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Circulating angiotensin converting enzyme 2 and COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a widespread outbreak since December 2019. The SARS-CoV-2 infection-related illness has been dubbed the coronavirus disease 2019 (COVID-19) by the World Health Organization. Asymptomatic and subclinical infections, a severe hyper-inflammatory state, and mortality are all examples of clinical signs. After attaching to the angiotensin converting enzyme 2 (ACE2) receptor, the SARS-CoV-2 virus can enter cells through membrane fusion and endocytosis. In addition to enabling viruses to cling to target cells, the connection between the spike protein (S-protein) of SARS-CoV-2 and ACE2 may potentially impair the functionality of ACE2. Blood pressure is controlled by ACE2, which catalyzes the hydrolysis of the active vasoconstrictor octapeptide angiotensin (Ang) II to the heptapeptide Ang-(1-7) and free L-Phe. Additionally, Ang I can be broken down by ACE2 into Ang-(1-9) and metabolized into Ang-(1-7). Numerous studies have demonstrated that circulating ACE2 (cACE2) and Ang-(1-7) have the ability to restore myocardial damage in a variety of cardiovascular diseases and have anti-inflammatory, antioxidant, anti-apoptotic, and anti-cardiomyocyte fibrosis actions. There have been some suggestions for raising ACE2 expression in COVID-19 patients, which might be used as a target for the creation of novel treatment therapies. With regard to this, SARS-CoV-2 is neutralized by soluble recombinant human ACE2 (hrsACE2), which binds the viral S-protein and reduces damage to a variety of organs, including the heart, kidneys, and lungs, by lowering Ang II concentrations and enhancing conversion to Ang-(1-7). This review aims to investigate how the presence of SARS-CoV-2 and cACE2 are related. Additionally, there will be discussion of a number of potential therapeutic approaches to tip the ACE/ACE-2 balance in favor of the ACE-2/Ang-(1-7) axis.

Key Words: Circulating angiotensin converting enzyme 2; Coronavirus disease 2019; Disease severity; Clinical outcome; Severe acute respiratory syndrome coronavirus 2 infection

Core Tip: Recently, conflicting results on circulating ACE2 (cACE2) levels in coronavirus disease 2019 (COVID-19) patients vs healthy people with low cACE2 values were published. cACE2 levels and activity were shown to be increased in severe COVID-19 patients. However, others showed no change or decreased cACE2 in severe COVID-19 patients compared to pre-pandemic controls. Furthermore, it is unclear how SARS-CoV-2 infection and recovery impact the cACE2 level. cACE2 levels increased throughout the first 2 wk of the acute phase of COVID-19. cACE2 levels, on the other hand, were elevated for 1-3 mo after infection and decreased by 4 mo of the illness course. The purpose of this review is to look at the relationship between SARS-CoV-2 and cACE2. A variety of prospective therapeutic options for inhibiting SARS-CoV-2 infection is also explored.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel enveloped RNA beta-coronavirus, is the culprit behind the coronavirus disease 2019 (COVID-19) outbreak, which has gained global attention. It may be asymptomatic or can cause symptoms of a severe acute respiratory infection, COVID-19 pneumonia[1-3]. The possibility of the disease spreading far more is greatly increased by the fact that COVID-19 is known to be transmitted from person to person. As of July 22, 2022, there have been 572700576 confirmed COVID-19 cases and 6398347 deaths worldwide, with the majority of cases reported from the United States, Europe, the Eastern Mediterranean, and Asia[4]. At the moment, the number of COVID-19 cases continues to rise around the world, raising global concerns about the outbreak. It is estimated that one in every 5-10 adult COVID-19 patients will require hospitalization, with rates of admission to the intensive care unit (ICU) ranging from 5% to 32% in China, Europe, and the United States[5-9]. The severity of COVID-19 was found to be particularly dangerous in patients over 65 years with pre-existing chronic medical disorders like obesity, cardiovascular disease (CVD), diabetes, cancer, chronic respiratory problems, and kidney disease[10,11].

The SARS-CoV-2 virus enters cells through membrane fusion and endocytosis after attaching to the angiotensin converting enzyme 2 (ACE2) receptor[12]. In addition to type II alveolar pneumocytes in the lungs, vascular endothelial cells, smooth muscle cells, nasal and oral mucosa, enterocytes in the intestines, and kidneys are among the tissues that have the ACE2 receptor. This distribution explains how the virus may enter cells and why target cells like pneumocytes are so prone to viral infection[13, 14]. For instance, circulating levels of ACE2 are low because it is a tissue enzyme, but it is still unclear how important it is to measure circulating ACE2 in pathologic situations[15]. Circulating ACE2 levels, on the other hand, are higher in individuals with active COVID-19 illness and in the time following infection. Furthermore, higher circulating ACE2 levels have been found in patients who had risk factors for severe COVID-19 conditions. Plasma levels of ACE2 were increased in males more than in females with heart failure. Major cardiovascular events are also more likely to occur when cACE2 concentrations are elevated. Finally, ACE2 levels in serum from smokers, obese, and diabetic people have recently been demonstrated to be substantially higher in severe COVID-19 patients[16-18]. There were conflicting results on cACE2 levels in COVID-19 patients. Furthermore, it is unclear how SARS-CoV-2 infection and recovery impact cACE2 levels. In general, rising levels of cACE2 were identified in the first 2 wk of the acute phase of COVID-19; nevertheless, cACE2 levels were elevated for 1-3 mo after infection and exhibited a decline after 4 mo of the clinical course. The goal of this review is to evaluate the association between cACE2 levels and clinical outcome in COVID-19 patients. Furthermore, we explore whether cACE2 concentration at the time of hospitalization might predict the severity and prognosis of severe COVID-19 outcome.

