



# The cardiovascular disorders and prognostic cardiac biomarkers in COVID-19

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## Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to the outbreak of coronavirus disease 2019 (COVID-19), a worldwide epidemic disease affecting increasing number of patients. Although the virus primarily targets respiratory system, cardiovascular involvement has been reported in accumulating studies. In this review, we first describe the cardiac disorders in human with various types of CoV infection, and in animals infected with coronavirus. Particularly, we will focus on the association of cardiovascular disorders upon SARS-CoV-2 infection, and prognostic cardiac biomarkers in COVID-19. Besides, we will discuss the possible mechanisms underlying cardiac injury resulted from SARS-CoV-2 infection including direct myocardial injury caused by viral infection, reduced level of ACE2, and inflammatory response during infection. Improved understandings of cardiac disorders associated with COVID-19 might predict clinical outcome and provide insights into more rational treatment responses in clinical practice.

**Keywords** COVID-19 · Cardiovascular disorders · Hs-cTnI · NT-proBNP · Prognosis

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) brings out the outbreak of a worldwide epidemic disease coronavirus disease 2019 (COVID-19). COVID-19 exhibits complex clinical symptoms, including moderate upper respiratory disease, serious viral pneumonia, systemic inflammatory syndrome and death [1]. SARS-CoV-2 primarily targets the respiratory system, however cardiovascular involvement has been reported in multiple studies. Some SARS-CoV-2-positive patients experience cardiac signs, for example aching in the chest and stuffiness or palpitation rather than respiratory problems [2].

It has been reported that cardiovascular complications of influenza and coronavirus infection including myocarditis, myocardial infarction and heart failure exert great impact

on mortality during previous epidemics [3]. Patients with preexisting cardiovascular disease demonstrated adverse outcomes including arrhythmia and sudden cardiac health in previous coronavirus epidemics [4]. According to the case report from the Chinese Center for Disease Control and Prevention, COVID-19 patients with cardiovascular disease exhibits a highest mortality rate of 10.5% compared to those with other comorbid conditions including diabetes, chronic respiratory disease, hypertension or cancer [5]. Accumulating evidence have linked COVID-19 with raised morbidity and mortality resulting from cardiovascular disorders [6]. In this paper, we will focus on the impact of preexisting cardiovascular diseases on disease severity of COVID-19, and the cardiac complications of the diseases. Elucidation of these issues might provide significant diagnostic or prognostic value in clinical practice.

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## Characteristics of SARS-CoV-2

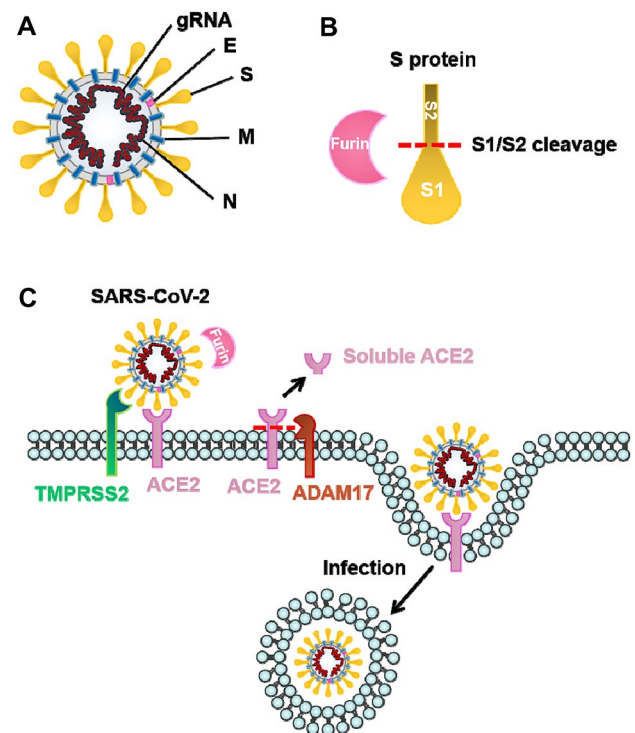
Coronaviruses (CoVs), members of the virus family Coronaviridae, are characterized as enveloped viruses with a sense and single-stranded RNA genome. CoVs, the largest known RNA viruses with genome sizes around 31 kb, encode structural proteins including the spike (S) protein, nucleocapsid

