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Increased complications of COVID-19 in people with cardiovascular disease: Role of the renin–angiotensin–aldosterone system (RAAS) dysregulation

Robin Augustine^{a,b,*}, Abhilash S^c, Ajisha Nayeem^d, Shaheen Abdul Salam^e, Priya Augustine^f, Pan Dan^{g,h}, Pablo Moreira^g, Fatima Mraicheⁱ, Carmine Gentile^{j,k,l}, Philip M. Hansbro^{m,n}, Lana McClementsⁿ, Anwarul Hasan^{a,b,**}

^a Department of Mechanical and Industrial Engineering, College of Engineering, Qatar University, 2713, Doha, Qatar

^b Biomedical Research Center (BRC), Qatar University, PO Box 2713, Doha, Qatar

^c Department of Microbiology, Majlis Arts and Science College, Puramannur, Malappuram, Kerala, 676552, India

^d Department of Biotechnology, St. Mary's College, Thrissur, 680020, Kerala, India

^e Department of Biosciences, MES College Marampally, Aluva, Ernakulam, 683107, Kerala, India

^f Department of Zoology, Kongunadu Arts and Science College, Coimbatore, Tamil Nadu, 641029, India

^g Department of Cardiovascular and Transplantation Surgery, Regional Central Hospital of Nancy, Lorraine University, France

^h Department of Thoracic and Cardiovascular Surgery, Zhongnan Hospital of Wuhan University, Wuhan, 430071, China

ⁱ College of Pharmacy, QU-Health, Qatar University, PO Box 2713, Doha, Qatar

^j School of Biomedical Engineering, Faculty of Engineering and IT, University of Technology Sydney, NSW, Australia

^k School of Medicine, Faculty of Medicine and Health, University of Sydney, NSW, Australia

^l Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

^m Centre for Inflammation, Centenary Institute and University of Technology Sydney, NSW, Australia

ⁿ School of Life Sciences, Faculty of Science, University of Technology Sydney, NSW, Australia

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ABSTRACT

The rapid spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19), has had a dramatic negative impact on public health and economies worldwide. Recent studies on COVID-19 complications and mortality rates suggest that there is a higher prevalence in cardiovascular diseases (CVD) patients. Past investigations on the associations between pre-existing CVDs and susceptibility to coronavirus infections including SARS-CoV and the Middle East Respiratory Syndrome coronavirus (MERS-CoV), have demonstrated similar results. However, the underlying mechanisms are poorly understood. This has impeded adequate risk stratification and treatment strategies for CVD patients with SARS-CoV-2 infections. Generally, dysregulation of the expression of angiotensin-converting enzyme (ACE) and the counter regulator, angiotensin-converting enzyme 2 (ACE2) is a hallmark of cardiovascular risk and CVD. ACE2 is the main host receptor for SARS-CoV-2. Although further studies are required, dysfunction of ACE2 after virus binding and dysregulation of the renin-angiotensin-aldosterone system (RAAS) signaling may worsen the outcomes of people affected by COVID-19 and with preexisting CVD. Here, we review the current knowledge and outline the gaps related to the relationship between CVD and COVID-19 with a focus on the RAAS. Improved understanding of the mechanisms regulating viral entry and the role of RAAS may direct future research with the potential to improve the prevention and management of COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is

responsible for coronavirus disease 19 (COVID-19) and its emergence as a pandemic. SARS-CoV-2 infection has a notably higher prevalence in patients with underlying cardiovascular disease (CVD) and/or diabetes,

* Corresponding author. Department of Mechanical and Industrial Engineering, College of Engineering, Qatar University, 2713, Doha, Qatar.

** Corresponding author. Department of Mechanical and Industrial Engineering, College of Engineering, Qatar University, 2713, Doha, Qatar.

E-mail addresses: robin.augustine@qu.edu.qa (R. Augustine), ahasan@qu.edu.qa (A. Hasan).

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which represents a huge challenge for healthcare professionals worldwide [1]. Understanding the mechanisms of the association between CVD and increased SARS-CoV-2 susceptibility, as well as the development of COVID-19 disease, is therefore critical to better manage patients and prevent complications and death. SARS-CoV-2 is a beta coronavirus and it belongs to the *Coronaviridae* family that includes SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) [2,3]. The lungs have been identified as the main target organ of SARS-CoV-2 infections and in humans, the most common complication of COVID-19 disease is pneumonia [4]. Patients who have an underlying compromised immune function, including those with chronic diseases such as chronic obstructive pulmonary disease (COPD) and the elderly, are likely to develop more severe forms of COVID-19 requiring hospitalization and thus have a higher incidence of mortality [5].

It is well documented that coronaviruses present in the vast majority of individuals as a common cold with mild symptoms [6,7]. A small percentage of such infections progress to develop severe disease, including SARS [8], MERS [9] and currently COVID-19 [10] that require hospitalization. SARS-CoV and MERS-CoV, the causal viruses for SARS and MERS diseases, respectively, are both zoonotic in origin similar to SARS-CoV-2 and follow similar etiologies with the potential to cause global epidemics [11]. The main tissue targets of SARS-CoV are the lungs, immune system, and small blood vessels. Damage to these tissues can lead to complications including pneumonia, lymphopenia, coagulopathy, disseminated intravascular coagulation (DIC), myositis, and renal or liver damage [12–20]. The clinical manifestations of SARS-CoV in the cardiovascular system include local fibrinoid necrosis, and infiltration of monocytes plasma cells (B cells) and other lymphocytes into blood vessel walls. These can lead to the development of vasculitis in the heart, lungs, liver, kidneys, adrenal gland, and the stroma of striated muscles as well as blood clot formation in small veins [14]. SARS can also damage capillary endothelial cells [14] and many critically ill patients present with stroke or venous thrombosis [21]. Several independent studies indicate that underlying CVD is a risk factor associated with complications and increased mortality in SARS patients [13,22–30] (Table 1).

