessen fibrosis and inflammation (South et al. 2019). Although the peripheral infusion of circulating Ang II can boost neuronal activity and it is also associated with autonomic and cardiovascular control, which can result in sympathetic hyperactivity and neurogenic hypertension (Ferguson and Bains 1997; Davern and Head 2007; McKinley et al. 1998). The main effects of Ang-(1–7) are to improve sodium and water excretion, increase nitric oxide generation and vasodilation, and decrease sympathetic nervous system tone (Sampaio et al. 2007). The main consequences of the ACE/Ang II/Ang II type 1 receptor pathway are countered by this, including vasoconstriction, sodium and water reabsorption, increased

sympathetic nervous system tone, and increased oxidative stress, which results in inflammation and fibrosis (Masi et al. 2019). Most tissues, including the heart, lungs, vasculature, kidney, and intestines, coexpress both routes. Thus, the balance between the two main RAAS pathways, ACE2/Ang-(1–7) and ACE/Ang II, plays a crucial role in cardiovascular and renal illness as well as the onset, progression, and remission of hypertension in both children and adults (Fig. 2). ACE inhibitors and angiotensin receptor blockers may upregulate ACE2 expression, so increasing the availability of target molecules for SARS-CoV-2, according to some animal studies. Although it might not be enough to offset the harmful effects of Ang II, ACE2 may act as a compensatory mechanism to maintain Ang (1–7) levels in response to hypertension-induced cardiac hypertrophy in this strain. Uncontrolled blood pressure and a high case fatality rate are also linked to COVID-19 infection (CFR). Young animals, including humans, exhibit low ACE2 levels [especially before puberty], and male animals have shown higher ACE2 levels, and high ACE2 levels are associated with both hypertension and diabetes (Thatcher et al. 2012). Hypertensive patients with SARS-CoV-2 infection were shown to have 2.27- and 3.48-fold higher risks of severity and fatality compared to the COVID-19 cases without hypertension, respectively. ACE2 has been measured as a protective factor against increases in blood pressure (Fig. 2). Therefore, it is hypothesized that the binding of SARS-CoV-2 to ACE2 can decrease the physiological function of ACE2, which in turn could cause immediate unfavorable effects of hypertension such multi-organ dysfunction (Tipnis et al. 2000). Age was a significant risk factor for the severity and fatality of COVID-19, according to epidemiological data of SARS-CoV-2 infection, which revealed that severe COVID-19 cases were more likely to be older patients with underlying comorbidities (such as diabetes mellitus and hypertension) (Zhou et al. 2020; Guan et al. 2020). According to recent data from the China CDC, individuals over the age of 80 had the highest case fatality rate of any age group at 14.8% (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020). In both the age 50 years and 50 years groups, hypertension was strongly linked to the severity and fatality of SARS CoV-2 infection, indicating that it can independently raise the risk of disease severity and predict unfavorable outcomes of SARS CoV-2 infection (Fig. 2). Based on the hypothesis that ACE2 can be increased by ACE inhibitors or ARBs, ACE inhibitors or ARBs may have negative impacts on COVID-19 patient morbidity and mortality. Patients with high blood pressure typically receive treatment with ACE2 inhibitors and ARBs. These inhibitors boost the expression of the ACE2 receptor when administered in high doses, which increases SARS-CoV-2 infection (Fang et al. 2020).