(N) protein, membrane (M) protein, and envelope (E) protein for viral particle production [7–9]. In addition to humans, CoVs also infect other vertebrates. On the whole, coronaviruses infecting humans (HCoVs) are divided into  $\alpha$ -CoVs and  $\beta$ -CoVs (Supplementary Table 1) [10, 11]. Low pathogenic  $\alpha$ -CoVs, consisting of HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU, infect upper airways and lead to respiratory illness resembling the common cold. However, high pathogenic  $\beta$ -CoVs infect the lower airways and lead to bronchitis and pneumonia, which might cause lung damage and acute respiratory distress syndrome (ARDS) [12–16]. For example, the outburst of severe acute respiratory syndrome CoV (SARS-CoV) results in 9.6% mortality rate by affecting around 8400 persons [17]. The outbreak of Middle East respiratory syndrome CoV (MERS-CoV) causes 36% mortality rate by infecting 1936 individuals [7].

COVID-19 is now affecting people globally, posing a great threat to human health and economy. COVID-19 is resulted from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new member of the HCoV family. The similarity between SARS-CoV-2 and SARS-CoV which lead to the outburst of SARS is high, around 80%. Both viruses share the same cell receptor angiotensin-converting enzyme 2 (ACE2) in humans. Compared with SARS-CoV, SARS-CoV-2 exhibits a more compact receptor binding domain and a higher receptor binding affinity [18]. SARS-CoV-2 infects cells by binding to cell receptor ACE2 through its S protein. (Fig. 1a). The S protein of SARS-CoV-2 consists of S1 and S2 two subunits with a furin cleavage site between the subunits, mediating target cell internalization (Fig. 1b). Furin, a member of the subtilisin-like proprotein convertase family, is a membrane binding protease [19]. Furin mediates cleavage of S protein after its binding with ACE2, which is critical for viral entry into the cell [20].

## Viral receptor ACE2

ACE2, first discovered to share around 60% similarity to ACE, is an important factor in protecting the renin-angiotensin system (RAS) [21, 22]. ACE2 acts as the physiological counterbalance of ACE by converting Angiotensin I and Angiotensin II into Ang-(1–9) and Ang-(1–7), which protect the function of tissues [23]. ACE2 exists in two forms, namely soluble and membrane binding forms [24–26]. In membrane binding form of ACE2, the enzymatic motif in the transmembrane domain located on the external surface of cells. After cleavage and secretion, ACE2 exists in soluble form, which is in low concentration in the circulation system. In stress state, membrane binding form of ACE2 is cleaved by membrane-anchored metalloprotease ADAM17 (A Disintegrin And Metalloproteinase Domain-Containing Protein 17), releasing ACE2 into the circulatory system [27].



**Fig. 1** Diagram of the structure of SARS-CoV-2 and viral infection. **a** The SARS-CoV-2 genomic RNA (gRNA) is packaged by the structural proteins consisting of the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein to assemble progeny virion. **b** Furin, which mediates cleavage of the S glycoprotein, is crucial in viral entry into the host cells. **c** SARS-CoV-2 infection is regulated by the binding of S protein with ACE2 on the host cells, and the cleavage of S protein by furin. ADAM17 modulates the level of ACE2 on plasma membrane, and accelerates the secretion of ACE2. The cellular serine protease TMPRSS2 also facilitates the ACE2 mediated viral entry

The role of ACE2 in circulation is undefined, although its level might be elevated in hypertension, diabetes or cardiovascular diseases [28].