STRUCTURE AND FUNCTIONALITY OF ACE2

ACE2 is a type I transmembrane glycoprotein found on the cell surface that was discovered in 2000 as the homolog of ACE[19]. The human body contains a large amount of ACE2. The kidneys, testicles, colon, lungs, retina, circulatory system, adipose cells, and the central nervous system have all been found to have it[20]. The human ACE2 gene has 18 exons and is found on chromosome Xp22. A claw-

like external protease domain (PD) and a collectrin-like cytoplasmic domain make up the 805 amino acid ACE2 protein. The receptor binding domain (RBD) of the SARS-CoV and SARS-CoV-2 spike proteins is bound by the N-terminal PD, leading to the development of the PD-RBD complex and enhanced viral entry[21,22]. The severity of COVID-19 may be explained by the affinity of ACE2 for SARS-CoV-2 binding, which is 1020 times larger than that of SARS-CoV[23]. A carboxypeptidase, the HEXXH zinc-binding metalloprotease motif at the N-terminus, converts angiotensin (Ang) I to Ang-(1-9) or Ang II to Ang-(1-7), in contrast to the viral binding site. ACE2 also removes the C-terminus of three other vasoactive peptides, neurotensin, kinetensin, and des-Arg bradykinin[24]. ACE, on the other hand, converts Ang I to Ang II and activates Ang II type 1 and type 2 receptors (AT1R and AT2R), contributing to vasoconstriction, inflammation, fibrosis, lung edema, and damage. The balance of ACE, Ang II, AT1R, AT2R, ACE2, Ang-(1-7), and mitochondrial assembly receptor (MasR) in the renin-angiotensin aldosterone system (RAAS) is crucial. In many diseases in humans, such as CVD, obesity, chronic kidney disease, liver disease, and lung damage, enhancing and activating the ACE2, Ang-(1-7), and MasR axis reduces cytokine release and guards against organ damage[25]. ACE2 activation promotes vasodilation and vasoprotection, preventing lung edema and damage[26] (Figure 1).

CIRCULATING ACE2 IN HEALTH AND DISEASES

A disintegrin and metalloprotease domain 17 (ADAM17)/tumor necrosis factor α -converting enzyme cleaves ACE2 off the cell surface, generating circulating ACE2, an enzyme with an active ectodomain (cACE2)[27]. In 2005, Lambert *et al*[28] validated the ectodomain shedding of endogenously produced ACE2 in Huh7 cells and heterologously synthesized ACE2 in HEK293 cells. Rice and colleagues studied the heritability of cACE, cACE2, and circulating neprilysin (cNEP), which impacted blood pressure in 534 Leeds Family Study participants a year later. They also revealed factors that influence plasma activity variation. Genetic variables were shown to account for 24.5%, 67%, and 22.7% of phenotypic variance in cACE, cACE2, and cNEP, respectively[29]. In addition, other studies found that calmodulin binding to the cytoplasmic tail of ACE2 prevented its shedding independently of phorbol ester (PMA)-mediated shedding[30,31]. ACE2 shedding occurs in healthy people as well. When isolated human CD34+ cells from healthy people were exposed to hypoxia, the ACE2 ectodomain was lost[32]. In healthy people, blood flow restriction increased hematopoietic stem/progenitor cell mobility and circulating ACE2 levels[33]. As a result, ACE2 shedding may be a normal stress response that becomes dysregulated in pathogenic conditions.

Clinical studies have found that people with hypertension, diabetes, and chronic kidney disease (CKD) have higher cACE2 activity. While some clinical trials revealed reduced cACE2 activity, several failed to demonstrate an increase in plasma ACE2 activity in hypertension[34]. Patients with pulmonary arterial hypertension have lower plasma ACE2 activity. A clinical experiment was then conducted to see if human ACE2 medication might reduce pulmonary arterial hypertension as a result[35]. The improvement in cardiac output and pulmonary vascular resistance following a single infusion of rhACE2 GSK2586881 suggests that ACE2 overexpression might be used as a therapeutic strategy[36]. In the Atherosclerosis Risk in Communities Study, Hussain and colleagues looked at the connections between cACE2 and cardiac biomarkers, structure, and function, as well as cardiovascular events in 497 individuals. They discovered that Cox regression analysis revealed prospective correlations of cACE2 with time to first CVD incident after a median 6.1-year follow-up period. Higher cACE2 levels were seen in men, Black people, and those with a history of CVD, diabetes, or hypertension. In hospitalized patients, greater cACE2 levels were associated with considerably higher biomarkers of cardiac damage, a larger left ventricular mass index (LVMI), decreased diastolic function, and an increased risk of heart failure. Furthermore, in an older multiracial patient, cACE2 was found to be associated with biomarkers indicating myocardial damage and neurohormonal activation, LVMI, poor diastolic function, CVD events, and all-cause mortality. They concluded that cACE2 may act as a warning sign of end-organ damage caused by pathological imbalances in the RAAS axis, increasing the risk of future CVD events [37].

Ramchand *et al*[38] conducted a study in 127 patients with aortic stenosis (AS) to assess the association between cACE2 and the degree of stenosis and myocardial remodeling, and to see if cACE2 could be used to predict all-cause death. The researchers discovered that the median cACE2 activity was 34.0 pmol/mL, which was linked to increased valvular calcification and LVMI. Patients with cACE2 levels higher than the median had greater LV end-diastolic volume. Over a median of 5 years, higher cACE2 activity was an independent predictor of all-cause mortality after controlling for relevant clinical, imaging, and biochemical indicators, including N-terminal pro-brain natriuretic peptide (NT-BNP) activation. They concluded that elevated cACE2 was associated with decreased cardiac ACE2 gene expression and severe myocardial fibrosis. In 1458 CKD stages 3-5 subjects without a history of cardiovascular events who were enrolled in the Spanish multicenter NEFRONA study, Anguiano *et al* [39] examined the associations between baseline cACE2 activity and renal parameters, carotid/femoral echography, atheromatous disease, ankle-brachial index, intima-media thickness, need for renal replacement therapy, cardiovascular events, and mortality at 24 mo. Patients with an increase in the

