



Review

Advances in the relationship between coronavirus infection and cardiovascular diseases



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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) has once again aroused people's concern about coronavirus. Seven human coronaviruses (HCoV) have been discovered so far, including HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU115, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus 2. Existing studies show that the cardiovascular disease increased the incidence and severity of coronavirus infection. At the same time, myocardial injury caused by coronavirus infection is one of the main factors contributing to poor prognosis. In this review, the recent clinical findings about the relationship between coronaviruses and cardiovascular diseases and the underlying pathophysiological mechanisms are discussed. This review aimed to provide assistance for the prevention and treatment of COVID-19.

1. Introduction

At the end of 2019, a number of patients with fever and clinical pneumonia of unknown origin were found in Wuhan, Hubei, China [1]. Through virus isolation, gene detection and the analysis of protein structure in the laboratories, the disease was identified as 2019 novel coronavirus pneumonia caused by a new kind of coronavirus. Researchers have found that this new coronavirus belongs to the severe acute respiratory syndrome coronavirus (SARS-CoV) [2–4]. This novel coronavirus is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On February 12, 2020, the World Health Organization (WHO) announced that the disease caused by SARS-CoV-2 was officially named "coronavirus disease 2019" (COVID-19). COVID-19 is another serious infectious disease caused by coronavirus after severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2015. SARS-CoV-2 is the seventh member of the coronavirus family to infect humans [1].

Since January 2020, COVID-19 has rapidly spread throughout China, causing serious harm to human health. Up to April 27, 2020, at least 2,878,196 patients have been confirmed to have COVID-19 all over the world, of whom 198,668 have died [5]. The WHO characterized COVID-19 as a pandemic on March 11, 2020, after it announced

that COVID-19 in China was a public health emergency of international concern (PHEIC) on January 31, 2020 [6,7]. Due to the severe outbreak of COVID-19 and its wide-ranging scope, strict prevention and control strategies should be implemented in the affected countries, and the treatment of infected individuals should receive more attention.

As reported by the China Centers for Disease Control and Prevention, approximately 12.8 % of patients with COVID-19 have hypertension, and 4% of patients have cardiovascular disease (CVD). The mortality rate of patients with cardiovascular disease is much higher than that of patients without comorbidities [8]. Growing evidence suggests that combined cardiovascular disease may increase the severity of coronavirus infection and lead to a poor prognosis [9–13]. At the same time, there is also evidence suggesting that serum levels of cardiac necrosis biomarkers have increased to varying degrees in both mild and severe COVID-19 patients, suggesting different degrees of myocardial damage [9–14]. Moreover, the study found that the markers of myocardial necrosis in severe and deceased COVID-19 patients were significantly higher than those in mild COVID-19 patients, suggesting that cardiac damage may be related to poor prognosis [9,10,12,13]. Existing evidence suggests that COVID-19 is closely related to cardiovascular disease, but the specific interaction between the two is unclear. This paper describes the relationship between coronavirus and

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cardiovascular diseases through a review of the literature and datasets about SARS, MERS and other diseases caused by the human coronavirus, hoping to provide some assistance for the prevention and treatment of COVID-19.

2. Human coronavirus

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes the Coronaviridae, Arteriviridae, and Roniviridae families. CoVs are further subdivided into four groups, the α , β , γ , and δ CoVs [15]. The newly discovered SARS-CoV-2 belongs to the β -CoVs [2]. All CoVs are enveloped, nonsegmented positive-sense RNA viruses [15]. The most significant feature of CoVs is the club-shaped spike projections emanating from the surface of the virion. Therefore, CoV look like a tiny corona, as depicted in studies by cryo-electron tomography and cryo-electron microscopy, prompting the name coronavirus [16–18]. CoV is a respiratory virus that exists widely in nature. Its natural hosts include humans and other mammals, such as pigs, dogs, cats, mice, and bats [19].

At present, seven human coronaviruses (HCoVs) have been discovered, in which HCoV-229E [20], HCoV-NL63 [21,22], HCoV-OC43 [23–25], HCoV-HKU1 [26], SARS-CoV [27–30] and MERS-CoV [31,32] are included, in addition to SARS-CoV-2 recently isolated from the respiratory tracts of patients with COVID-19 in Wuhan [2–4]. HCoVs mainly cause respiratory infections, of which four endemic HCoVs (HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1) mainly cause mild respiratory infections, and the other three epidemic HCoVs (SARS-CoV, MERS-CoV, SARS-CoV-2) can cause acute severe pneumonia [19,33].

Coronaviruses originally discovered as HCoV-229E are the cause of respiratory infections in children and adults, but they are not particularly dangerous. Patients' respiratory symptoms are mild, similar to those of the common cold [34]. Most clinically significant coronavirus infections occur in children under two years of age, although adults can also be severely infected [35,36]. Mortality is negligible [37]. However, SARS-CoV and MERS-CoV, which have appeared since 2003, are highly contagious and cause a high incidence and mortality rate of pneumonia [33,37–39]. In addition to SARS-CoV and MERS-CoV, SARS-CoV-2 is another human coronavirus that can cause severe pneumonia [1]. The researchers compared the sequence of SARS-CoV-2 from Wuhan with that of SARS-CoV and MERS-CoV through genetic testing and found that the gene sequence of SARS-CoV-2 is almost identical, with a homology to MERS of approximately 40 % and a higher degree of homology to SARS of approximately 70 % [40]. The differences between the sequences are mainly in the ORF1a gene and the spike gene, encoding S-protein, which is the key protein for the interaction between coronavirus and host cells [40].

The coronavirus spike protein is a multifunctional molecular machine that mediates coronavirus entry into host cells. It first binds to a receptor on the host cell surface through its S1 subunit and then fuses viral and host membranes through its S2 subunit [41,42]. Some cellular receptors of human coronavirus have been identified, including angiotensin-converting enzyme 2 (ACE2) [40,43,44], dipeptidyl peptidase 4 (DPP4) [45] and aminopeptidase N (APN) [46]. Coronavirus enters the human body through receptors on the surface of host cells, multiplies in the body, and causes inflammation in the body and diseases such as pneumonia.