Similarly, evidence also shows that the severity of MERS-CoV infection is higher in patients with underlying CVDs [31–34] (Table 1). Amongst the different types of coronavirus infections, cardiovascular comorbidities as well as mortality are most prevalent in MERS patients [35], compared to SARS-CoV and SARS-CoV-2 infected patients [36]. The most common cardiovascular complications in MERS

patients include pericarditis [31], cardiac arrhythmias [37] and acute myocarditis [38]. Myocardial injury can affect the normal rhythm of the heart and cause cardiac arrhythmia similarly to what has been observed in MERS-CoV patients [39,40].

Evidence of the impact of SARS and MERS coronaviruses in individuals with CVD and CVD risk factors suggest that these comorbidities increase susceptibility to coronaviruses and associated complications, however further mechanistic studies are needed to improve risk stratification and management of these individuals.

An initial study of 5000 COVID-19 patients indicated that pre-existing diseases such as CVDs, cancers, or diabetes are the main determinants of increased mortality (Fig. 1) [65]. This study demonstrated that individuals with SARS-CoV-2 and without pre-existing conditions had <1% mortality. However, this increased to 10% in COVID-19 patients with some form of heart disease. In addition, the presence of hypertension alone in infected patients increased mortality to 6%. Similarly, cardiovascular complications were also exacerbated due to COVID-19 [36]. The potential mechanism of association between increased susceptibility to SARS-CoV-2 infection and CVD has been attributed to increased angiotensin-converting enzyme-2 (ACE2)

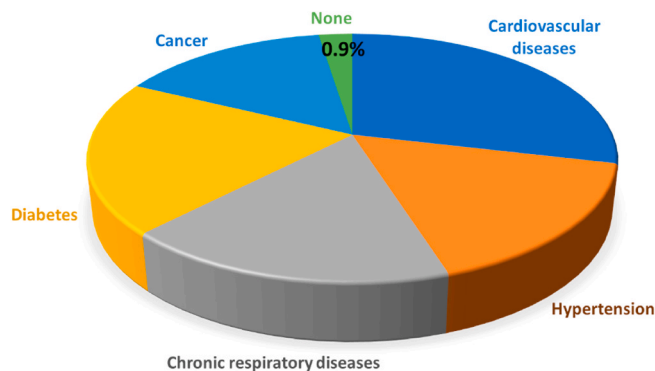


Fig. 1. Mortality incidence of COVID-19 patients with pre-existing diseases. Patients with pre-existing heart diseases had the highest mortality rate of 10%. Diabetes was associated with the second-highest fatality rate of ~7%. Approximately 6% mortality was observed in those with underlying hypertension. Thus, ~16% of mortality of COVID-19 patients was associated with some form of pre-existing CVDs or the risk factors for CVD. Data adapted from the Chinese Center for Disease Control and Prevention [65].

Table 1

Epidemiological data showing the numbers of patients affected, deaths, and clinical characteristics of SARS, MERS and COVID-19 patients with a focus on preexisting CVD or cardiovascular complications.

Epidemiology→	SARS-CoV	MERS-CoV	SARS-CoV-2
Clinical characteristics↓			
Period of outbreak	2002–2004 [22]	2012, 2015, 2018 [31,41]	2019–ongoing
Total confirmed cases	8422 [42,43]	2494 [43,44]	>241 million (As on 17-10-2021) [45]
Total deaths	916 [42,43]	858 [43,44]	>4.9 million (As on 17-10-2021) [45]
Mortality rates (%)	10–12 [46]	35–76 [33,46]	≈3 [45,47]
Age groups most affected (Years)	37–43 [48]	36–65 [33,48]	44–58 [48,49]
ICU admissions (%)	26 [22,50–52]	57 [41,53–55]	32 [56,57]
Mortality among ICU admissions (%)	49 [22,50–52]	60 [41,53–55]	31 [56]
Patients with preexisting CVD (%)	25–30 [58–60]	30–40 [32,61,62]	20–30 [63,64]
Mortality with preexisting CVD (%)	30–40 [36,58–60]	77 (CVD), 81 (HT) [31,32,61,62]	16–37 [65,66]
Preexisting cardiovascular/ Cardiac complications	Hypotension (40–50%), tachycardia (50–60%), bradycardia (10–20%), reversible cardiomegaly (10–15%), and transient atrial fibrillation [58,59]	Acute myocarditis, acute myocardial infarction, and rapid-onset heart failure (~30%), hypertension (~50%) and heart diseases [31,33,41]	Hypertension (15–30%), congestive heart failure (~40%), hyperlipidemia (5%), arrhythmia (3.6%), stroke (2.1%), coronary heart disease (11.2%), and cardiopathy (4.3%), arrhythmias (15–20%), Cardio-cerebrovascular disease (18.79%), myocardial injury (27.8%), ventricular tachycardia/fibrillation (5.9%), acute coagulopathy (34.1%) [48,64,67]