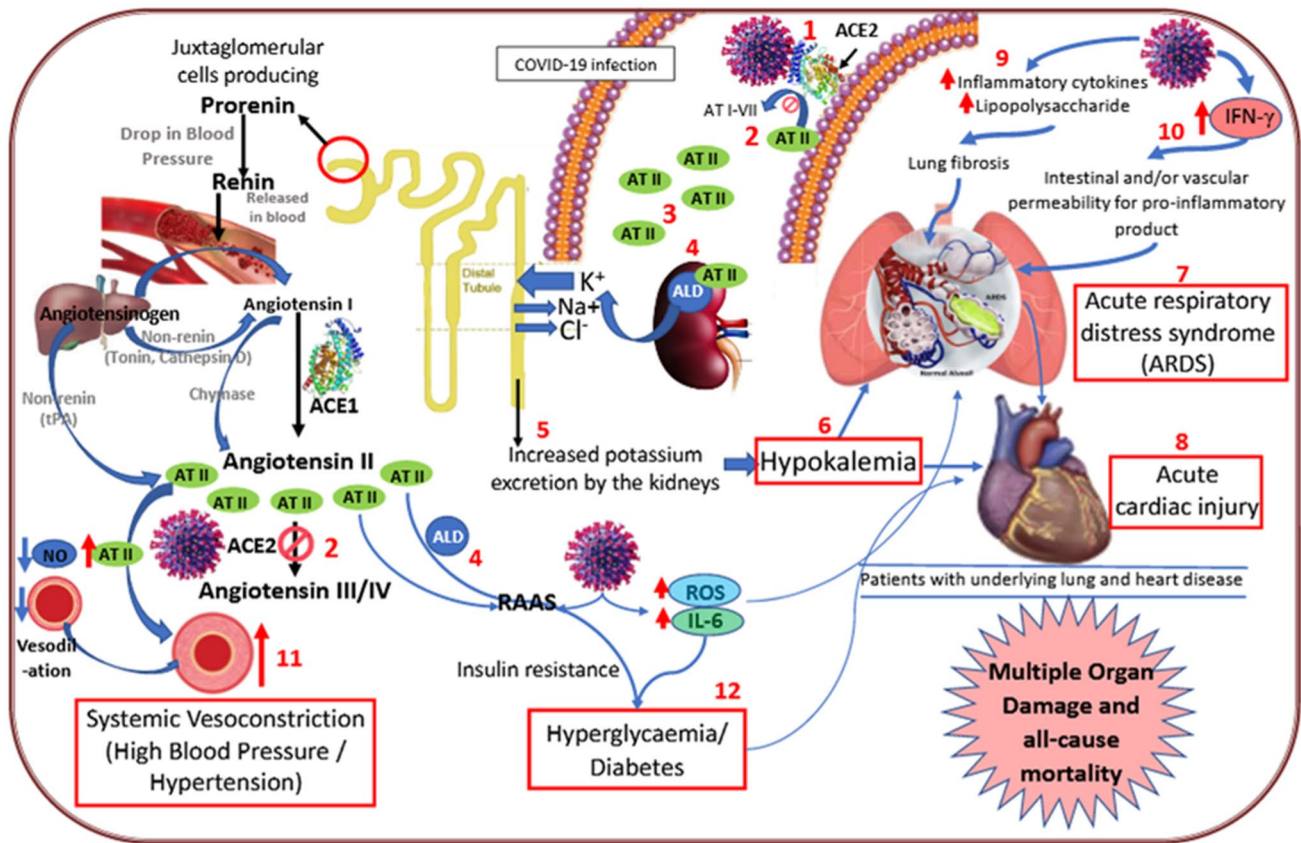


Fig. 2 Brief representations of the organ damaging mechanisms of COVID-19 associated anomalies in comorbid situation

Effect of ACE2 on diabetes

A metabolic condition known as diabetes mellitus is characterized by hyperglycemia and insufficient endogenous insulin production. It has become a major health concern and is predicted to be the fifth most common cause of death worldwide (Roglic et al. 2005). Renal disease, myocardial infarction, hypertension, and stroke are all more likely to develop in people with diabetes (Grundy et al. 1999). For the treatment and prevention of diabetic nephropathy, a progressive condition characterized by proteinuria, thickening of the glomerular basement membrane, mesangial matrix expansion, and associated with chronic renal failure, ACE2 may be a significant target. In kidneys, ACE2 is largely localized in tubular and glomerular epithelial cells (Fig. 2). In both mice and people with type 2 diabetes, there may be a correlation between decreased ACE2 expression in glomerular epithelial cells and increased ACE expression in diabetic kidney disease. Additionally, it has been demonstrated that ACE2 genetic ablation and pharmacological ACE2 inhibition both induce albuminuria, mesangial matrix deposition, glomerular damage, and fibronectin production. Increased albuminuria and glomerular damage are brought on by ACE2 downregulation, which may also result in excessive