3. ACE2

Similar to SARS-CoV, ACE2 was found to be a receptor for SARS-CoV-2 [43,47,48]. ACE2 is also an important member of the renin-angiotensin-aldosterone system (RAAS). It catalyzes the conversion of angiotensin II (Ang II) to angiotensin 1–7, activates downstream Mas receptors, and finally exerts anti-inflammatory and antiproliferative effects [49]. In addition, ACE2 can also decompose Ang II into

angiotensin 1–9. Angiotensin 1–9 not only can be catalyzed by ACE and further decompose into angiotensin 1–7 but also can directly activate Ang II type 2 receptor (AT2R), exerting its anti-inflammatory and anti-angiotensin II type 1 receptor (AT1R) effects [50].

ACE2 is primarily expressed in the heart, kidneys, and testes, and it is widely distributed in human alveolar epithelial cells, small intestinal epithelial cells, arterial smooth muscle and endothelial cells, and vein endothelial cells [51,52]. In the heart, ACE2 is expressed in the endothelium [51] and cardiomyocytes [53]. Increasing evidence suggests that ACE2 enzyme activity has a protective role in cardiovascular disease. The loss of ACE2 can be harmful because it may lead to worsened heart function and the progression of heart and vascular disease [49,54]. Virus-induced ACE2 down regulation may attenuate its function, diminish its anti-inflammatory role, and heightened angiotensin II effects in the predisposed patients [55]. The tissue localization of the receptors correlates with COVID-19 presenting symptoms and organ dysfunction. In the lung, ACE2 is expressed in type I and type II alveolar epithelial cells. In addition, 83 % of type II alveolar cells express ACE2 [56]. The combination of SARS-CoV-2 with ACE2 results in increased expression of ACE2, which can lead to alveolar cell damage, in turn triggering a series of whole-body reactions and even death [48].

Wrapp et al. [18] found that the receptor-binding ability of SARS-CoV-2 is 10–20 times stronger than that of SARS-CoV, providing a laboratory basis to prove that SARS-CoV-2 is more infectious than SARS-CoV [3]. There is evidence showing that ACE2 levels are higher in men than in women [48]. However, the male-to-female ratio of NCP-confirmed cases is 0.99:1 in Wuhan, 1.04:1 in Hubei Province, and 1.06:1 in China [8], meaning that there are few differences in prevalence between men and women. However, the crude case fatality rate for men (2.8 %) is slightly higher than that for women (1.7 %) [8]. However, the relationship between ACE2 expression level and SARS-CoV-2 infection rate and mortality remains unclear.

RAAS inhibitors, including angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) drugs, are commonly used in the treatment of hypertension, heart failure, and myocardial inflammation. They can control the level of Ang II in the body, slow down the deterioration of inflammation, and improve patient survival. ACEIs and ARBs can also exert their protective effects by activating the ACE2/angiotensin 1–7/Mas axis, which may lead to increased ACE2 in patients [57,58]. Increased ACE2 expression levels may lead to an increased risk of infection. However, there are no reports indicating that patients using ACEIs/ARBs are more likely to become infected. Whether ACEI / ARB can be widely used in COVID-19 patients with comorbid cardiovascular disease was unclear or even controversial [59]. But recently, Guo et al. reported that although more patients with higher troponin T (TnT) were using ACEI and ARB medications owing to their baseline CVD, their use was not associated with patients' mortality rate [60]. A research published in Circulation Research by Zhang et al. showed that Among hospitalized COVID-19 patients with hypertension, inpatient use of ACEI / ARB was associated with lower risk of all-cause mortality compared with ACEI / ARB non-users [61]. We can see that in-hospital use of ACEI / ARB was not associated with an increased mortality risk. There is no need for patients with hypertension to stop using ACEI / ARB or switch to other antihypertensive medicine.

4. Coronavirus and CVD

4.1. HCoV-229E, HKU1, NL63, and OC43 and CVD

HCoV-229E and HCoV-OC43 [35] were discovered in the 1960s, and HCoV-NL63 [22] and HCoV-HKU1 [26] were later discovered in upper respiratory tract infections, asthma, bronchiolitis, and pneumonia. There is evidence showing that infant, elderly and immunocompromised patients are more likely to be infected with high mortality rates [37,62–64]. These infected patients are more likely develop severe disease states [65–68].

Table 1
Underlying CVD in HCoV Infection.