receptor expression particularly in patients taking ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) [68]. Many recent studies show the importance of the ACE2 receptor in mediating SARS-CoV-2 infection. ACE2 is widely expressed in diverse range of species throughout the subphylum *Vertebrata*. However, a couple of recent studies indicate that patients receiving ACEI/ARB therapy are not at increased risk of severe COVID-19 or hospital admission [69,70]. Nevertheless, whether there is an increased or the same expression of ACE2 in CVD or as a result of ACEi or ARBs remains controversial and needs to be explored further. Increased circulating ACE2 levels were also observed in patients after myocardial infarction (MI), which is likely a mechanism that counteracts the activation of the renin-angiotensin-aldosterone system (RAAS) [71,72]. Defining this correlation is critical as ACE2 is the main host receptor for SARS-CoV-2, which binds to it *via* its spike proteins [73,74]. The interaction between virus and its host cell ACE2 receptor is the initial step in promoting virus infection and is a vital determinant of host species range and tissue tropism [75,76]. The envelope protein of SARS-CoV-2 (spike protein, S) are separated into S1 and S2 subunits upon interaction with ACE2 [77]. Even though the S2 subunit does not directly bind with the ACE2 receptor, it keeps the functional components essential for membrane fusion of the virus [78]. The S1 protein/receptor binding is the critical element for the cellular entry of SARS-CoV-2. S1 comprises the receptor binding domain (RBD) that facilitates direct binding to the peptidase domain (PD) of ACE2 to enable entry into host cells [79]. Proteolytic cleavage of the RBD at the C-terminus of the S1 protein is mandatory to commence interaction with the peptidase domain (PD) of the ACE2 receptor [79–81]. Proteolytic cleavage of spike proteins is followed by fusion of the virus and host cell membranes. This is followed by the development of a funnel-like structure constituted by two heptad repeats in the S2 protein in an antiparallel six-helix bundle, thereby catalyzing fusion followed by the delivery of viral genetic material into the cytoplasm.

ACE2 is responsible for metabolizing the key vasoconstrictor, angiotensin II, to angiotensin (1–7). Hence, the ACE2 system acts as a preventive mechanism against MI, hypertension, lung disease, and diabetic complications [82]. Earlier studies suggested that there is a substantial expression of ACE2 receptor within the heart tissue cells including cardiomyocytes [83], cardiac myofibroblasts [84], and endothelial cells [85] and that it has a protective role against cardiac damage [86]. In a murine model of SARS-CoV infection, ACE2 expression was reduced, which led to an increase in angiotensin II levels and hence increased vascular permeability and respiratory complications, which were reversed by treatment with recombinant ACE2 or an ARB (losartan) [87]. A study also indicated that low activity of ACE2 can result in thrombosis in animal models [88]. Therefore, SARS-CoV-2 mediated dysfunction of ACE2 could cause the accumulation of angiotensin II, which eventually deteriorate the capability to counteract the activation of the RAAS pathway leading to the worsening of existing CVD [89].

Increased mortality due to COVID-19 in CVD patients may also be attributed to underlying vascular damage, hypoxia-induced vasoconstriction and heart failure [90]. Furthermore, SARS-CoV-2 infection induces potent pro-inflammatory responses and a cytokine storm that develops within the lungs and expands to the heart causing viral myocarditis and increased troponin levels in the bloodstream that could lead to fatal heart failure [91]. Indeed, inflammation is now well-established as the cause of heart failure [92] particularly as multisystem inflammatory syndrome in children (MIS-C) [93] [–] [102].

A number of reviews have already discussed cardiovascular complications as a result of COVID-19 in CVD patients [90,94,103,104]. Here we provide an up-to-date and critical review of the available literature related to increased prevalence of COVID-19 in CVD patients by focusing on ACE2 mechanisms and subsequent complications and mortality in these patients.

2. Increased risk of COVID-19 and complications in people with cardiovascular risk factors or CVD

COVID-19 is particularly prevalent in patients with pre-existing history of CVD, hypertension, diabetes mellitus, COPD and the elderly [105–108]. COVID-19 severity and mortality rates have been reported more frequently in patients experiencing cardiovascular complications [4,109–114]. The COVID-19 has been reported to increase the risk of cardiogenic shock, arrhythmias, acute myocardial injury, and sometimes sudden death in CVD patients (Table 2 and Fig. 2). Moreover, drug interactions with COVID-19 targeted therapies may predispose patients with underlying CVDs to increased risk of developing cardiomyopathy, arrhythmias, and sudden death [115,116]. The antimalarial medication (i.e. hydroxychloroquine) and the antibiotic (i.e. azithromycin), which have been investigated as potential treatments for COVID-19, can cause serious side effects in people with existing CVDs [117]. Complications include significant irregular electrocardiography measurement indicating the presence of arrhythmia, polymorphic ventricular tachycardia (including Torsade de Pointes) and long QT syndrome, and increased risk of sudden death [117].

Several mechanisms have been described to explain the impact of different coronaviruses on the heart based on studies investigating SARS-CoV and MERS viruses as well as recent reports with SARS-CoV-2 [4,113,118,119]. The cytokine storm caused by increased interleukin (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein 1 A (MIP1A), and tumor necrosis factor α (TNF α) following coronavirus infection can lead to acute increases in left ventricular (LV) dysfunction in patients with underlying CVD or new onset cardiomyopathy due to heart muscle inflammation (myocarditis). Broken heart syndrome or myocardial ischemia have also been reported that can lead to heart failure, increasing the risk of mortality among critical patients [114]. A recently published case study reported the presentation of chest pain and ST-segment elevation in COVID-19 patient without underlying coronary obstruction as well as left ventricular dysfunction and elevated cardiac biomarkers [120].