Ang II buildup, particularly at the glomerular level (Ye et al. 2006). Increased protein excretion is caused by Ang II's interference with a glomerular barrier function. Ang II inhibitors and AT1 blockers also lower the filtration of macromolecules across the glomerular barrier (Ma and Fogo 2001). In mice lacking ACE2, there may be changes in glucose tolerance, a reduction in first-phase insulin production, and a possible function for ACE2 in the onset of diabetes (Niu et al. 2008). Diabetes and COVID-19 interact with one another in a reciprocal manner. Diabetes increases a person's susceptibility to COVID-19, and SARS-CoV-2 infection can exacerbate dysglycemia, inflammatory responses, and diabetic complications such as diabetic ketoacidosis (Pal and Bhadada 2020) and hypokalemia, which raise the likelihood of developing a life-threatening illness. Diabetes of both kinds I and II is linked to higher plasminogen levels, which has been theorized to make SARS CoV-2 more virulent (Fig. 2). Conversely, obesity common comorbidity of diabetes reduces systemic chronic inflammation by impacting the both innate and adaptive immune systems as well as the level of IL-6 and even TNF- α (Coelho et al. 2013). Diabetes and obesity have been linked to cytokine storm induction (Papadokostaki et al. 2020; Kaye et al. 2012), as well as coagulation system and thrombotic processes impairment,

which are also identified in COVID-19 (Magro et al. 2020). Due to the glycosylation process, the expression of ACE2 is downregulated in diabetics, which may be a contributory factor for the severity of lung complications in comorbidity with SARS-CoV-2 invasion (Pal and Bhansali 2020). Overexpression of ACE2 is caused by the use of ACEis and ARB. When ACE2 is overexpressed, it can break down Ang II and produce angiotensin 1–7, which has beneficial effects on COVID-19 (anti-fibrotic, anti-oxidant, anti-inflammatory, and vasodilatory). DPP4 inhibitors influence the activity of fibroblasts and myofibroblasts to have anti-fibrotic effects while also having anti-inflammatory effects in the lung. The lower rate of lung injury and mortality in COVID-19 may be a result of these effects.

Effect of ACE2 on cardiovascular disease

According to the cardiovascular continuum, vascular disease, tissue damage, pathological remodeling, hypertension, target organ dysfunction, organ failure, and mortality are all risk factors for cardiovascular disease development. The preclinical cardiovascular disease manifests as hypertension, dyslipidemia, and diabetes in its early stages. An essential part of the pathogenesis of CVD (cardiovascular disease) is played by the renin-angiotensin system, and RAS blocking is a key component of the therapeutic approach for the management of CVD. It is now recognized that there is a kind of RAS in which ACE2 degrades Ang II, the primary effectors of the traditional RAS, and generates Ang (1–7). Through vasoconstriction and salt-water retention, Ang II raises blood pressure and promotes cardiac remodeling, fibrosis, inflammation, thrombosis, and plaque rupture. Numerous pieces of evidence show that ACE2 is essential for maintaining cardiovascular homeostasis. In addition, ACE2 is elevated in failing human hearts and atherosclerotic arteries, and its altered expression of cardiac and vascular disease in experimental models of CVD, and ACE2 is increased in failing human hearts and atherosclerotic vessels. ACE plays physiological functions through Ang II and AT1 receptors. Through the development of non-classical Ang (1–7) and Mas receptors, ACE2 acts the opposite functions to the ACE/Ang II/ATR1 axis (Santos et al. 2013; Burns 2007). The vasodilating and antiproliferative effects of this peptide are mediated via the binding of Ang (1–7) to the Mas receptor (Santos et al. 2003). The ACE2-Ang-(1–7) axis has been proven to be a unique RAS protective arm. A protective mechanism against renal injury may be reflected by increased ACE2 expression, principally by tipping the scales in favor of vasoprotective Ang (1–7) from Ang II. According to studies, loss of ACE2 can prevent the evolution of heart failure, while an increase in ACE2 expression can delay or even reverse the phenotype of heart failure. Patients with heart failure also

have much higher circulating ACE2 activity than healthy individuals. The enhanced ACE2 activity in individuals with heart failure may be caused by the membrane-bound ACE2 being shed (Fig. 2).