HCoV	Authors and Research types	Study Region	Study Period	Case Size	Underlying CVD	Major Findings
229E, HKU1, NL63, OC43	Varghese et al. [37]	New York	1/2013 ~ 12/2014	261	congenital heart disease (CHD)	16.5 % of patients had CHD, and they were more likely to enter the PICU.
	TK, C et al. [69]	Sao Paulo	6/2001 ~ 9/2010	1137	CHD	17.3 % of patients had CHD
	Lee et al. [70]	Saint Louis	12/2012 ~ 12/2013	4315	CHD	17.7 % of patients with CoV infections had congenital heart disease; CHD is a risk factor for adverse outcomes
SARS	Chen et al. [89]	Taipei	3/2003 ~ 5/2003	67	hypertension; cerebrovascular disease	a risk factor for ARDS development.
	Wong et al. [88]	Taipei	3/2003 ~ 5/2003	8	hypertension; coronary artery disease	60 % of deceased patients had hypertension, coronary artery disease or other comorbid conditions
	Chan et al. [86]	Hongkong	3/2003 ~ 6/2003	115	cardiac disease	a risk factor for adverse outcomes
	Tsang et al. [87]	Hongkong	2/2003 ~ 3/2003	10	heart disease	a risk factor for mortality
	Hu et al. [90]	Beijing	5/2003 ~ 12/2003	1291	cardiovascular and cerebrovascular disease	People with cardiovascular and cerebrovascular diseases were 1.83 times more likely to die than those without underlying diseases
	Assiri et al. [105]	Saudi Arabia	9/2012 ~ 6/2013	47	hypertension; chronic cardiac disease	34 % of patients had hypertension; 28 % had other chronic cardiac diseases.
MERS	Jaffar et al. [106]	Saudi Arabia	4/2013 ~ 6/2013	17	cardiac disease	53 % of patients had cardiac disease.
	A, B et al. [107]	Saudi Arabia	2013 ~ 2016	637	hypertension; heart disease	50 % of patients had hypertension; 30 % of patients had heart disease.
	Garout et al. [108]	Saudi Arabia	3/2014 ~ 7/2014	52	hypertension	51.9 % of patients had hypertension.
	CDC [8]	China	12/2019 ~ 2/2020	44,672	hypertension; other CVD	15.7 % of deceased patients had hypertension, and 9% had other cardiovascular diseases
	Huang et al. [9]	Wuhan	12/2019 ~ 1/2020	41	hypertension; other CVD	15 % of patients with COVID-19 had hypertension, and 15 % had other CVDs.
SARS-CoV-2	Wang et al. [10]	Wuhan	1/2020 ~ 2/2020	138	hypertension; other CVD	31.2 % of patients with COVID-19 had hypertension, and 14.5 % had other CVDs.
	Chen et al. [11]	Wuhan	1/1/2020 ~ 20/1/20020	99	cardiovascular and cerebrovascular disease	40 % of patients had cardiovascular and cerebrovascular disease.
	Yang et al. [12]	Wuhan	12/2019 ~ 1/2020	52	chronic heart disease	10 % of patients had chronic heart disease and were more likely to die.
	Li et al. [13]	Wuhan	1/2020 ~ 2/2020	25	hypertension; heart disease	64 % of deceased patients had hypertension and 32 % had heart disease.
	Li et al. [119]	China	12/2019 ~ 3/2020	1527	hypertension; cerebrovascular disease	17.1 % of patients with COVID-19 had hypertension and 16.4 % had cardiovascular disease. The incidences of hypertension and cardiovascular diseases were approximately two-fold and three-fold higher, respectively, in patients in the ICU with severe cases than in their non-ICU/severe case counterparts.
	Zhang et al. [132]	Wuhan	12/2019 ~ 3/2020	82	hypertension; heart disease; cerebrovascular disease	56.1 % of deceased patients had hypertension, 20.7 % had heart disease, 12.2 % had cerebrovascular disease.

Abbreviation: CDC: Chinese Center for Disease Control and Prevention; PICU: pediatric intensive care unit; ICU: intensive care unit.

Table 2
CVD Complication of HCoV infection.

HCoV	Authors and Research types	Study Region	Study Period	Case Size	CVD Complication	Abnormal Indicator	Major Findings
OC43	Lee et al. [70]	Saint Louis	12/2012 ~ 12/2013	4315	hypotension	Blood pressure	Hypotension was found in a small number of patients with CoV infection.
SARS	Yu et al. [92]	America	2003	121	hypotension; tachycardia; bradycardia; cardiomegaly; cardiac arrhythmia	Blood pressure; heart rate	hypotension and tachycardia are common in SARS patients. Bradycardia and cardiac hypertrophy are less common, and arrhythmias are rare.
	Li et al. [91]	Hongkong	2003	46	cardiac injury; diastolic impairment	CK; LDH; echocardiogram	SARS patients had subclinical diastolic impairment without contraction involvement, and this damage may be reversible upon clinical recovery.
	Yin et al. [94]	...	2018	...	vasculitis	...	SARS-CoV also attacks small blood vessels throughout the body, causing systemic vasculitis.
	Oudit et al. [99]	Toronto	2013	20	myocardial damage	...	Decreased ACE2 expression may be responsible for the myocardial dysfunction and adverse cardiac outcomes in patients with SARS.
MERS	Alhaghani et al. [110]	Saudi Arabia	2016	1	myocarditis; heart failure	hs-TnI; echocardiogram	This was the first case to show that MERS coronavirus may cause acute myocarditis and acute heart failure.
SARS-CoV-2	Huang et al. [9]	Wuhan	12/2019 ~ 1/2020	41	cardiac injury	hs-TnI	The levels of hs-TnI of 5 patients increased significantly after infection
	Wang et al. [10]	Wuhan	1/2020 ~ 2/2020	138	cardiac injury	CKMB; LDH; hs-TnI	10.2 % patients had acute cardiac injury
	Li et al. [124]	China	1/2020 ~ 3/2020	1527	cardiac injury	...	At least 8% of patients with COVID-19 suffered acute cardiac injury
	Wang et al. [125]	Wuhan	1/2020 ~ 2/2020	53	tachycardia; electrocardiography abnormalities; diastolic dysfunction; elevated myocardial enzymes; acute myocardial injury	Heart rate; CRP; D-dimer	15 of the 53 patients had tachycardia, 11 had electrocardiography abnormalities, 20 had diastolic dysfunction, 30 had elevated myocardial enzymes and 6 had acute myocardial injury.
	Yang et al. [12]	Wuhan	12/2019 ~ 1/2020	52	cardiac injury	hs-TnI	The level of hs-TnI is higher in severe infections.
	Li et al. [13]	Wuhan	1/2020 ~ 2/2020	25	cardiac injury	hs-TnI; proBNP	The risk of heart injury in deceased patients is higher than that in survivors. 94.7 % patients' serum hs-TnI or/and proBNP levels were increased.
	Wu et al. [131]	Wuhan	12/2019 ~ 1/2020	188	heart injury	hs-TnI; CRP; IL-6; lymphocytes	Hs-TnI at admission may be associated with increased mortality.
	Zhang et al. [132]	Wuhan	12/2019 ~ 3/2020	82	cardiac injury	hs-TnI; CRP; IL-6	89 % of deceased patients had cardiac injury, cardiac damage may have something to do with the cytokine storm resulting from an overaggressive host immune response.
	Lippi et al. [133]	China	12/2019 ~ 3/2020	...	cardiac injury	hs-TnI	Hs-TnI was 2.2-fold higher in ICU patients than in patients with mild cases.
	Liu et al. [134]	Wuhan	12/2019 ~ 3/2020	291	cardiac injury	hs-TnI; proBNP	Patients in the ICU had much higher troponin I and NT-proBNP than the patients not in the ICU.
	Gao et al. [135]	Wuhan	12/2019 ~ 3/2020	102	cardiac injury	proBNP	Patients with higher levels of proBNP had a higher risk of hospital death.
	Guo et al. [60]	Wuhan	30/1 ~ 30/2/2020	187	cardiac injury	TnT; proBNP	Myocardial injury is significantly associated with fatal outcome of COVID-19; Myocardial injury is associated with cardiac dysfunction and arrhythmias; Inflammation may be a potential mechanism for myocardial injury.
	Shi et al. [136]	Wuhan	20/1 ~ 10/2/2020	416	cardiac injury	hs-TnI; CK-MB; myohemoglobin	Cardiac injury is a common condition among hospitalized patients with COVID-19 in Wuhan, China, and it is associated with higher risk of in-hospital mortality.