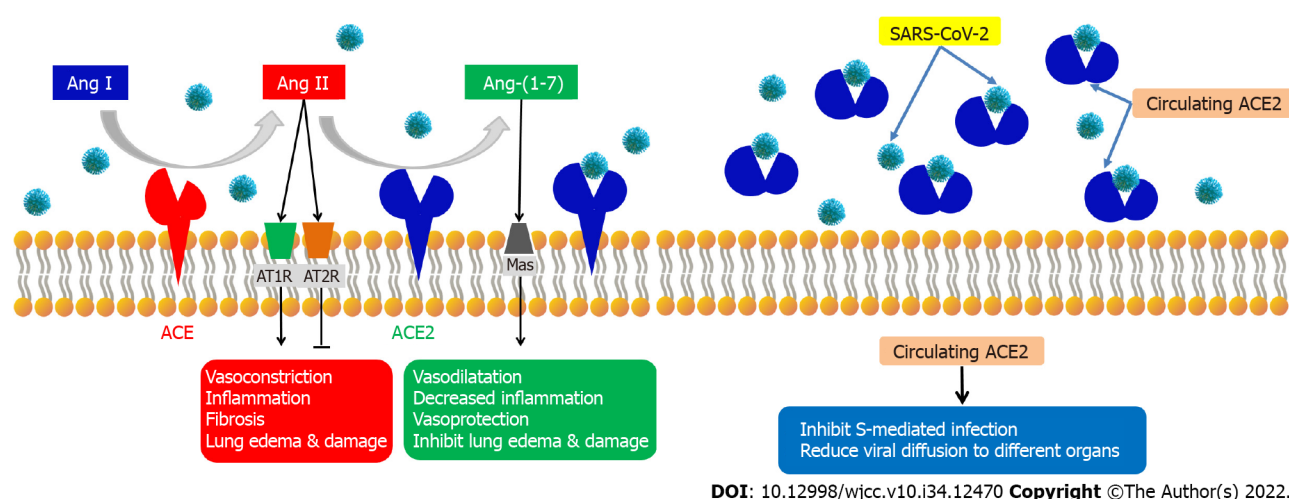


Figure 1 Mechanism of action of angiotensin converting enzyme 2. The angiotensin converting enzyme (ACE) metabolizes angiotensin (Ang) I to Ang II, which activates Ang II type 1 receptors (AT1R) and Ang II type 2 receptors (AT2R), leading to increased vasoconstriction, inflammation, fibrosis, lung damage, and edema. Conversely, angiotensin converting enzyme 2 (ACE 2) counteracts Ang I by generating angiotensin 1-7 [Ang-(1-7)], which then interacts with the G-protein-coupled receptor Mas to exert vasoprotective actions. Circulating ACE2 (cACE2) inhibits S-mediate infection and reduces viral diffusion to different organs.

number of plaque-infested regions after 24 mo had significantly higher levels of baseline cACE2 than stable patients. Multivariate linear regression analysis showed that higher baseline cACE2 activity was significantly associated with male gender, pathological ankle-brachial index, and progressive silent atherosclerosis, defined as an increasing number of plaques at 24 mo. After 24 mo of follow-up, factors such as male gender, older age, smoking, diabetes, and higher baseline cACE2 were all independent predictors of atherosclerosis. They concluded that higher baseline cACE2 activity is associated with an increased risk of silent atherosclerosis in CKD stages 3-5 patients, implying that cACE2 could be used as a biomarker to predict CV risk before CVD develops.

Chirinos *et al*[40] investigated the clinical and proteomic correlates of cACE2 in 2248 heart failure patients from the Penn Heart Failure Study using a modified aptamer test. They assessed the interaction of cACE2 with over 5000 different plasma proteins using the SomaScan technology. They discovered that ACE inhibitors and angiotensin-converting enzyme inhibitors (ACEi) had no effect on cACE2. Furthermore, advanced age, male sex, diabetes mellitus, a lower estimated glomerular filtration rate (GFR), a poorer NYHA class, a history of coronary artery bypass surgery, and greater NT-proBNP levels were related to cACE2. They concluded that cACE2 was substantially connected to various cellular pathways involved in cellular endocytosis, exocytosis, and intracellular protein trafficking in a large cohort of HF patients. It is not apparent if these pathways cause cACE2 or are relevant to SARS-CoV-2 infection, despite the fact that they are known to be involved in other viral infections and may be crucial for CVD. Recently, Fagyas *et al*[41] have conducted research to assess the effects of common comorbidities on ACE2 expression by measuring ACE2 activity in serum, lung, and heart samples from patients with hypertension ($n = 540$), recipients of heart transplantation ($n = 289$), and patients with thoracic surgery ($n = 49$), as well as 46 healthy individuals. cACE2 activity was shown to be elevated in hypertensive individuals (132%) and highly elevated in patients with end-stage heart failure (689%), with a strong inverse relationship to left ventricular ejection fraction. Male (147%), overweight (122%), obese (126%), and elderly hypertensive patients (115%) had increased cACE2 activity. Primary lung cancer increased cACE2 activity while having little effect on ACE2 levels in surrounding lung tissue. In patients having thoracic surgery or heart transplantation, male sex was linked to elevated cACE2 activity (146% and 150%, respectively). The level of left ventricular ACE2 activity was lower in patients with end-stage heart failure who were overweight (67%), obese (62%), or older (73%), regardless of gender. There was no association between circulating and tissue ACE2 activity. RAAS inhibitory drugs had no effect on circulating or tissue ACE2 levels. They concluded that cACE2 levels are correlated with the severity of cardiovascular illnesses, suggesting that ACE2 is involved in the pathomechanisms of CVD and providing a credible justification for the greater mortality of COVID-19 among cardiovascular patients.