ACE2, cellular receptor of SARS-CoV-2, exhibits high expression in vessel and heart which regulate circulation system, and in other organs including kidney, lung and small intestine [2]. Approaches to block viral infection like targeting ACE2 or downregulating ACE2 on cell membrane have been proposed in some studies. In vitro study has shown that recombinant protein linking the Fc domain of the human immunoglobulin IgG1 with ACE2 extracellular region neutralized both SARS-CoV and SARS-CoV-2 [29]. ADAM17 is highly expressed in heart and lung, and regulates ACE2 secretion [30]. It is speculated that ADAM17 elevation can promote shedding and increase soluble ACE2 level, which might inhibit the viral entry into the cells [19] (Fig. 1c). A recent study shows that SARS-CoV-2 employs ACE2 for viral infection and the cellular serine protease TMPRSS2 (Transmembrane Serine Protease 2) for S protein

priming [31]. It is demonstrated that inhibitor of serine protease inhibits viral infection of lung cells, indicating that TMPRSS2 might act as a possible target in intervening viral infection.

### Cardiac disorders are presented during various CoVs infection

Interestingly, it is described that patients with SARS show severe cardiac dysfunction [32, 33]. SARS-CoV infects the heart and regulates the level of ACE2 in a mice SARS model, indicating the important function of ACE2 in regulating viral entry into cardiac cells [34]. In heart tissues from SARS patients, viral RNA of SARS-CoV has been examined. Consistent with mice model, the presence of SARS-CoV was also associated with decreased level of ACE2. In SARS patients, pulmonary viral infection can trigger heart infection evidenced by increased myocardial inflammation and interstitial fibrosis, leading to a more serious disease and mortality. In addition, some SARS patients were investigated and examined 12 years after infection [35]. Among various diseases that these patients experienced, around 44% had cardiovascular disorders.

A report shows that one prominent symptom of an old man infected with MERS-CoV is congestive heart failure [36]. The patient showed elevated troponin-I level, severe global left ventricular systolic dysfunction, as well as acute myocarditis evidenced by cardiovascular magnetic resonance. MERS-CoV was positive in sputum samples, while any virus known to cause myocarditis was negative. This case suggested that MERS-CoV might result in acute myocarditis and heart failure.

In addition to the cardiac disorder in humans infected with coronavirus, it has also been reported that some animal models develop myocarditis after viral infection. For example, rabbits infected with coronavirus exhibited myocytes degeneration and necrosis, pleural effusion and congestion of the lungs and liver, and further progressed to myocarditis and congestive heart failure [37]. A study of myocarditis resulted from feline coronavirus has been published recently. Bilateral atrial expansion and left ventricular hypertrophy have been observed in the cat, which might further cause heart failure [38].

### Preexisting cardiovascular diseases associate with disease severity in COVID-19 patients

A systematic analysis of 637 MERS-CoV cases suggested that patients with underlying chronic cardiovascular diseases tend to develop severe symptoms [39]. 50% of

cases show hypertension and diabetes, and around 50% of patients present cardiovascular diseases. The increased risk of developing severe MERS-CoV in people with underlying chronic cardiovascular diseases was similarly noted for other respiration illnesses such as influenza. A number of key comorbidities are related with more severe clinical outcomes in COVID-19 patients [40]. A study of 44,672 patients recorded by the Chinese Center for Disease Control and Prevention showed that patients with cardiac diseases exhibit higher fatality rate (10.5%) compared to overall case fatality rate (2.3%) [5].

It has been demonstrated that patients with preexisting cardiac diseases such as hypertension, diabetes or coronary heart disease tend to develop severe symptoms in COVID-19 (Table 1). We first review several major studies which qualified the disease severity by non-ICU/ICU or survivor/non-survivor. Although no significance was observed in the association of preexisting cardiovascular comorbidities with disease severity, which might be arisen from the small size of 41 cases in the study [41]. Another study with 138 hospital patients showed that ICU patients tend to present diabetes (8 [22.2%] vs 6 [5.9%]), hypertension (21 [58.3%] vs 22 [21.6%]) and cardiac disease (9 [25.0%] vs 11 [10.8%]) compared to non-ICU patients [42]. In addition, underlying diabetes (17 [31%] vs 19 [14%]), hypertension (26 [48%] vs 32 [23%]) and cardiovascular disease (13 [24%] vs 1 [1%]) tend to exist in dead than living patients in another study with 197 hospital patients [1]. It has been suggested that patients with coronary heart disease or diabetes displays higher hospital mortality in univariable analysis.