Abbreviation: CK, creatine kinase; LDH, lactate dehydrogenase; hs-TnI, hypersensitive troponin I; CKMB, creatine kinase-myocardial band isoenzyme; proBNP, pro brain natriuretic peptide; CRP, C-reactive protein; IL, Interleukin; TnT, troponin T.

Varghese et al. [37] retrospectively analyzed the clinical data of 261 children with HCoV infection (including 229E, HKU1, NL63, OC43) and found that approximately 16.5 % of the children had cardiovascular disease. HCoV-infected children with cardiovascular disease are more likely to receive respiratory support and enter a pediatric intensive care unit (PICU), suggesting that the underlying cardiovascular disease increased the severity of HCoV infection in the children. Cabeça et al. found that children with heart disease are more likely to be infected by HCoVs [69]. The presence of congenital heart disease was a significant risk factor for severe coronavirus infection in children who were less than five years old [70] (Table 1).

Hypotension was found in a small number of patients with these four HCoV infections [70] (Table 2). There is no relevant evidence showing that HCoV infection can cause heart injury. However, Kim et al. reported that HCoVs were detected in children with Kawasaki disease, which is characterized by acute systemic vasculitis in childhood and may induce severe cardiovascular complications [71]. Serological tests suggest that HCoV-229E may be involved in the occurrence of Kawasaki disease [72]. Therefore, we still need to pay attention to cardiovascular complications when facing these four kinds of HCoV infection.

4.2. SARS-CoV and CVD

The severe acute respiratory syndrome [27] that broke out globally in 2003 is different from the human coronavirus described previously. It is a severe acute respiratory infection with clinical manifestations of fever and dry cough, with the lungs as the main locations of lesions. Some patients quickly develop acute respiratory distress syndrome (ARDS) and multiple organ failure with high mortality [73–77].

There is much relevant evidence showing that pre-existing comorbid conditions are one of the major determinants of fatality [76,78–83]. It has been reported that the presence of cardiovascular diseases, such as hypertension and heart disease, is associated with adverse outcomes and mortality in SARS patients [84–87]. Wong et al. reviewed the medical records of fatal cases and found that 60 % of the patients who died had comorbid conditions such as hypertension and coronary artery disease [88]. Chen et al. found that patients with combined hypertension and cerebrovascular diseases are more likely to develop ARDS [89]. Another study by Hu et al. showed that the incidence rates of critical conditions and multiple organ dysfunction syndrome (MODS) among SARS patients with cardiovascular and cerebrovascular diseases were 1.8-fold and 1.9-fold higher than those of patients without underlying disease, suggesting that cardiovascular and cerebrovascular diseases are major risk factors for SARS patients to devolve into critical conditions and MODS and eventually lead to death [90] (Table 1).

Regarding the cardiovascular complications of SARS patients, it was found that SARS patients had subclinical diastolic impairment without contraction involvement, and this damage may be reversible upon clinical recovery [91]. Another study by Yu et al. found that cardiovascular complications, including hypotension and tachycardia, are common in SARS patients but are usually self-limiting. Bradycardia and cardiac hypertrophy were less common, and arrhythmias were rare [92]. Acute myocardial infarction can also be seen in a few SARS patients [93]. SARS-CoV was reported to be found in 40 % (7/18 patients) of heart samples from patients who died of SARS during the Toronto outbreak [76], which might explain the myocardial damage discovered in SARS patients [89]. There are reports indicating that SARS-CoV also attacks small blood vessels throughout the body, causing systemic vasculitis [94] (Table 2). In addition to clinical studies, laboratory studies were performed to look for the pathophysiological mechanism associated with myocardial dysfunction caused by SARS-CoV infection [95–99]. It was reported that pulmonary infection with SARS-CoV in mice led to a myocardial infection with a marked decrease in ACE2 expression, which may be responsible for the myocardial dysfunction

and adverse cardiac outcomes in patients with SARS [99].

4.3. MERS-CoV and CVD

MERS is a severe respiratory infectious disease caused by MERS-CoV that was first reported in Saudi Arabia in September 2012 [29]. The symptoms are similar to those of SARS, and severe cases can manifest as pneumonia with ARDS and other severe life-threatening complications, such as septic shock, acute myocarditis and multiple organ failure [100–105]. The mortality rate of MERS is 35.5 %, which is much higher than that of SARS (10 %) [39].

It has been reported that people with underlying diseases such as diabetes, cardiovascular disease, renal failure, obesity, and immune deficiency are more likely to develop severe diseases after being infected with MERS-CoV [105,106]. Badawi et al. found that 50 % of MERS patients have diabetes and hypertension and that approximately 30 % of patients have heart disease [107]. They believed that these underlying disease conditions inhibit the synthesis of proinflammatory cytokines, damage the host's natural and humoral immune systems, and lead to an increased risk of severe MERS complications. Another study found that 46.2 % of the patients who died had hypertension, suggesting that the presence of underlying cardiovascular disease increased the mortality of MERS [108]. Banik suggested that sufficient attention should be paid to MERS patients with combined underlying diseases to reduce the occurrence of serious complications and mortality [109] (Table 1).