In order to measure cACE2 concentrations and evaluate potential determinants of cACE2 levels as well as the association of ACE2 with cardiovascular events, Narula *et al*[42] conducted a case-cohort study in 10753 Prospective Urban Rural Epidemiology (PURE) participants from 14 countries across five continents. They found that elevated levels of cACE2 were linked to higher risks of overall mortality as well as cardiovascular and non-cardiovascular fatalities. A higher risk of incident myocardial infarction, stroke, diabetes, and heart failure was also associated with cACE2 levels. These findings were unaffected by age, gender, ancestry, or traditional risk factors for heart disease. After adjusting for BNP, the independent relationship of cACE2 with clinical endpoints, including death, remained robust, with

the exception of incident heart failure events. Sex, geographic ancestry, and body mass index (BMI) were the top three determinants of cACE2 concentrations. cACE2 outperformed multiple risk variables as a predictor of heart failure, stroke, myocardial infarction, and mortality when compared to clinical risk factors (smoking, diabetes, blood pressure, lipids, and BMI).

A validation cohort of 1123 men and 575 women and an index cohort of 1485 men and 537 women with heart failure were used in Sama *et al*'s[43] study of cACE2 levels. The authors discovered that male sex was the strongest predictor of higher cACE2 values in both groups. cACE2 in the index cohort was not independently predicted by the use of ACE medications, angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists. Use of an ACE inhibitor or an ARB was a reliable predictor of lower cACE2 concentrations in the validation cohort, whereas use of an MRA was a reliable predictor of higher cACE2 concentrations. They found that in two distinct cohorts of patients with heart failure, males had higher cACE2 concentrations than females did, but neither the use of an ACE inhibitor nor an ARB was associated with higher cACE2 concentrations. Although it does not support past research indicating ACE inhibitors or ARBs increase COVID-19 susceptibility through increasing cACE2 concentrations, it may help to explain the greater incidence and fatality rate of COVID-19 in men.

In a large cohort of individuals without a history of heart failure but with established cardiovascular disorders ($n = 1864$) or cardiovascular risk factors ($n = 2144$), Zimmermann *et al*[44] conducted a research to evaluate the *in vivo* correlation of ACE inhibitor and ARB treatment with cACE2. The authors noted that the mean cACE2 levels in 1250 patients on ACE inhibitors and those who were not (mean 5.98, $P = 0.54$) were the same. Similarly, cACE2 levels were comparable in 1260 ARB-treated patients (mean 5.99 *vs* 5.98, $P = 0.50$). The mean circulating ACE2 value in 2474 patients using ACE inhibitors or ARB (mean 5.99) and that in the control group (mean 5.98, $P = 0.31$) were similar. A multivariable quartile regression model found no correlation between cACE2 values and ACE inhibitor or ARB therapy. BMI was the only variable that positively correlated with cACE2 levels [impact 0.015, 95% confidence interval (CI): 0.002 to 0.028, $P = 0.024$]. The investigators concluded that a sizable cohort of people with established CVD or cardiovascular risk factors but without heart failure were not associated with greater cACE2 levels while taking ACE inhibitors or ARB medicines.

The angiotensin system is important in both kidney and cardiovascular physiology. ACE2 is also expressed in kidney tubules, which could explain why COVID-19 infection is associated with a high risk of acute kidney injury. Schmidt *et al*'s prospective cohort analysis of individuals who had native kidney biopsy examined cACE2 levels in the Boston Kidney Biopsy Cohort[45]. ACE2 levels in the blood were tested in 551 people with glomerulonephritis (30%), non-proliferative glomerulopathy (18%), vascular disease (10%), diabetic nephropathy (12%), and other diagnoses (30%). They discovered that cACE2 levels were significantly higher in men, diabetics, and those with lower eGFR. Furthermore, they noticed no significant relationship between the use of ACE-Is/ARBs and cACE2 levels. In a study of 239 patients with kidney disease, Roberts *et al*[46] assessed cACE2 activity and its clinical associations. The authors discovered that in CKD ($n = 59$), the median (interquartile range) of cACE2 activity was 15.9 pmol/mL (8.4-26.1) in CKD patients ($n = 59$), 9.2 pmol/mL (3.9-18.2) in hemodialysis patients ($n = 100$), and 13.1 pmol/mL (5.7-21.9) in kidney transplant recipients ($n = 80$). Circulating ACE2 activity in male hemodialysis patients was 12.1 pmol/mL (6.8-19.6) compared to 4.4 pmol/mL (2.5-10.3) in females. They concluded that cACE2 activity is lower in hemodialysis patients than in CKD patients, and in female hemodialysis patients than in male hemodialysis patients. The differences in cACE2 activity between male and female hemodialysis patients imply that cACE2 activity may have a different role in CVD depending on gender.

Emilsson *et al*[47] studied the associations of cACE2 levels in 5457 elderly patients with hypertension, T2D, obesity, CHD, or COPD from the Age, Gene, and Environment Susceptibility Reykjavik Study (AGES-RS). They observed that those who were overweight or obese had greater cACE2 levels than people who were lean (BMI = 25). Circulating ACE2 was also higher in adults with severe obesity, but this did not achieve significance, possibly due to the small number of people with severe obesity in this cohort. Increased cACE2 was shown in the violin plots in response to increasing adiposity, as indicated by different BMI groups. Individuals with impaired fasting glucose levels, as well as those with established T2D, exhibited greater cACE2 levels than those without T2D or with normal glucose levels. Current smokers had significantly higher cACE2 levels than non-smokers. On the other hand, cACE2 concentration was not associated with age, eGFR, COPD, hypertension, or CHD.

Elemam *et al*[48] studied the levels of cACE2 and the upstreaming of miRNA in 50 T2DM patients compared to 50 healthy controls who were age, gender, and BMI matched. The T2DM patients in the trial did not have hypertension and did not use any sort of ACE medication, including ARBs. They discovered that cACE2 levels were greater in obese healthy controls, but there were substantial increases in cACE2 levels in overweight and obese diabetes patients. In healthy controls, males had greater cACE2 levels than females, but diabetes patients had the opposite tendency.