Apart from the mentioned COVID-19 severity standard, a study which defined the disease severity with the American Thoracic Society guidelines has also been included [43]. Patients were divided into 926 with mild symptoms and 173 with severe symptoms according to disease severity [44]. The study displayed that severe patients were more likely to have coronary heart disease, diabetes and hypertension than non-severe patients. Besides, the COVID-19 severity was categorized as the presence of myocardial damage in other retrospective analysis. In a study with 414 cases, patients with myocardial damage were more inclined with diabetes (20 [24.4%] vs 40 [12%]), hypertension (49 [59.8%] vs 78 [23.4%]), coronary cardiac disease (24 [29.3%] vs 20 [6.0%]) and chronic heart failure (12 [14.6%] vs 5 [1.5%]) compared to those without myocardial injury [45]. A retrospective study also showed that patients with cardiac damage as shown by increased level of troponin T (TnT) were more likely to have coronary heart disease, cardiomyopathy, diabetes as well as hypertension compared to patients without myocardial injury [46].

These observations are confirmed by a study of COVID-19 patients admitted to intensive care units (ICUs) of the Lombardy Region in Italy [47]. Of the 1043 patients with

**Table 1** Association of preexisting cardiovascular comorbidities in patients infected with SARS-CoV-2 according to disease severity

Study	Hospital (patient number)	Severity classification	Comorbidities	Number of patients	Low severity	High severity	P value
Huang et al. [41]	Jinyintan Hospital (n=41)	Non-ICU/ ICU	Diabetes	8 (20%)	7 (25%)	1 (8%)	0.16
			Hypertension	6 (15%)	4 (14%)	2 (15%)	0.93
			Cardiovascular disease	6 (15%)	3 (11%)	3 (23%)	0.32
Wang et al. [47]	Zhongnan Hospital of Wuhan University (n=138)	Non-ICU/ ICU	Diabetes	14 (10.1%)	6 (5.9%)	8 (22.2%)	0.009
			Hypertension	43 (31.2%)	22 (21.6%)	21 (58.3%)	<0.001
			Cardiovascular disease	20 (14.5%)	11 (10.8%)	9 (25.0%)	0.04
Zhou et al. [1]	Jinyintan and Wuhan Pulmonary Hospital (n=191)	Survivor/ Non-survivor	Diabetes	36 (19%)	19 (14%)	17 (31%)	0.0051
			Hypertension	58 (30%)	32 (23%)	26 (48%)	0.0008
			Coronary heart disease	15 (8%)	2 (1%)	13 (24%)	<0.0001
Guan et al. [43]	552 hospitals in China (n=1099)	Nonsevere/ Severe	Diabetes	81 (7.4%)	53 (5.7%)	28 (16.2%)	–
			hypertension	165 (15.0%)	124 (13.4%)	41 (23.7%)	–
			Coronary heart disease	27 (2.5%)	17 (1.8%)	10 (5.8%)	–
Shi et al. [44]	Renmin Hospital of Wuhan University (n=416)	Without/with cardiac injury	Diabetes	60 (14.4%)	40 (12.0%)	20 (24.4%)	0.008
			Hypertension	127 (30.5%)	78 (23.4%)	49 (59.8%)	<0.001
			Coronary heart disease	44 (10.6%)	20 (6.0%)	24 (29.3%)	<0.001
			Chronic heart failure	17 (4.1%)	5 (1.5%)	12 (14.6%)	<0.001
Guo et al. [45]	Seventh Hospital of Wuhan City (n=187)	Normal/ elevated TnT level	Diabetes	28 (15.0%)	12 (8.9%)	16 (30.8%)	<0.001
			Hypertension	61 (32.6%)	28 (20.7%)	33 (63.5%)	<0.001
			Coronary heart disease	21 (11.2%)	4 (3%)	17 (32.7%)	<0.001
			Cardiomyopathy	8 (4.3%)	0 (0)	8 (15.4%)	<0.001

available data, 509 (49%) had hypertension, 223 (21%) had cardiovascular disease and 180 (21%) had diabetes. Among patients with hypertension, 195 (38%) died in ICU. These data show that patients with cardiovascular diseases tend to demonstrate serious symptoms with virus infection.