Heart damage was also reported in MERS patients [110]. MERS-CoV was found in the kidneys of deceased patients but was not detected in the heart tissue, and the heart showed no significant histological changes [111,112]. However, an animal model study clearly stated that MERS-CoV RNA could be seen in cardiac tissue, implying direct cardiac pathology [113]. The mechanism of heart injury in MERS infection remains unclear and requires more research.

4.4. SARS-CoV-2 and CVD

COVID-19, which broke out at the end of 2019, is a disease caused by infection with SARS-CoV-2 [1,2,4]. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 is a β -CoV [2]. COVID-19 is similar to SARS and MERS and manifests as extensively pathological viral lung inflammation [1]. Although similar to SARS-CoV and MERS-CoV, SARS-CoV-2 has its own characteristics [1,114]. Early cases suggest that COVID-19 may not be as severe as SARS and MERS. However, the rapidly increasing number of cases and increasing evidence of human-to-human transmission suggest that SARS-CoV-2 is more contagious than SARS-CoV and MERS-CoV and has a lower fatality [3,9,115–117]. Up to April 27, 2020, the overall mortality of COVID-19 was 6.9 % globally [5]. But the fatality rate is different in different regions and times, ranging from 0.7%–13.5 % [5,118].

The symptoms of COVID-19 infection appear after an incubation period of approximately 6.4 days [119]. Fever, fatigue, and dry cough are the main manifestations of COVID-19, and a few patients have symptoms such as nasal congestion, runny nose, sore throat, and diarrhea [2,9,120,121]. Patients with severe cases often experience dyspnea and/or hypoxemia one week after onset [122]. Severe cases of COVID-19 progress rapidly to acute respiratory distress syndrome, septic shock, and metabolic acidosis, which is difficult to correct, and coagulopathy [10].

Current case reports show that SARS-CoV-2 infection may have cardiovascular symptoms in addition to the typical respiratory symptoms. A small number of patients have atypical clinical manifestations and may start with cardiovascular symptoms such as chest tightness, palpitations and chest pain. A study by Liu et al. found that 7.3 % (10/137) of patients had palpitations as the first symptom [123]. It was also reported that 2% of patients experienced chest pain during hospitalization [11]. In addition, Wang et al. found that 16.7 % of patients with

COVID-19 had arrhythmias [10].

According to relevant studies [9–11,124], the proportion of COVID-19 patients with comorbid CVDs, such as hypertension, coronary artery disease and cerebrovascular disease, was larger than that of patients with other comorbidities or without comorbidities, suggesting that patients with CVD may be more susceptible to SARS-CoV-2 infection. Moreover, the incidence of CVD in patients with severe or fatal cases with COVID-19 was higher than that in patients with nonsevere cases or in those who survived [12,13,124]. According to the reports of the Chinese Center for Disease Control and Prevention, 15.7 % of the deaths were hypertension, and 9% had other cardiovascular diseases, further suggesting that underlying cardiovascular diseases may be one of the important risk factors for poor prognosis in patients with COVID-19 [8]. It can be seen not only that the number of COVID-19 patients with cardiovascular disease is large but also that these patients have poor tolerance to severe pneumonia and are more likely to develop severe cases (Table 1).

Cardiac complications such as electrocardiography abnormalities, diastolic dysfunction, and acute myocardial injury were reported in patients with COVID-19 [124–127]. Cases of severe myocarditis with reduced systolic function have been reported after COVID-19 [128–130]. And SARS-CoV-2 infection-related myocarditis is likely associated with myocardial injury [60,128]. According to the study by Li et al., the most common organ damage outside the lungs was heart injury [13]. Serum myocardial necrosis markers such as hypersensitive troponin I (Hs-TnI) and creatine kinase (CK) increased to varying degrees in patients with mild and severe cases of COVID-19 [9–14,131–134]. However, the risk of heart injury was higher in patients with severe cases, approximately 22.2%–31% [9,12,126,133,134], than in patients with mild cases, approximately 2%–4% [9,10]. The percentage of heart injury in COVID-19 patients who died, approximately 28%–89% [12,13,132], was higher than that in those who survived. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were also reported to be increased [13,134,135]. Increased Hs-TnI and proBNP expression levels may be risk factors for severe illness and high mortality of COVID-19 [133–135]. Furthermore, it was found that high Hs-TnI levels were associated with increased levels of inflammation (neutrophils, IL-6, CRP, and PCT) and decreased levels of immunity (lymphocytes, monocytes, and CD4+ and CD8+ T cells), suggesting that cardiac injury may have something to do with the cytokine storm resulting from an overaggressive host immune response [131,132] (Table 2).

Two recent studies published in JAMA Cardiology reported the cardiovascular complications of COVID-19 in detail [60,136]. Shi et al. found that cardiac injury was a common condition among hospitalized patients with COVID-19 in Wuhan, China, and it is associated with higher risk of in-hospital mortality [136]. Guo et al. reported that Myocardial injury was significantly associated with fatal outcome of COVID-19. Myocardial injury was associated with cardiac dysfunction and arrhythmias. Inflammation may be a potential mechanism for myocardial injury [60] (Table 2).

COVID-19 may induce new cardiovascular diseases and / or aggravate potential cardiovascular diseases. The short-term and long-term cardiovascular effects of COVID-19 and the effects of specific treatments are unclear and need further investigation.