Severe COVID-19 coupled with cardiac abnormalities is more prevalent in elderly patients as well as in individuals with compromised immune systems [4,105]. Inflammation of the vascular system and cardiac injury seems to occur in 20–30% of hospitalized COVID-19 patients and contributes to 40% of deaths [122]. Although concerns still exist, more concrete evidence is needed for or against the use of ACEIs and ARBs in patients with or without CVD infected with SARS-CoV-2. Currently, the majority of international clinical guidelines do not recommend stopping or adding the RAAS antagonists in COVID19 patients [4]. These agents are known to improve survival in patients with hypertension, ischemic heart disease or heart failure [126]. Cytokine release syndrome (CRS) may result in elevated levels of cytokines and impaired T lymphocyte function with lymphocytopenia in early stages and is substantially increased in the later stages of COVID-19 [127]. This is accompanied with elevated levels of CRP (C-reactive protein), cytokines such as IL-2 and IL-6, and cardiac natriuretic peptides. These factors may lead to cardiac dysfunction or inflammation due to atrial natriuretic factor elevation and high serum ferritin, which may progress to arrhythmias, myocardial dysfunction, heart failure, or stress cardiomyopathy. These conditions can increase the likelihood of death substantially [128,129].

Furthermore, Mehra and Ruschitzka suggested that underlying structural heart diseases can lead to increased risk of heart failure as a result of pulmonary dysfunction [130]. A report from the Chinese National Health Commission, stated that there are cases of hospitalized COVID-19 patients with unknown CVD (~12%), who had increased troponin or symptoms of MI [113]. In a study by Zhou et al., COVID-19 patients developed increased troponin levels during the course of the disease and some patients showed significantly increased levels of

Table 2
Studies investigating the implications of COVID-19 in CVD patients.

Patient sample size	Age	Underlying CVD	CVD complications	Molecular markers studied	Mortality	Reference
N = 187	58.50 (mean age)	66 (35.3%) CVD, 52 (27.8%) – myocardial injury	CHD, cardiomyopathy, myocardial injury, frequent malignant arrhythmias	TnT, NT-proBNP	69.44% (25 of 36)	[121]
N = 416	64 (median age)	Cardiac injury (19.7%)	CHD (10.6%), cerebrovascular disease (5.3%)	hs-TnI, CK-MB, NT-proBNP, MYO	51.2% (42 of 82)	[122]
N = 191	56 (median age)	HT (30%), CHD (8%)	HF, arrhythmia, MI	D-dimer, serum ferritin, IL-6, LDH, hs-cTnI, SOFA	n/a	[123]
N = 273	58 (mean age)	n/a	Heart injury	CK-MB, MYO, Ultra Tn I, NT-proBNP	10.5%	[124]
N = 1	64 (F)	Atrial fibrillation, HT	HF, cardiogenic shock, tachyarrhythmias	Hs-TnT, IL-6, ferritin	n/a	[125]
N = 38,906	59 (median age)	CVD (17%) HT (50%)	n/a	n/a	37% (CVD) 66% (HT)	[66]

CVD=Cardiovascular disease, HT = hypertension, CHD = coronary heart disease, NT-proBNP = N-terminal pro-B-type natriuretic peptide, CK-MB = creatinine kinase myocardial band, IL-6 = interleukin 6, LDH = lactate dehydrogenase, hs-cTnI = high-sensitivity cardiac troponin I, HF = heart failure, MI = myocardial infarction, MYO = myohemoglobin, Ultra Tn I = cardiac troponin I, SOFA = sequential organ failure assessment, hs-TnI = high sensitivity troponin I, n/a = not applicable.

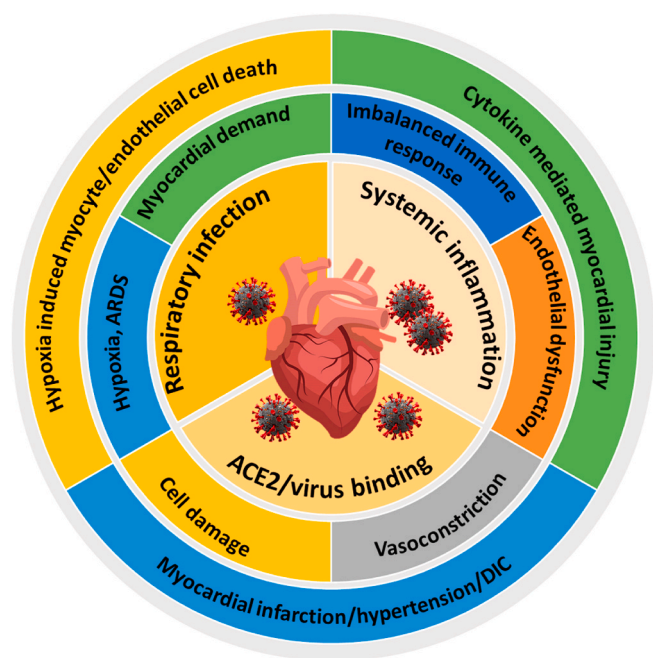


Fig. 2. Major complications associated with SARS-CoV-2 infection in CVD patients. The manifestations of COVID-19 in CVD patients begin soon after the entry of the virus through ACE2 receptor (myocardial cell damage, ACE/ACE2 imbalance) and can result in myocardial infarction, hypertension or DIC. Respiratory infections due to SARS-CoV2 can result in hypoxia, ARDS and higher myocardial demand in CVD patients. These can result in hypoxia-induced cardiomyocyte or endothelial cell death. Further, SARS-CoV2 associated systemic inflammation can result in disrupted immune response, endothelial dysfunction and cytokine mediated myocardial injury.

natriuretic peptides, leading to MI and heart failure (1 in 4 cases), and eventually death [123].