### Myocardial injury associates with fatal outcome of COVID-19

Although COVID-19 primarily affects lungs causing interstitial pneumonitis, in the most severe cases multiorgan failure develops, particularly the cardiovascular system. According to the reported cases by the National Health Commission of China (NHC), some SARS-CoV-2-positive patients experience cardiac signs, for example aching in the chest and stuffiness or palpitation rather than respiratory problems [2]. Indication of cardiac damage with COVID-19 was examined in five patients in Wuhan who displayed an increased level of high-sensitivity cardiac troponin I (hs-cTnI) [41]. Moreover, the cardiac injury symptom further aggravated the severity of the disease (Table 2). In another study, the expression of

markers indicating cardiac damage such as creatine kinase-myocardial band (CK-MB) and hs-cTnI were dramatically increased in ICU patients than in non-ICU patients [42]. Besides, ICU patients were more tend to display arrhythmia than non-ICU patients (16 [44.4%] vs 7 [6.9%]), indicating that patients in high severity often have complications in cardiovascular system.

Interestingly, a cohort study showed that myocardial damage is common among patients infected with SARS-CoV-2 and is related with hospital mortality [45]. Cardiac injury occurred in 82 (19.7%) of total 416 patients, and these patients demonstrated higher expression of N-terminal pro-B-type natriuretic peptide (NT-proBNP), CK-MB and hs-cTnI than those without myocardial damage. Patients with myocardial damage displayed higher mortality rate compared to those with normal cardiac function (42 [51.2%] vs 15 [4.5%]). Besides, patients with myocardial damage demonstrated a higher mortality rate from symptom initiation and admission to end point in a Cox regression model. Apart from respiratory failure and ARDS in COVID-19 patients, defects in cardiovascular system were the most frequently observed complications in a multicenter cohort study [1]. The frequency of cardiac injury

**Table 2** Cardiac associated outcomes in hospitalized patients with COVID-19

Study	Severity classification	Cardiac disorders	All patient	Low severity	High severity	P value	Biochemical markers
Huang et al. [41]	Non-ICU/ICU	Cardiac injury	5 (12%)	1 (4%)	4 (31%)	0.017	Increase in hs-cTnI level in ICU patients
Wang et al. [47]	Non-ICU/ICU	Cardiac injury	10 (7.2%)	2 (2%)	8 (22.2%)	<0.001	Increase in levels of CK-MB, hs-cTnI, d-dimer, lactate dehydrogenase in ICU patients
		Arrhythmia	23 (16.7%)	7 (6.9%)	16 (44.4%)	<0.001	
Shi et al. [44]	Non-survivor/ Survivor	Cardiac injury	82 (19.7%)	40 (11.1%)	42 (73.7%)	<0.001	Increase in levels of CK-MB, hs-cTnI, NT-proBNP in patients with cardiac injury
Zhou et al. [1]	Non-survivor/ Survivor	Cardiac injury	33 (17%)	1 (1%)	32 (59%)	<0.0001	Increase in levels of creatine kinase, hs-cTnI, d-dimer, serum ferritin, lactate dehydrogenase, IL-6 in non-survivors
		Heart failure	44 (23%)	16 (12%)	28 (52%)	<0.0001	
Guo et al. [45]	Normal/ elevated TnT level	Ventricular tachycardia/ventricular fibrillation (VT/VF)	11 (5.9%)	2 (1.5%)	9 (17.3%)	<0.001	Increase in levels of CK-MB, NT-proBNP, hsCRP, procalcitonin in patients with myocardial injury

(32 [59%] vs 1 [1%],  $P < 0.0001$ ), heart failure (28 [52%] vs 16 [12%],  $P < 0.0001$ ) as well as the expression of CK-MB and hs-cTnI were remarkably elevated in non-survivors than survivors. Apart from the biomarkers of myocardial injury, levels of d-dimer, serum ferritin, lactate dehydrogenase and IL-6 in non-survivors were significantly increased than survived patients.