4.5. SARS-CoV-2 subtypes and CVD

As the epidemic spread, SARS-CoV-2 evolved multiple subtypes. In a recent study, researchers proposed the subdivision of the global SARS-CoV-2 population into sixteen well-defined subtypes by focusing on the widely shared polymorphisms in nonstructural (nsp3, nsp4, nsp6, nsp12, nsp13 and nsp14) cistrons, structural (spike and nucleocapsid) and accessory (ORF8) genes [137]. Six virus subtypes were predominant in the population, accounting for more than 97 % of the samples isolated from around the world. And the subtypes showed some

geographical structure with two clusters: a smaller one comprised of isolates mostly sampled from Western hemisphere (Subtypes II, VI, IX, X and XI) and a larger one whose isolates were sampled from Western and Eastern hemispheres (Subtypes I, III, IV, V, VII, VIII, XII, XIII, XIV, XV and XVI) [137]. The researchers believed that the genetic structure determined for the SARS-CoV-2 population provides substantial guidelines for maximizing the effectiveness of trials for testing the candidate vaccines or drugs [137].

In another earlier study, population genetic analyses of 103 SARS-CoV-2 genomes indicated that these viruses evolved into two major types (designated L and S), that are well defined by two different single nucleotide polymorphisms (SNPs) [138]. The L type (~70 %) is more prevalent than the S type (~30 %), but the S type was found to be the ancestral version. The L type is more aggressive and spread more quickly. And it was more prevalent in the early stages of the outbreak in Wuhan. But the frequency of the L type decreased after early January 2020 for more severe selective pressure placed by human intervention on the L type [138]. Contrary to the L type, the S-type, which is evolutionarily older and less aggressive, might have increased in relative frequency due to the weaker selective pressure [138].

It was also reported that among the 27 viruses isolated from Wuhan, 26 (96.3 %) were L type, and only 1 (3.7 %) was S type [138]. However, among the other 73 viruses isolated outside Wuhan, 45 (61.6 %) were L type, and 28 (38.4 %) were S type [138]. This comparison suggests that the L type was significantly more prevalent in Wuhan than in other places. And recent studies about the clinical characteristics and outcomes of patients with COVID-19 in Wuhan [9–11,139] or outside Wuhan [134,140,141] have showed that the mortality of COVID-19 patients and the proportion of patients with cardiac injury outside Wuhan was lower than that in Wuhan (Table 3). Although there were many reasons for the different incidence of cardiac injury and outcome of COVID-19 in and outside Wuhan, such as the shortage of medical resources in Wuhan, the role of different SARS-CoV-2 subtypes cannot be ignored. The relationship between SARS-CoV-2 subtypes and the mortality of COVID-19 or the CVD complications need for further immediate, comprehensive studies that combine genomic data, epidemiological data, and records of the clinical symptoms of patients with coronavirus disease 2019.

5. Possible mechanisms underlying the increased susceptibility and severity of SARS-CoV-2 infection in patients with CVD

According to the references above, we can see that patients with underlying CVD may be more likely to become infected with coronavirus, and CVD may be one of the risk factors for poor prognosis and high mortality of CoV infection. Few studies, however, have explored the mechanisms underlying these associations. We believe that the possible mechanisms may be related to inflammation.

Cardiovascular diseases such as hypertension, coronary heart disease, and cerebrovascular disease are all metabolic-related diseases. It has been reported that metabolic syndrome can downregulate the key mediator of the host's innate immune response to pathogenesis, affecting the function of the innate and humoral immune systems [142]. Chronic low-grade inflammatory disease has been widely recognized as a feature of coronary heart disease, and its occurrence is closely related to inflammation [143]. The occurrence of hypertension is associated with oxidative stress, inflammation and the activation of the immune system [144]. IL-6, IL-1 and tumor necrosis factor α (TNF- α) levels are higher in patients with hypertension than in patients with normal blood pressure [145]. This may explain why patients with underlying cardiovascular disease found in the clinic are more susceptible to infection.

Kulcsar et al. showed that MERS-CoV infection can lead to prolonged respiratory tract inflammation, immune cell dysfunction, and changes in the expression profile of inflammatory mediators [146]. Lymphopenia and increased inflammatory mediators were found in SARS-CoV-2 infection [147]. Immune disorders caused by SARS-CoV

Table 3
Comparison of clinical data in and outside Wuhan.

Hospital	Wuhan				Outside Wuhan			
	Study 1 [19]	Study 2 [111]	Study 3 [139]	Study 4 [10]	Study 5 [134]	Study 6 [140]	Study 7 [141]	
	Jin Yin-tan Hospital	Jin Yin-tan Hospital	Union hospital in Wuhan	Zhongnan Hospital of Wuhan University	Guangzhou Eighth People's Hospital	Hospitals in Hainan province	10 designated hospitals in Shaanxi province	
Study Duration	12/2019–2/1/2020	1/1–20/1/2020	16/1–29/1/2020	1/1–28/1/2020	10/1–24/2/2020	22/1–13/2/2020	23/1–7/3–2020	
Case Numbler	41	99	69	138	291	168	134	
Any comorbidity	13 (32 %)	50 (51 %)	...	64 (46.4 %)	...	...	...	
Diabetes	8 (20 %)	13 (13 %)	7 (10 %)	14 (10.1 %)	22 (7.6 %)	12 (7.1 %)	9 (6.7 %)	
Hypertension	6 (15 %)	40 (40 %)	9 (13 %)	43 (31.2 %)	54 (18.5 %)	24 (14.3 %)	20 (14.9 %)	
Cardiovascular disease	6 (15 %)	...	8 (12 %)	20 (14.5 %)	15 (5.1 %)	12 (7.1 %)	6 (4.5 %)	
Chronic obstructive pulmonary disease	1 (2%)	1 (1 %)	4 (6 %)	4 (2.9 %)	...	10 (6%)	5 (3.7 %)	
Malignancy	1 (2%)	1 (1 %)	4 (6 %)	10 (7.2 %)	...	2 (1.2 %)	5 (3.7 %)	
Chronic liver disease	1 (2%)	11 (11 %)	1 (1%)	4 (2.9 %)	...	6 (3.6 %)	5 (3.7 %)	
Complications								
Acute respiratory distress syndrome	12 (29 %)	17 (17 %)	...	27 (19.6 %)	...	17 (10.1 %)	3 (2.2 %)	
Acute cardiac injury	5 (12 %)	...	...	10 (7.2 %)	15 (5.1 %)	4 (2.4 %)	...	
Acute kidney injury	3 (7 %)	3 (3 %)	...	5 (3.6 %)	...	6 (3.6 %)	3 (2.2 %)	
Secondary infection	4 (10 %)	5 (5%)	...	...	...	7 (4.2 %)	32 (23.9 %)	
Shock	3 (7%)	4 (4%)	...	12 (8.7 %)	...	12 (7.1 %)	1 (0.7 %)	
Prognosis								
Hospitalization	7 (17 %)	57 (58 %)	44 (65.7 %)	85 (61.6 %)	...	160 (95.2 %)	123 (91.8 %)	
Discharge	28 (68 %)	31 (31 %)	18 (26.9 %)	47 (34.1 %)	...	6 (3.6 %)	9 (6.7 %)	
Death	6 (15 %)	11 (11 %)	5 (7.5 %)	6 (4.3 %)	1 (0.3 %)	2 (1.2 %)	1 (0.7 %)	