ACE2 is a versatile enzyme with a variety of biological substrates (Fig. 2). It functions as a monocarboxypeptidase and cleaves a number of different non-RAAS peptides, including (des-Arg9)-bradykinin, a component of the kininogen-kinin system, which is involved in regulating cardiovascular homeostasis (Turner et al. 2002). In patients with COVID-19 precursors SARS (8%) and MERS (30%), CVD was one of the most prevalent co-morbidities. Intestinal epithelium, vascular endothelium, and the heart and lung all express ACE2, which provides a mechanism for the multi-organ dysfunction that can be seen with SARS-CoV-2 infection (Tikellis and Thomas 2012; Zhang et al. 2020b). There is mounting evidence that COVID-19 is associated with higher cardiovascular disease morbidity and death (CVD). The presence of ACE2 receptors on cardiac muscle cells may contribute to the high risk of COVID-19 in individuals with preexisting cardiovascular disease, indicating a potential role for the cardiovascular system in SARS-CoV-2 infection (Fig. 2). There is a significant risk of serious coronary infections in patients with CVD. Additionally, a higher prevalence of inflammatory cytokines is associated with COVID-19 instances and mediates atherosclerosis, procoagulant activation, and hemodynamic instability that result in ischemia and thrombosis (Bonow et al. 2020). Additionally, a higher prevalence of inflammatory cytokines is associated with COVID-19 instances and mediates atherosclerosis, procoagulant activation, and hemodynamic instability that result in ischemia and thrombosis (Bonow et al. 2020).

Conclusions

Compared to female patients with COVID-19, male patients had a much higher chance of dying. In contrast to patients who were older than 50, patients fewer than 50 had a much higher risk of dying. Patients with cancer, diabetes, kidney disease, pulmonary illness, cerebrovascular disease, hypertension, and other diseases had a significantly increased mortality rate. The risk of death linked with COVID-19 may be greatly decreased by implementing proper protection and interventions for COVID-19 patients in general, and in particular male patients with age 50 years who have comorbidities. The COVID-19 symptoms resemble those of the flu (e.g., fever, cough, or fatigue). A year with a high prevalence of respiratory illnesses brought on by the flu, respiratory syncytial virus, and other respiratory viruses saw COVID-19 outbreaks. There are significant effects of COVID-19 on pregnancies and ACE2 expression in the placenta as well as in maternal and fetal circulations. In addition, there are a number of potential

therapeutic strategies that can cure pregnancy difficulties brought on by COVID-19 infections and inhibit the binding of ACE2 and SARS-CoV-2 by employing recombinant ACE2 or by blocking the viral S-protein RBD (AzinheiraNobrega Cruz et al. 2021). Pregnant women were more likely to seek hospitalization among reproductive women (15–44 years old) who tested positive for COVID-19 than nonpregnant women. Compared to pregnant women without the condition or even nonpregnant women with COVID-19, admission to the ICU was more common in pregnant women diagnosed with COVID-19 (Allotey et al. 2020; Ellington et al. 2020). Aging, diabetes, and obesity are the three primary risk factors for disease severity in pregnant women (AzinheiraNobrega Cruz et al. 2021; Ahlberg et al. 2020). The fact that older people are at higher risk of contracting COVID-19 infection may be related to their deteriorating immune systems, T-cell control, and declining CD4 counts (Liu et al. 2020). Knowing these indicators will help identify COVID-19 individuals who are more at risk and will enable a more focused and targeted strategy for preventing those fatalities. Success in vaccination efforts may derive from modifications in spike protein structure during receptor-mediated host cell entrance and further prediction of post-fusion events (Zemlin and Wiese 2020; Banerjee et al. 2020).

Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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