CIRCULATING ACE2 IN COVID-19 PATIENTS

Kragstrup *et al*[49] investigated the correlations between cACE2 and outcome in 306 COVID-19 patients

vs 78 COVID-19 negative patients. They observed that increased admission cACE2 was associated with higher maximal disease severity within 28 d in COVID-19 patients (odds ratio = 1.8, 95% CI: 1.4-2.3, $P < 0.01$). When compared to patients without hypertension, COVID-19 patients with hypertension had a significantly higher concentration of cACE2 ($P < 0.01$). Additionally, it was significantly higher in COVID-19 patients with pre-existing renal and cardiac conditions compared to patients without these conditions ($P = 0.03$ and $P = 0.03$, respectively). They concluded that assessing cACE2 might be useful in predicting COVID-19 results. Additionally, there may be a connection between the severity of the COVID-19 result and its noted risk factors, such as hypertension, a history of heart disease, or a history of kidney disorder (Table 1).

In their investigation, Reindl-Schwaighofer *et al*[50] compared cACE2 levels in 94 non-severe and 32 severe COVID-19 patients to 27 influenza patients. The results demonstrated that cACE2 levels in COVID-19 patients rose with time, particularly in those who were severe, where they peaked at 15.1 ng/mL in the late time period (days 9-11), compared to 3.2 ng/mL in non-severe patients ($P < 0.001$). In addition, they noticed that early Ang II level in patients with severe COVID-19 was substantially greater than that of patients with non-severe COVID-19 (165.7 vs 47.7 pmol/L; $P < 0.01$), but that these levels afterwards fell in both groups. Ang-(1-7) concentrations in individuals with severe COVID-19 rose concurrently, rising from 10.8 pmol/L (early) to 49.8 pmol/L (late). In those with severe COVID-19, the Ang-1-7/Ang II ratio rose from 7% (early) to 31% (late), indicating an increase in the generation of Ang-(1-7) from Ang II. They detected no statistically significant increase in alternative RAAS metabolites in those with non-severe COVID-19. Although cACE2 was significantly lower in COVID-19 patients than in influenza patients, it followed a similar time-dependent pattern, with higher values found in samples taken at later time points after intubation (2.4 ng/mL and 5.3 ng/mL, respectively, for the days 0-3 time interval and after day 5; $P < 0.05$). They noticed that in cases with severe COVID-19, cACE2 levels rose to the degree where they may directly influence systemic Ang levels, tipping the RAAS in the other direction. Thus, the rise in cACE2 activity in severe COVID-19 may be a sign of a pathogenic, inflammatory process intended to counteract an Ang II excess.

Osman *et al*[51] compared cACE2 levels in 30 COVID-19 patients with extended viral shedding to 14 COVID-19 patients with short viral shedding and 15 healthy control participants in a prospective cohort study. They discovered that cACE2 level in the protracted viral shedders was significantly lower than that in the healthy volunteer group (19396 pg/mL vs 22600 pg/mL; $P = 0.015$) but not statistically different than in the short viral shedders (22141 pg/mL, $P = 0.153$). Additionally, they noticed that COVID-19 patients had plasma Ang I and Ang II concentrations that were much greater than those of healthy individuals. It means that ACE2 expression was decreased in COVID-19 patients while Ang II plasma concentrations rose, suggesting a major risk of hypertension. They discovered that the expression of ACE2 mRNA and cell-surface ACE2 decreases during COVID-19 and that COVID-19 types with extended viral shedders are related to low cACE2 concentrations. As a result, ACE2 no longer breaks down Ang II, raising plasma concentrations. The plasma concentrations of Ang-(1-7) in COVID-19 patients, however, are unaffected by this and continue to be steady. This shows that Ang-(1-7) is created by Ang I metabolism, most likely *via* neprilysin and/or thimet oligopeptidase, when the ACE2 route is ineffective or absent. This strategy ought to be advantageous given that COVID-19 patients have high plasma levels of Ang I.

In a retrospective study that was conducted by Gerard *et al*[52], in order to assess the expression of alveolar epithelial type II cells (AT2) and endothelial cells, 15 COVID-19 patients with acute respiratory distress syndrome (ARDS), 13 non-COVID-19 patients with ARDS, and 15 control patients with solitary lung tumors were studied. Additionally, 84 severe COVID-19 patients, 24 ARDS patients who had no COVID-19, and 18 control subjects participated in a prospective experiment to measure the levels of cACE and ACE2. They found a substantial change in the expression of ACEs from ACE to ACE2 in the lungs and serum of ARDS patients, suggesting that this clinical attribute is a feature of the general response of the lungs to acute damage rather than a particular feature of severe COVID-19. On the other hand, a decrease in AT2 cells may help distinguish between ARDS caused by COVID-19 and ARDS unrelated to COVID-19, the latter of which may have an increased cell death mechanism brought on by SARS-CoV-2. Particular consideration should be given to how decreased AT2 cell numbers may affect the likelihood of developing pulmonary fibrosis. They concluded that ACE2 levels in lung tissue and serum are higher in both COVID-19-related and unrelated ARDS, but AT2 cell loss is only detected in COVID-19-related ARDS.

Fagyas *et al*[53] examined characteristics that indicate COVID-19 severity in 128 non-severe COVID-19 patients and 60 severe COVID-19 patients, concentrating on RAAS-components and variance in the genes encoding for ACE2 and transmembrane protease, serine 2 (TMPRSS2) genes. They observed that in an ethnically diverse group, a lower aldosterone/renin ratio is related to COVID-19 severity. This happened whether or not ACEi/ARBs, diuretics, or steroids were used. In addition, they confirmed that individuals with severe COVID-19 were older, were more likely to have diabetes, and had higher cACE2 levels. The TMPRSS2 rs2070788 AA genotype was also shown to have an independent protective effect as a severity determinant, which is likely reflective of participation of the protease in coronavirus entry given that this genotype is associated with low TMPRSS2 expression. Additionally, renin was correlated to aldosterone in non-severe COVID-19 patients who were not using RAAS inhibitors. The fact that Ang II promotes aldosterone production and release is shown in this connection. Notably,

Table 1 Circulating angiotensin converting enzyme 2 in coronavirus disease 2019 patients