infection have also been reported [148]. These may lead to the exacerbation of the original cardiovascular disease, which is related to the death of some patients found in the clinic due to heart failure [88,103,132]. According to information released by the Shanghai Municipal Health and Family Planning Commission, the first COVID-19 death in Shanghai was in an individual who was 88 years old with a severe history of hypertension and cardiac insufficiency. An analysis of the cause of death suggested that the patient died of heart failure and systemic multiple organ dysfunction. Therefore, SARS-CoV-2 infection was just an inducement for exacerbations [124].

Overall, the heart and lungs are inseparable in the normal physiological functions of the human body. On the one hand, comorbidities and complications of the heart increase the risk of pneumonia infection and exacerbation; on the other hand, pneumonia infection may aggravate existing cardiovascular diseases, such as increased blood pressure, increased heart failure, and the recurrence of myocardial infarction.

6. Possible pathophysiology of CVD complications caused by coronavirus

6.1. Fever

Fever is a common symptom in patients with coronavirus infection [9,27,149]. Fever promotes the immune functions of humans and some animals and decreases the pathogenicity of some microbes. Antibody production, T-cell activation, neutrophil function, and macrophage oxidative metabolism have been reported to increase in the presence of fever [150–154]. However, to avoid excessively elevated body temperature affecting normal physiological functions, the body will activate sympathetic nerves and regulate circulatory function, which will increase the heart rate and cardiac output [155]. An increase in heart rate over a long period of time will lead to increased myocardial oxygen consumption and decreased cardiac output, which may cause ischemia or heart failure [156]. Many diseases with fever symptoms may be complicated by myocarditis, such as spotted fever rickettsiosis infection [157], severe fever with thrombocytopenia syndrome [158], drug reaction with eosinophilia and systemic symptoms [159], dengue [160–162], complicated scrub typhus [163], herpes simplex virus infection [164], enteric fever [165].

A decrease in cardiac function may occur in febrile illnesses, but whether myocardial damage is due to fever or the underlying infection is not known [166]. Weissinger et al. found that in pigs with a bacterial infection with elevated body temperature, serum CK, lactate dehydrogenase (LD), and gamma-globulin (GG) levels were increased. The administration of antibiotics to these pigs and lowering their body temperature reduced CK and LD levels, but GG levels remained elevated, suggesting that the infection did not decrease. This study indicated that the levels of CK and LD were elevated due to fever caused by infection [167]. K L et al. discovered that a longer duration of fever was related to the occurrence of pericarditis after myocardial infarction [168]. Therefore, heart injury in coronavirus infection may be related to fever.

6.2. Hypoxemia

Severe pneumonia can cause significant gas exchange disturbances and lead to hypoxemia. Hypoxia reduces the energy production required for cell metabolism and increases the body's anaerobic digestion. Acidosis and oxygen free radicals accumulated in the cell destroy the phospholipid layer of the cell membrane. As hypoxia continues, the intracellular calcium ion concentration increases significantly, leading to a series of cell damage processes, including apoptosis [169]. At the same time, hypoxia can also induce inflammatory reactions, such as the infiltration of inflammatory cells and the release of cytokines, leading to further tissue ischemia, and may even cause myocardial infarction

[13,170,171].

6.3. Inflammation

Previous lessons from coronavirus and influenza have shown that viral infections can cause acute coronary syndrome [172,173], arrhythmia [174], and exacerbation of heart failure [175], mainly due to a combination of significant systemic inflammation response and localized vascular inflammation at the arterial plaque, along with other effects [176–178]. Evidence has shown that SARS-CoV induces the expression of proinflammatory cytokines such as monocyte chemoattractant protein 1 (MCP-1), transforming growth factor-beta 1 (TGF-beta1), TNF, IL-1 and IL-6 and interferon- β (IFN- β) in SARS patients and experimental animal models infected with SARS-CoV [179,180]. TNF and IL-1 family and IL-6 family cytokines are considered proinflammatory mediators of heart failure, and they have obvious negative inotropic effects, which may explain heart failure complications in SARS infection [181]. The acute heart injury might be due to the cytokine storm resulting from an overaggressive host immune response to SARS infection [30]. There is evidence indicating that myocardial inflammation induced by SARS-CoV is mainly mediated by macrophages and the resultant production of chemokines [95,96]. The nuclear factor- κ B (NF- κ B) signaling pathway associated with the induction of proinflammatory cytokines is activated in SARS-CoV-infected mice. Treatment with drugs that inhibited NF- κ B activation led to a reduction in inflammation in both SARS-CoV-infected cultured cells and mice and significantly increased mouse survival after SARS-CoV infection, indicating that the activation of the NF- κ B signaling pathway represents a major contribution to the inflammation induced after SARS-CoV infection and that NF- κ B inhibitors are promising antivirals in infections caused by SARS-CoV and potentially other pathogenic human coronaviruses [182].