Emerging evidence has implicated coagulation system impairment in severe cases of COVID-19 [131]. These coagulation abnormalities can induce DIC, with fatal consequences in both young and elderly people, mainly due to stroke [132]. Hence, there is potentially a need for the initiation of treatment with anticoagulants and pharmacokinetic monitoring for patients admitted to ICU in order to prevent thrombosis [133]. Coagulopathy is characterised by abnormal levels of thrombocytes ($<50 \times 10^9/L$, thrombocytopenia), prolongation of prothrombin time (PT), extension in activated partial thromboplastin time (aPTT), D-dimer level increase, and low fibrinogen levels ($<1.0 \text{ g/L}$). Significant prolongation of aPTT with extended PT can lead to impaired coagulation in COVID-19

patients that may be due to impaired prothrombin (factor-II) production and the condition, hypoprothrombinaemia. Manifestation of COVID-19-associated coagulopathy involves swelling in the lower extremities, purple rashes, bleeding in and around catheters and clot formation in the brain that can be fatal [134]. Around 20–30% people with severe COVID-19 develop clot formation as demonstrated by two studies from Europe [135,136]. COVID-19 can also cause thrombosis in young people predisposing them to fatal stroke. Nevertheless, treatment with anti-coagulants does not seem to prevent thrombosis in COVID-19 patients, especially in the presence of CVD [137]. In COVID-19 patients, thrombosis may develop due to the binding of the SARS-CoV-2 spike protein to the ACE2 receptor that trigger the clotting process by directly damaging endothelial cells lining of the pulmonary blood vessels [138]. Evidences also suggest that inhibition of ACE2 activity [88] and higher concentration of Ang II [139] can result in thrombus formation. In some COVID-19 patients, immune cells cause inflammation by discharging cytokines and chemokines that can affect coagulation and clotting through various pathways. For instance, activation of the complement system following virus entry can result in thrombosis [140]. Apart from the COVID-19-associated risk in CVD patients, limited mass diagnosis options [141–143] and decreased treatment availability can also have severe consequences. As a result of the pandemic, there have been significant delays globally in elective surgeries, limited availability of ICU beds and ventilation sites, shortage of healthcare workers, restrictions on the numbers of clinical staff on ward rounds, patients developing COVID-19 after cardiac surgery, and COVID-19 patients needing urgent cardiac interventions [144].

3. Cellular and molecular mechanism of coronavirus infection and its association with cardiovascular system

Coronaviruses enter human hosts through the respiratory tract by infecting epithelial cells of the trachea, bronchi, bronchioles and lungs [145,146]. The virus also hijacks resident, infiltrating and circulating immune cells [147] leading to weakening of immune defences, and rapid deterioration of lung function, often manifested as pneumonia. The extent of immune cell damage, measured by the lymphocyte count, reflects the patient’s immune status and is a reliable predictor of disease outcome. In addition, hijacked circulating immune cells are capable of delivering the virus to other organs facilitating further colonisation and organ damage [148]. Coronaviruses can also affect various endocrine and metabolic pathways through the RAAS system within the kidneys and acute β -cell dysfunction within pancreas, respectively [149]. *In vitro* cell culture studies of SARS-CoV-2 infected human colorectal adenocarcinoma cells (Caco-2) showed that the virus causes downregulation of the anti-apoptotic genes (Bcl-2 and A20) and upregulation of the pro-apoptotic genes (Bid, Bad, caspase-2 and caspase-6) [150].

COVID-19 associated complications are likely to occur as a result of: (1) disturbed cell metabolism due to rapid viral replication and a release of a large number of viral particles; (2) intense local vascular reactions; and (3) immune impairment mediated by the SARS-CoV-2 –induced abrogation of cellular immunity and cytokine functions [107].

There are several underlying risk factors and pathogenic pathways (e.g. ACE2) aberrantly activated in CVD patients, which have adverse impacts on the prognosis of COVID-19. ACE2 is a metalloprotease that is abundantly expressed in cardiomyocytes, endothelial cells and cardiac fibroblasts, which comprise the vast majority of the heart tissue [151]. As described above, one of the main functions of ACE2 is to regulate cardiovascular pathophysiology and blood pressure by negatively regulating the RAAS system [20,72,86,152–156]. These functions occur through the enzymatic conversion of Ang II, a vasoconstrictor and inflammation mediator, to Ang-(1–7) that are vasodilation and anti-inflammatory mediators, as part of the RAAS pathway [157]. In addition to its expression in the heart tissue, ACE2 is also present in the lungs, intestine, liver, testis and kidney tissues [158].

Studies show that high expression of ACE2 can be protective against heart failure by abrogating ACE activity and hypertension (Fig. 3) [159, 160]. Upon SARS-CoV-2 infection, this protective effect could be altered due to the impairment of the conversion of Angiotensin I to Angiotensin 1-9 and Angiotensin II to Angiotensin 1-7. Angiotensin 1-9 and Angiotensin 1-7 have important cardioprotective functions including reducing blood pressure. The concentration of circulating ACE2 in patients with heart failure was found to be higher compared to controls [161]. Overexpression of ACE2 to minimize heart damage and subsequent

shedding of membrane-bound ACE2 may be responsible for increased circulating ACE2 levels in patients with heart failure [71]. This could also explain the predisposition to low blood pressure in heart failure patients [162]. In a pre-clinical rat model of MI, an increase in ACE and ACE2 mRNA expression was observed in the viable myocardium of injured rats compared to that of the control rats [163]. It is likely that increased expression of ACE2 is a compensatory mechanism to ameliorate the damage caused by acute cardiac stress [164,165]. Considering that the main binding site for SARS-CoV-2 is the ACE2 receptor, possible increased expression of ACE2 in CVDs is likely linked to increased susceptibility to the infection [73,166].