Ref.	Country	Study design	No. of Participants COVID-19 +ve/ COVID-19-ve	Association with disease severity	Conclusion
Kragstrup <i>et al</i> [49]	Denmark	Longitudinal	306/78	Yes	High admission cACE2 was associated with increased maximal disease severity within 28 d in COVID-19 participants
Reindl-Schwaighofer <i>et al</i> [50]	Austria	Retrospective cohort	126/27	Yes	When compared to non-severe patients, cACE2 in COVID-19 patients increased throughout time, peaking at 15.1 ng/mL in the late time period (days 9-11), notably in the more severe patients
Osman <i>et al</i> [51]	France	Prospective cohort	44/15	Yes	cACE2 levels were not statistically different in the short viral shedders (22141 pg/mL), but they were considerably lower in the prolonged viral shedders (19396 pg/mL) than in the healthy volunteer group (22600 pg/mL)
Gerard <i>et al</i> [52]	Belgium	Retrospective and prospective	15/28 (Retrospective); 84/42 (Prospective)	Yes	In contrast to patients with ARDS who do not have COVID-19 and control subjects, ACE2 is raised in lung tissue and blood from both COVID-19-related and unrelated ARDS, but AT2 cell loss is only observed in COVID-19-related ARDS
Fagyas <i>et al</i> [53]	Hungary	Retrospective cohort	188/0	N/A	Severe COVID-19 is distinguished by a decreased proportion of the <i>TMPRSS2</i> rs2070788 AA genotype, increased renin and cACE2, lower aldosterone levels, an aldosterone/renin ratio, and lower aldosterone levels
Lundström <i>et al</i> [54]	Sweden	Retrospective cohort	114/10	Yes	COVID-19 patients had greater levels of cACE2 than healthy controls (median 5.0 (2.8-11.8) ng/mL <i>vs</i> 1.4 (1.1-1.6) ng/mL). cACE2 levels were greater in males than in females, but were unaffected by other risk factors for severe COVID-19
Maza <i>et al</i> [55]	Spain	Retrospective	147/30	Yes	cACE2 levels were considerably greater in infected individuals who had cutaneous symptoms rather than respiratory symptoms, and cACE2 levels were similarly higher in patients with milder symptoms
Elrayess <i>et al</i> [56]	Qatar	Cross-sectional	200/0	N/A	Patients with severe COVID-19 condition had greater levels of cACE2 than those with mild or moderate disease. There is a link between cACE2 levels and length of hospital stay
Elemam <i>et al</i> [57]	United Arab Emirates	Retrospective cohort	59/60	Yes	In COVID-19 patients, cACE2 and its regulatory miRNAs were shown to be increased and associated to laboratory results, suggesting their clinical use as biomarkers for SARS-CoV-2 infection
Zhang <i>et al</i> [58]	China	Prospective cohort	245/404	Yes	The use of hypoglycemic drugs was associated with significantly lower cACE2 concentrations in COVID-19 diabetics with chronic disease (2973.83 ± 2196.79 pg/mL) than in control patients (4308.21 ± 2352.42 pg/mL)
Silva <i>et al</i> [60]	Argentina	Prospective cohort	93/40	Yes	Hospitalized COVID-19 patients showed lower circulating Ang-(1-7) and Ang II levels, as well as increased cACE2 enzymatic activity and protein levels, with no difference between normotensive and hypertensive COVID-19 patients
Daniell <i>et al</i> [61]	United States	Retrospective	59/27	Yes	COVID-19 patient plasma had significantly lower cACE2 activity than controls. Regardless of patient age, demographic variations, or comorbidity, nadir cACE2 activity in early hospitalization was regained after disease recovery
Mariappan <i>et al</i> [62]	India	Prospective cohort	42/10	Yes	When compared to healthy controls, SARS-CoV-2 infected patients showed noticeably greater cACE2 at the time of admission. In addition, in severe cases compared to moderate cases of infection, there was a significant increase in cACE2. Cases with both diabetes and hypertension had significant increases in cACE2

Ang-(1-7); Angiotensin-(1-7); Ang II; Angiotensin II; ARDS: Acute respiratory distress syndrome; cACE2; Circulating angiotensin converting enzyme 2; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

neither non-severe COVID-19 patients using RAAS inhibitors nor severe COVID-19 patients taking these drugs had this missing. Surprisingly, among individuals with severe COVID-19 who did not use RAAS inhibitors, there was no evidence of a substantial relationship between renin and aldosterone. They concluded that severe COVID-19 is characterized by a decreased incidence of the *TMPRSS2* rs2070788 AA genotype, higher renin and cACE2, lower aldosterone levels, an aldosterone/renin ratio,

and lowered levels of aldosterone. These variables, along with age, produced a C-index for predicting disease severity of 0.79. This proved that a condition akin to RAAS obstruction was brought on by the illness itself. In COVID-19 patients, decreased pulmonary ACE because of lung injury is a potential factor. Establishing a cut-off number for the aldosterone/renin ratio might aid in identifying COVID-19 individuals at risk.

Lundström *et al*[54] conducted a study to measure cACE2 levels in 114 hospitalized COVID-19 patients compared to 10 healthy controls. They discovered that COVID-19 patients had greater levels of cACE2 than healthy controls (median 5.0 (2.8-11.8) ng/mL *vs* 1.4 (1.1-1.6) ng/mL, $P < 0.01$). cACE2 levels were greater in males than in females, but were unaffected by other risk factors for severe COVID-19. After 4 mo, cACE2 was reduced to 2.3 (1.6-3.9) ng/mL ($P < 0.01$) but remained higher than that in healthy controls ($P = 0.012$). However, the cACE level in COVID-19 was slightly lower than that at the 4 mo follow-up (57 (45-70) ng/mL *vs* 72 (52-87) ng/mL, $P = 0.008$). cACE and cACE2 levels did not differ according to survival or disease severity. They concluded that cACE2 levels in COVID-19 were transiently raised, most likely due to enhanced shedding from infected cells. cACE and cACE2 exhibited varying associations with markers of inflammation and endothelial dysfunction during COVID-19, indicating release from various cell types and/or vascular beds.