An investigation showed that cardiac damage is strikingly correlated with death outcome of COVID-19 [46]. Cardiac damage is related to abnormal cardiac function and arrhythmias. In-hospital patients with increased level of TnT tend to develop more frequent symptoms, such as arrhythmias, ventricular tachycardia/ventricular fibrillation. The levels of cardiac biomarkers CK-MB, NT-proBNP as well as inflammatory biomarker hsCRP were markedly upregulated in cardiac injury patients than those without cardiac damage, suggesting that inflammation might act as a possible target for cardiac damage.

### Prognostic cardiac biomarkers in COVID-19 patients

Many studies showed that increased levels of cardiac biomarkers including NT-proBNP, CK-MB and hs-cTnI have been detected in patients with high severity compared with patients

with low severity. Among these biomarkers, hs-cTnI (marker for cardiac damage) and NT-proBNP (marker for myocardial stress) are likely to be prognostic. It has been reported that initial examination of increased levels of hs-TnI and NT-proBNP predicts death rate in COVID-19 patients [48]. The study including 397 patients infected with SARS-CoV-2 demonstrated that patients with elevated hs-TnI, NT-proBNP or both exhibited higher mortality rate than those with normal levels of myocardial markers. Besides, a multivariate analysis showed that concurrence increased levels of both hs-TnI and NT-proBNP might predict the all-cause mortality rate. In another study focused on the comprehensive cardiovascular characterization in COVID-19 patients, it was found that impaired cardiac function as well as elevated levels of NT-proBNP and hs-TnI were linked to poor prognosis [49]. These studies indicate that the levels of hs-cTnI and NT-proBNP combined with cardiac function assessment might predict the mortality in COVID-19 patients.

### Potential mechanism of myocardial damage in patients infected with SARS-CoV-2

The underlying mechanism of cardiac participation in COVID-19 are still under study. A possible mechanism is cardiac injury resulted from SARS-CoV-2 infection (Fig. 2).

Even though there is no abundant pathological evidence, it has been suggested that viral infection might lead to fulminant myocarditis according to the analysis of clinical data [50]. A 63 years old male COVID-19 patients displayed fulminant myocarditis five days after disease initiation [51]. The patient exhibited significantly elevated levels of biomarkers associated with the function of heart including cardiac troponin 1, BNP, CK-MB, as well as depressed left ventricular ejection fraction (LVEF) and enlarged left ventricular diameter. The myocarditis occurred with a high viral load of SARS-CoV-2, suggesting that the initial examination of high viral load might be correlated with development of myocarditis. Besides, the direct evidence linking myocardial damage to cardiac localization of SARS-CoV-2 has been reported [52]. The patient started with symptoms similar to flu which degenerated into respiratory distress and cardiogenic shock. Endomyocardial biopsy revealed mild inflammation and viral particles in cardiac tissues, indicating either a viraemic stage or lung migration of infected macrophage.

It is considered that the decreased ACE2 level upon viral infection is a major contributor to the cardiac involvement in COVID-19. ACE2 acts as a key element in regulating RAS system by antagonizing ACE and decreasing Angiotensin II [53]. It has been reported that the abnormal elevation of Angiotensin II is associated with hypertension, heart failures, and lung dysfunction [54]. It has been suggested that ACE2 is crucial in SARS-mediated cardiac inflammation and injury. Viral RNA of SARS-CoV and reduced ACE protein have been examined in heart tissues from SARS patients [34]. A mice model of pulmonary infection with SARS-CoV suggested that viral infection in heart is dependent on ACE2. Intriguingly, the level of Angiotensin II in plasma from COVID-19 patients were strikingly higher than