ACE2 is widely expressed in the lungs and cells of the cardiovascular system and it plays a vital role in the cardio-protective functions of the RAAS pathway [91,168]. The N-terminal portion (S1 domain) of the SARS-CoV-2 spike glycoprotein has high-affinity for binding to ACE2 receptors on the surface of the susceptible cells [169,170]. The spike proteins sit in the viral envelope and project outwards to give a ‘corona’-like appearance to the virus [171]. Direct evidence of ACE2 as the entry point of SARS-CoV was provided by Li et al., who isolated ACE2 from SARS-CoV-permissive Vero-E6 cells and showed attachment to the S1 domain of the SARS-CoV spike protein [170]. Also highly abundant ACE2 expression on endothelial and smooth muscle cells indicates that once SARS-CoV-2 enters the respiratory system, it can easily spread throughout the body [20]. Murine models and human autopsy samples revealed that SARS-CoV pulmonary infection downregulates ACE2 expression in both myocardial cells and type 2 alveolar epithelial cells/pneumocytes, causing inflammatory responses and respiratory

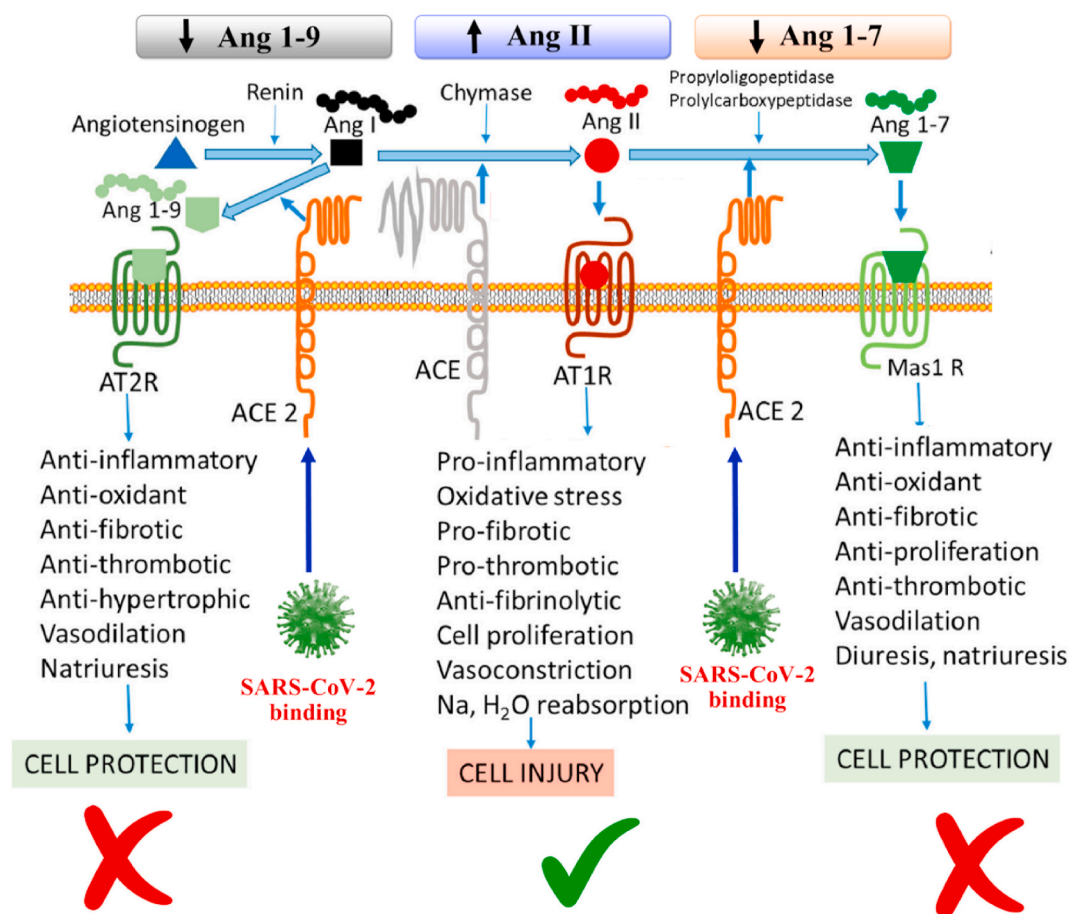


Fig. 3. Links between SARS-CoV-2 infection and highly abundant Angiotensin II leading to various pathogenic downstream effects. Binding of SARS-CoV-2 to the ACE2 receptor on the cell surface decreases ACE2 abundance and increases the level of Angiotensin II whilst reducing Ang 1–9 and Ang 1–7. This can lead to inflammation, oxidative stress, fibrosis, thrombosis, cell proliferation, salt and water retention and vasoconstriction, hence inducing cell injury. Adapted from Ref. [167] with the permission of Elsevier.

distress [20,156], further indicating the association between SARS-CoV and ACE2 within the cardiovascular system. In addition to the increased susceptibility of CVD patients to SARS-CoV infections, CVD medications including aspirin, statins, beta-blockers, and ACEIs/ARBs could also contribute to this effect [119,172,173]. Several experimental animal studies showed that ACEIs and ARBs upregulate ACE2 expression as part of their pharmacological effect that inhibits ACE and angiotensin II synthesis in the cardiovascular system [174–177]. The use of ACEIs and ARBs as therapeutics is a double-edged sword in COVID-19 patients as they allow increased viral entry due to augmented expression of ACE2 at the membrane, but also attenuate the hypertensive effects of angiotensin II by converting it to Ang (1–7) [178]. Thus, although ACEIs/ARBs could potentially increase susceptibility to SARS-CoV/-CoV-2 infections, these agents could also have protective effects against respiratory complications and hospitalization in infected patients [87,161].