In a retrospective study, Maza *et al*[55] looked at plasma concentrations of ACE2, Ang II, and anti-spike antibodies in several groups of persons who were at high risk of virus exposure: Heavily exposed but uninfected people, high-risk healthcare professionals, people living with infected close relatives, and seropositive patients with symptoms. They discovered that highly exposed but uninfected subjects had significantly higher cACE2. Furthermore, sera from these seronegative people had a better capacity in cellular experiments to neutralize SARS-CoV-2 infection than sera from non-exposed individuals. Interestingly, they found that cACE2 levels were considerably greater in infected individuals who experienced cutaneous symptoms rather than respiratory symptoms, and cACE2 was also higher in those with milder symptoms. They came to the realization that cACE2 might be utilized as a biomarker to distinguish various COVID-19 disease subtypes and predict the probability of getting SARS-CoV-2.

Elrayess *et al*[56] compared the severity of the disease, the level of circulating ACE2, and the amount of circulating Ang II in 200 COVID-19 hypertensive patients receiving treatment with ACEi, ARBs, beta-blockers (BBs), and calcium channel blockers (CCBs). In this study, it was discovered that 57 patients took ACEi, 68 took ARBs, 15 took BBs, 30 took CCBs, and 30 had no data for anti-hypertensive drugs. The clinical presentation was mild in 76 COVID-19 patients, moderate in 76, and severe in 52. In COVID-19 patients with severe disease, cACE2 level was higher than that in patients with mild or moderate disease. cACE2 levels and hospital stay duration were correlated ($r = 0.3$, $P = 0.003$). With the increase in severity, angiotensin II levels decreased ($P = 0.04$) but CRP and D-dimer levels rose in response to higher cACE2 levels. Low levels of troponin, D-dimer, and CRP were correlated with elevated levels of Ang II. Patients taking an ARB experience an increase in cACE2 levels as their disease progresses ($P = 0.01$), while those taking ACEi experience a decrease in cACE2 levels as their disease progresses. Patients treated with BBs had the mildest disease symptoms. They determined that cACE2 and Ang II levels varied in COVID-19 patients who were using different antihypertensive medicines and had diverse degrees of disease severity. COVID-19 severity rises with increasing cACE2 levels and falls with increasing Ang II levels, demonstrating that BB therapy lowers severity regardless of cACE2 or Ang II levels.

Elemam *et al*[57] looked at the serum concentration of cACE2 and four miRNAs (miR-421, miR-3909, miR-212-5p, and miR-4677-3p) in 59 COVID-19 patients and 60 healthy controls and compared them to clinicopathological characteristics. They discovered that regardless of gender, diabetes status, or obesity, cACE2 levels were elevated in COVID-19 patients. Furthermore, the four miRNAs investigated were elevated in COVID-19 patients and associated favorably with one another. Additionally, miR-421, miR-3909, and miR-4677-3p were all shown to be associated with cACE2, demonstrating a significant relationship between these markers. Notably, miR-212-5p was preferentially increased in moderate, male, and non-obese COVID-19 patients. Interestingly, miR-212-5p was linked to D-dimer, whilst cACE2 was linked to coagulation tests including aPTT and platelets, indicating their potential as COVID-19 coagulopathy markers. Interestingly, there was a strong relationship between cACE2 and C-reactive protein in diabetic COVID-19 patients, indicating that this measure may have a role in the inflammatory state of these patients. They concluded that cACE2 and its regulatory miRNAs were higher in COVID-19 patients and were associated with laboratory results, suggesting their clinical utility as biomarkers in SARS-CoV-2 infection.

Zhang *et al*[58] performed a study to assess the relationship between 245 diabetics and 404 patients with concurrent chronic diseases who were not infected with SARS-CoV-2 for the high risk of severe SARS-CoV-2 infection. They discovered that plasma concentrations of cACE2 in diabetics with chronic illness were substantially lower (2973.83 ± 2196.79 pg/mL) than in control patients (4308.21 ± 2352.42 pg/mL), and that the use of hypoglycemic medications was related to lower cACE2 levels ($P < 0.05$). Diabetics with decreased cACE2 plasma levels may be more vulnerable to severe COVID-19. They found that low cACE2 levels may be to blame for the poor prognosis in diabetic individuals infected with SARS-CoV-2. Rieder *et al*[59] compared the serum concentrations of cACE2, Ang II, and aldosterone in 24 COVID-19 patients to 61 control patients who had similar symptoms and came to the emergency room. They discovered that baseline features, symptoms, and clinical presentation did not

differ between SARS-CoV-2 positive patients and control people. The SARS-CoV-2 positive and control groups had the same mean serum concentrations of cACE2, Ang II, and aldosterone. They concluded that COVID-19 subjects did not exhibit altered RAAS activity, including altered levels of Ang II, aldosterone, potassium, or blood pressure.

In 93 hospitalized COVID-19 patients and 40 healthy people, the levels of plasmatic cACE2 protein, ACE2 enzymatic activity, Ang II, and Ang-(17) were compared by Silva *et al*[60]. They also compared the parameters of COVID-19 between normotensive and hypertensive subjects. When compared to healthy participants, COVID-19 patients had considerably greater cACE2 enzymatic activity and protein levels. When non-hypertensive healthy participants were compared to non-hypertensive COVID-19 patients, cACE2 enzymatic activity and protein levels were still greater in the COVID-19 group. However, within the COVID-19 group, there was no difference in cACE2 activity or protein levels between normotensive and hypertensive individuals. There was no difference between normotensive and hypertensive COVID-19 patients in terms of circulating Ang-(17) and Ang II levels, cACE2 enzymatic activity, or protein levels in hospitalized COVID-19 patients. The greater baseline ACE2 expression in these patients' plasma membranes and therefore a higher susceptibility to infection are suggested by the enhanced cACE2 levels, which may be caused by increased ACE2 expression, increased ACE2 shedding, or both.