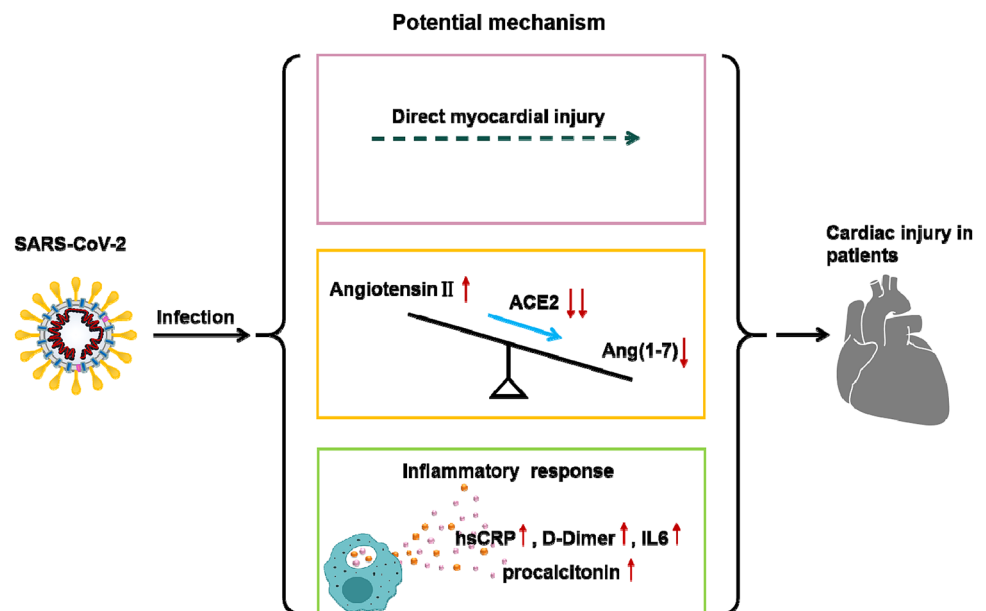
that of healthy individuals [51]. Besides, the Angiotensin II level in COVID-19 patients was closely correlated with viral load and lung damage. It is possible that ACE2 plays an important role in myocardial involvement in COVID-19 given the similarity between SARS-CoV-2 and SARS-CoV.

Noteworthy, downregulation of ACE2 would inhibit cardioprotective role of Ang-(1–7), leading to increased level of TNF $\alpha$  production [53, 55]. As a common inflammatory cytokine, TNF $\alpha$  involved inflammatory response might lead to myocardial injury in many studies. It has been reported that increased levels of inflammatory biomarkers hsCRP and procalcitonin, and TnT were observed in patients with cardiovascular diseases and poor outcomes, suggesting that severe inflammatory response might act as a regulator in cardiomyocyte injury [46]. Many studies showed that patients with myocardial damage or coronary heart disease present higher hospital mortality [1, 45]. The levels of inflammatory biomarkers including d-dimer, serum ferritin, and IL-6 were significantly increased in non-survivors compared to survivors, which further indicating the important role of cytokine storm in cardiac injury during SARS-CoV-2 infection.

## Conclusion

COVID-19 pandemic, caused by SARS-CoV2, has posed a significant impact on global health and economy. SARS-CoV2 infection of the host cells is regulated by cell receptor ACE2, which also contributes to cardiac injury. Cardiovascular diseases are common in COVID-19 patients, and these patients have an adverse prognosis and high risk of mortality. Besides, the elevated expression of hs-cTnI and NT-proBNP predict poor prognosis patients. The potential

**Fig. 2** The potential mechanisms of cardiac damage in COVID-19 might be direct injury of cardiomyocytes by SARS-CoV2, decreased level of ACE2 upon viral infection, and inflammatory response



mechanisms of cardiac damage in COVID-19 could be direct injury of cardiomyocytes by SARS-CoV2, decreased level of ACE2 upon viral infection, and inflammatory response. Thus, cardiac protection should be a major consideration in the clinical treatment of COVID-19.

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**Author contributions** All authors contributed to the study design. Based on discussions with all authors, Dr. Xingjuan Shi drafted the manuscript, Mengying Chen draw the models and Yu Zhang organized the tables. All authors approved the final version submitted for publication.

### Compliance with ethical standards

**Conflict of interest** The authors declare that there are no conflicts of interest.

**Research involving human participants and/or animals** Not applicable as this is a review article.

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