Findings by Zhang et al. [179] suggest that the mortality rate in patients with concurrent hypertension and COVID-19 was lower among patients taking ACEIs/ARBs compared with those not on these medications. In addition, many studies have suggested that ACEIs/ARBs can improve the clinical outcome of COVID-19 patients [180–185]. Increased ACE2 expression was effective in ameliorating acute lung injuries in animal models and treatment with RAAS inhibitors improved lung damage [186,187]. Studies show that ACEi and ARBs such as enalapril, losartan, and olmesartan can either restore ACE2 expression levels or even upregulate it [187–189].

A study by Rico-Mesa et al., did not find a link between ACEI/ARB use and effects on SARS-CoV-2 infection [190]. However, Meng et al., [191], found that the severity of COVID-19 was lower in patients receiving ACEI or ARB treatment, IL-6 levels were reduced and CD3 and CD8 T cell counts were higher in peripheral blood. Nevertheless, in an observational study by Reynolds et al. [192], ACEI, ARB, beta-blockers [193], calcium channel blockers, or thiazide diuretics presented no increased risk of COVID-19 among CVD patients [194]. A study by Choksi et al., [195], reported that RAAS blockers used to treat hypertension and CVDs had better outcomes in COVID-19 patients than those who received other anti-hypertensive drugs such as calcium channel blockers, which could be due to the high levels of ACE2 expression enhancing anti-inflammatory and antifibrotic effects. On the contrary, Guo et al. [196] and Toprak et al. [197], reported that mortality rates in patients taking ACEI/ARB treatments along with old age and other comorbidities was significantly higher than patients not taking ACE I/ARB therapy.

To date, there is little or no conclusive evidence regarding increased infectivity, morbidity, or case fatality rates among ACEIs/ARBs users. Global healthcare, cardiology departments, and health authorities recommend continuing RAAS inhibitor treatment of COVID-19 patients because of their proven anti-hypertensive activity and lack of evidence to corroborate any serious harm to the patients [198,199]. Several retrospective studies also reported that ICU requirements and COVID-19 death rates were inversely related to ACEIs/ARBs treatment in hypertensive, non-hypertensive and elderly patients [200–203]. As there is conflicting evidence regarding the role of ACEIs/ARB in COVID-19 susceptibility and outcomes, further studies should be performed in this direction by considering multiple factors related to ACEIs/ARB-associated ACE2 expression and level of Angiotensin II in such patients with and without COVID-19 [204].

Published studies show that blocking ACE2 receptors with an ACE2 antibody can prevent the entry of SARS-CoV into cells [170]. A pre-clinical murine study demonstrated downregulation of the ACE2 gene expression upon infection with SARS-CoV [156]. This ACE2 downregulation may also result in high Ang-II and low Ang1-7 leading to vasoconstriction and inflammation as well as hypertension and lung damage [72,205]. Higher levels of Ang-II were also confirmed in a cohort of 12 patients with SARS-CoV-2 compared to healthy controls in China [189]. Nevertheless, this finding was not replicated in an American cohort of 30 patients with SARS-CoV-2 compared to 14 healthy

controls; which showed no differences in plasma levels of Ang-II or aldosterone, suggesting that Ang-II could be metabolized by a different pathway than ACE2 [206]. Ang-II levels also did not correlate with disease severity. However, the same group also showed low levels of Ang1 and Ang1-7 in the same cohort of 27 SARS-CoV-2 positive patients compared to 14 healthy controls; lower levels were also observed in patients admitted to intensive care unit (ICU) compared to non-ICU treated COVID-19 patients. In the future, ACE and ACE2 levels should be determined in conjunction with Ang-II and Ang1-7, in order to improve our understanding of the RAAS system regulation by SARS-CoV-2 [207].

Both SARS-CoV and SARS-CoV-2 show relatively similar mechanisms of cell entry and pathogenesis [208]. However, unlike SARS-CoVs [209], MERS virus uses its spike protein as adhesive factors that are proinflammatory through a different specific receptor, dipeptidyl peptidase-4 (DPP4) [210]. Although further research is required, the uptake of MERS-CoV into cardiac tissues seems to use the same machinery as with other organs. Similar to other coronaviruses, MERS-CoV can generally enter the target cells in two ways. The first is through endocytosis aided by cathepsin-L and the second *via* plasma membrane fusion. The entry of the virus into the host cell can be either pH-dependent or -independent [211,212]. In pH-dependent endocytosis, virus entry occurs following internalization and fusion within the acidic environment of endosomal compartment [213]. When pH-independent plasma membrane fusion takes place, the virus fuses directly with the cell surface, following its binding to the receptor. Interestingly, pH-independent virus entry is ~100- to 1000-fold more efficient than pH-dependent endocytosis [62, 213]. Immediately after the cleavage of MERS-CoV spike protein by serine proteases during virus maturation, the virus can enter the cell through fusion between the viral envelope and the plasma membrane at neutral pH, resulting in substantial syncytia formation [211,214]. Laboratory investigations using cell lines show that MERS-CoV more frequently uses the plasma membrane fusion pathway [215]. Other studies suggest that viral fusion with the host cell plasma membrane is mediated by the cleaved S1 and S2 subunits of the spike protein [211, 214]. Despite some differences between SARS-CoVs and MERS viruses in terms of the mechanism of host entry, the presence of CVD is a risk factor both for susceptibility to these infection and prognosis.