Daniell *et al*[61] looked at the levels of cACE2 and cAng-(1-7) in plasma as well as the levels of mACE2 in lung autopsy samples from 27 non-COVID-19 volunteers and 80 hospitalized COVID-19 patients. They discovered that cACE2 activity was significantly lower in COVID-19 plasma ($n = 59$) than in controls ($n = 27$) ($P < 0.01$). Regardless of patient age, demographic characteristics, or comorbidity, cACE2 activity in early hospitalization was regained following disease recovery; restoration was statistically higher in convalescent plasma administered patients ($n = 45$) than in matched controls ($n = 22$, $P = 0.002$). cACE2 activity was likewise significantly lower in COVID-19 patients' saliva than in controls ($P = 0.006$). In participants' plasma, there was a substantial negative association between cACE2 concentration, cACE2 activity, and Ang (1-7) levels. In the lungs of autopsy tissues, membrane ACE2 levels did not differ between COVID-19 ($n = 800$) and other circumstances ($n = 300$). These clinical findings point to cACE2 activity as a possible COVID-19 biomarker and treatment target.

A study by Mariappan *et al*[62] examined the levels of cACE2 in 42 COVID-19 patients and 10 healthy controls during the early stages of infection. They discovered that SARS-CoV-2 patients had significantly higher cACE2 at the time of admission as compared to healthy controls. Additionally, they discovered a substantial rise in cACE2 during the course of infection in severe cases compared to mild cases ($P < 0.01$). Cases with diabetes mellitus and hypertension showed a substantial rise in cACE2. It is interesting to note that there is a significant positive association between cACE2 and D-dimer ($P < 0.01$). They concluded that the severe form of SARS-CoV-2 frequently exhibits increased ACE2 shedding during the early phase. The levels of cACE2 may act as a clinical biomarker for illness outcome along with D-dimer. However, further research is required to determine its function in host-virus interaction.

DISCUSSION

By interacting with the membrane-bound ACE2 and the virus spike protein, for the fusion and endocytosis of SARS-CoV-2 into the pulmonary endothelium, ACE2 serves as a receptor[63]. The protease ADAM17 sheds ACE2 onto the surface of endothelial cells[20]. The identification and validation of new blood-based biomarkers for COVID-19 are regarded as crucial due to the importance of early diagnosis and efficient clinical monitoring in preventing serious effects or death. cACE2 levels in the blood are typically modest, but they increase in several CVDs such as hypertension, aortic stenosis, heart failure, and atrial fibrillation[34,35,37,40,41]. When COVID-19 patients were compared to healthy controls, cACE2 was shown to be considerably elevated. These results suggest that high cACE2 levels at rest may increase the likelihood of severe COVID-19 infection, and SARS-CoV-2 infection can further increase ACE2 activity. Despite these findings, current research on cACE2 levels and activity in several cohorts of COVID-19 patients has generated controversy. These studies range from very high or high[49,50,52,54,55,57,62] to unaltered or even decreased cACE2 levels[51,58,60] compared to controls. The effect of age and gender on cACE2 was explored, and there was a trend for cACE2 levels to rise with age. Male patients had greater baseline cACE2 levels than females in the whole research cohorts, predominately in the seriously ill group[64]. We propose that at least two consequences result from SARS-CoV-2 binding to membrane ACE2. First, it downregulates membrane ACE2, leading to a localized RAAS that is dysregulated and favors inflammation and persistent tissue damage as a result of too much Ang II. Second, the prolonged release of the catalytically active site of ACE2 into the circulation is linked to the dysregulated local RAAS.

In addition to the initial multisystem symptoms of COVID-19, some patients also have long-lasting illness, or "long-COVID," whose characteristics have not yet been completely elucidated. It is now necessary to conduct larger studies to ascertain if consistently elevated cACE2 levels can help identify those who are at a higher risk of developing a chronic disease or experiencing cardiac events after SARS-CoV-2 infection. Interesting investigations showed that recombinant human cACE2 efficiently

inhibited SARS-CoV-2 infection[65,66]. Recombinant cACE2 protein was demonstrated to offer therapeutic promise for treating SARS-CoV-2 infection, but it was cleared from blood circulation quickly and had a short half-life. It has been suggested that soluble proteins can increase their *in vivo* efficacy by increasing their plasma residence time and immunoreactive activities when fused with the immunoglobulin (Ig) constant domain Fc (fragment crystallizable) fragment. A few investigations revealed that the human ACE2-recombinant protein (ACE2-Ig), in which ACE2 was fused with the human IgG1 Fc region, exhibited a high affinity to bind to the RBD of the SARS-CoV-2 virus and thereby exerted a desirable pharmacological characteristic. While membrane-bound ACE2 may facilitate SARS-CoV-2 cell entrance, a genetically modified soluble isoform of ACE2 (hrsACE2), which competes with membrane-bound ACE2, may inhibit SARS-CoV-2 cell entry. As a result, it may reduce SARS-CoV-2 cell entry, reducing lung damage and organ dysfunction. Additionally, hrsACE2 injection effectively neutralized both SARS-CoV and SARS-CoV-2. The SARS-CoV-2 copy counts in COVID-19 patients fell dramatically from 32000 copies/mL 2 d before the injection of hrsACE2 to 2500 and 270 copies/mL after the first and second days of therapy, respectively. The patient's plasma also rapidly cleared the virus during everyday checking till the finish of the duration of the study[67]. In addition to lowering the viral load, ACE2-IgG may significantly contribute to delaying or stopping the systemic transmission of the virus [68,69].

CONCLUSION

Circulating ACE2 proteins capable of binding SARS-CoV-2 are thus an intriguing possibility for preventing viral particle attachment to surface-bound full-length ACE2, a step required for cell entrance and infection. Almost all investigations into cACE2 in COVID-19 patients found it to be high or extremely high, and it was linked to disease severity. Furthermore, recombinant cACE2 protein has shown therapeutic potential in the treatment of SARS-CoV-2 infection. As a result, combining recombinant cACE2 with other medications may be more effective in preventing SARS-CoV-2 infection.

FOOTNOTES

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