4. Prospects

Overall, it is well documented that coronavirus infections and complications are more prevalent in people with underlying CVD [113,216]. However, due to the presence of multiple comorbidities in COVID-19 patients, clearly identifying the main determinants of associated complications and mortality is challenging in the clinical setting [217]. Thus, future studies should focus on the development of reliable *in vitro* and *in vivo* models that can mimic various cardiovascular complications in a controlled manner as well as pathogenic mechanisms associated with increased susceptibility to SARS-CoV-2 infections and complications in CVD patients [218]. Published reports suggest that patients with cardiovascular complications who develop COVID-19 are at the highest risk of death [219]. According to the mortality data released by the National Institutes of Health, 35% of patients with COVID-19 disease had a history of hypertension and 17% had a history of coronary heart disease [220]. Although there is substantial evidence that cardiovascular risk factors can contribute to the severity of symptoms and mortality in COVID-19 patients, detailed post-mortem studies are necessary to provide better understanding of this association. The most plausible mechanism of increased complications of SARS-CoV-2 in CVD patients could be associated with the higher accumulation of Angiotensin II in CVD patients. In infected individuals, ACE2 receptors may have reduced capability to convert Angiotensin II into Angiotensin (1–7) (Fig. 4). However, detailed investigations are still required to invariably prove this hypothesis. Collection of post-mortem cardiac biopsies and spatial gene expression studies may help to identify underlying mechanisms

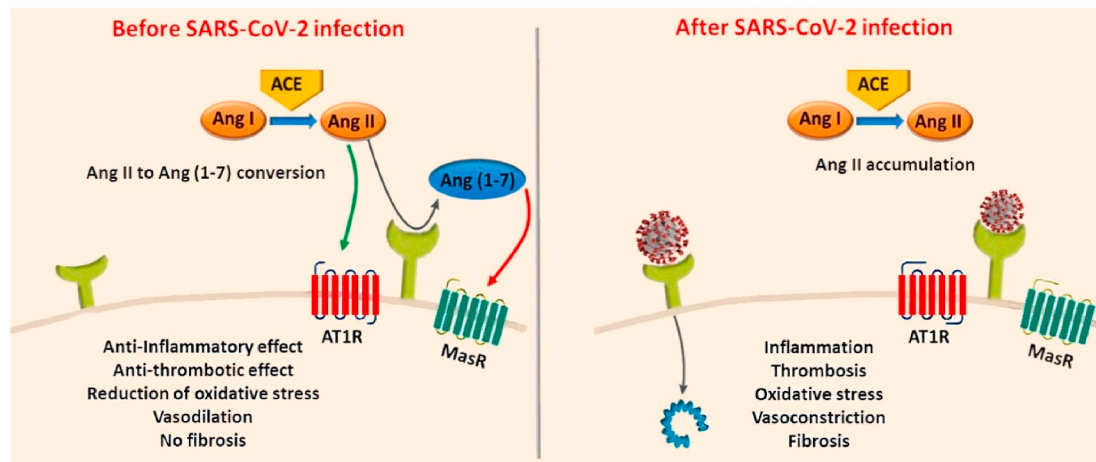


Fig. 4. In healthy individuals, Angiotensin II is converted into Angiotensin (1–7) via ACE2. However, in COVID19, ACE2 may be dysfunctional due to the binding of SARS-CoV-2, which can affect the conversion of Angiotensin II to Angiotensin (1–7). This results in the accumulation of Angiotensin II in the infected person and induces proinflammatory, prothrombotic, fibrotic and vasoconstrictive downstream effects. In the presence of CVD, however, the RAAS could be impaired. Consequently, upon infection with SARS-CoV-2, more Angiotensin II could accumulate resulting in serious cardiovascular complications.

that increase the severity of cardiovascular complications in COVID-19 patients [221]. Other comorbidities including diabetes mellitus, pulmonary/systemic hypertension and obesity as well as the age of the patient, play significant role in cardiac complications [222,223] and the severity of COVID-19 [224]. Further research using experimental models to determine the effects of SARS-CoV-2 on the heart both in the presence and absence of CVD is crucial. Also, further investigations into the effects of ACEIs and ARBs and the mechanisms involved would shed light on how patients with or without CVD should be managed once infected with SARS-CoV-2. The cardiac effects and mechanisms of certain antiviral drugs should be elucidated given their potential side effects that could lead to cardiac insufficiency, arrhythmia, or other cardiovascular complications [225].

Strict regulations and the availability of quality patient data in many countries is still a challenge for researchers. This has impeded our understanding of the interactions and mechanisms between SARS-CoV-2 and other comorbidities leading to inadequate management and poor outcomes for high-risk patients. Valuable bioinformatics tools can be utilised to perform predictive *in silico* modelling using patient data including patients' clinical characteristics, medical history, medications, biochemical and viral data that can enable correlation with clinical outcomes and mortality. Multidisciplinary efforts are required to elucidate the links between COVID-19 disease and other comorbidities such as CVD, and to identify mechanisms and effective treatments that can improved outcomes for patients.

5. Conclusions

Many studies report that patients with cardiovascular complications and risk factors are more susceptible to coronavirus infections. Despite the need for further rigorous studies in this field, available data obtained from studies investigating SARS, MERS and COVID-19 patients shows clear epidemiological link. The presence of hypertension or CVDs has also been shown to lead to higher CoV-associated complications. Both SARS and COVID-19 patients have increased incidence of myocardial injury, DIC and coagulopathies. Although the mechanisms implicated, so far, include inflammation and the ACE2 pathway effects, further studies are needed to confirm conflicting results on the involvement of the RAAS system and to establish the effects and pathogenic mechanisms associated with SARS-CoV-2 and cardiovascular complications.

Author contributions

Conceptualization: R.A. Investigation: R.A. Resources: R.A., A.S., P. D., P.A. Writing—original draft preparation: R.A., A.S., S.A.S. A.N., P.A. Writing—review and editing: L.M., C.G, P.M.H., R.A., A.S., P.D., P.M., F.M., A.H. Visualization: R.A. Supervision: A.H. Project coordination: R. A. Funding acquisition: A.H. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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