SARS-CoV-2 appears to affect the myocardium and cause myocarditis [128]. Myocardial injury is likely associated with infection-related myocarditis and/or ischemia [60]. Increases in inflammatory factors such as CRP, IL-1 and IL-6 were also discovered in SARS-CoV-2 infection [131,132,147]. Wu et al. believed that SARS-CoV-2 may cause heart damage by the cytokine storm [131]. Evidence has shown that SARS-CoV-2 may mainly affect T lymphocytes, especially CD4 + T cells, resulting in a significant decrease in lymphocyte numbers [183]. The extent of lymphopenia and an increase in inflammatory cytokines are related to the severity of the disease [147]. Critically ill COVID-19 patients had higher levels of IL6, IL10, TNF α , lactate dehydrogenase (LDH), and C-reactive protein than patients with mild COVID-19 [9,139,184], suggesting that inflammatory indicators are an important factor in the early diagnosis of severe COVID-19.

Most patients with coronavirus infection are in an inflammatory state, which places the patients in a hypercoagulable state. For example, COVID-19 leads to an increase in D-dimer levels in 40 % of patients, a decrease in activated partial thromboplastin time (APTT) in 16 % of patients, and a decrease in PT in 30 % of patients, further increasing the risk of embolism [11]. Hypercoagulability induced by inflammation might contribute to plaque rupture, with subsequent thrombosis and myocardial injury [185]. Therefore, clinicians should pay attention to COVID-19 patients with coronary heart disease to prevent myocardial injury and myocardial infarction.

6.4. Shock

Septic shock can be seen as a serious complication in SARS, MERS and COVID-19 [13,76,103]. Approximately 6.2 % of SARS-CoV-2 infections are complicated by shock [126]. It was reported that left ventricular dysfunction occurs in approximately 20 % of patients within 6 h after the onset of septic shock, and the incidence can increase to 60 % by 1–3 days after the onset of septic shock [186]. Myocardial dysfunction and cardiovascular inflammation might lead to elevated

creatinine kinase and troponin [187], which might explain the high Hs-TnI in deceased patients.

6.5. Stress and anxiety

In addition to the abovementioned accompanying symptoms, anxiety and stress can also lead to adverse reactions such as accelerated heart rhythms and elevated blood pressure, especially in critically ill patients [188,189]. Health anxiety could be found in coronavirus-infected patients [190]. Generally, everyone experiences health anxiety to some degree, and the associated vigilance to a potential health-related threat can be protective. However, excessive health anxiety can be detrimental [190]. The literature indicates that stress can activate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to an increase in peripheral glucocorticoid and catecholamine levels [191]. High plasma catecholamine levels are associated with an increased risk of heart failure. Altered autonomic activity during depression can lead to arrhythmias. The activated SNS alters cardiac wall contractility and increases apoptotic pathways in cardiomyocytes, contributing to CVD development.

Although there is no relevant study on COVID-19 patients suffering from anxiety, medical workers have been reported to be anxious after direct contact with the patients [192,193]. A study by Sun et al. showed that some Chinese showed acute posttraumatic stress symptoms during the COVID-19 outbreak [194]. Therefore, psychological counseling should be conducted on patients in a timely manner, and anxiolytic drugs could be used when necessary.

6.6. Direct effect of coronavirus

As mentioned above, SARS-CoV was reported to lead to myocardial infection with a marked decrease in ACE2 expression, which may be responsible for myocardial dysfunction and adverse cardiac outcomes in patients with SARS [99]. Direct SARS-CoV infection of cardiomyocytes may also lead to myocarditis and impaired myocardial function. Coronavirus-induced myocarditis and its subsequent progression to dilated cardiomyopathy have been described in rabbit models [195]. SARS-CoV was found in heart samples from patients who died of SARS [76]. Pathological findings showed a marked increase in macrophage infiltration in patients with SARS-CoV in the heart, with evidence of myocardial damage. MERS-CoV was not detected in the heart tissue, and the heart showed no significant histological changes in MERS patients [111,112]. However, an animal model study clearly stated that MERS-CoV RNA could be seen in cardiac tissue, implying direct cardiac pathology [113]. Although myocarditis was reported in sporadic autopsy cases [128], there is still no clear pathological evidence supporting that SARS-CoV-2 can directly cause heart damage.

6.7. Complications of the drugs used in COVID-19 patients

The most frequently used drugs during hospitalization are glucocorticoids and antiviral drugs, as well as antibiotics. The secondary QT interval prolongation caused by the use of drugs during hospitalization cannot be ignored. Antiviral drugs (lopinavir, ritonavir), antibiotics (azithromycin, moxifloxacin, levofloxacin), antifungal drugs, glucocorticoids and some antiarrhythmic drugs, there is a potential risk of prolonging the QTc interval [196,197]. Drug-associated QT prolongation is associated with increased arrhythmic and non-arrhythmic mortality and it therefore continues to be an important metric of drug safety [198].

A small study in France enrolling 26 treated patients and 16 non-randomized controls showed that hydroxychloroquine alone or in combination with azithromycin shortened the time to resolution of viral shedding of COVID-19 [199]. Based on this study, clinicians in many countries have begun using these medications in clinical practice, and multiple randomized trials are being initiated. But there were

occasional case reports of hydroxychloroquine prolonging the QT interval and provoking torsade de pointes when used to treat systemic lupus erythematosus [200–203]. The widely used antibiotic azithromycin was gradually recognized as a rare cause of prolonged QT, severe arrhythmia, and increased risk of sudden death [204–207]. Although there were no reports of arrhythmia death caused by the use of hydroxychloroquine, the use of hydroxychloroquine and azithromycin should also be noted [208].

7. Treatment related issues

Active support with expected management based on early prognostic indicators may improve recovery. Appropriate treatment of heart failure, arrhythmia, acute coronary syndrome and thrombosis are still important. With continued global cooperation on multiple methods, specific evidence-based treatment strategies for COVID-19 will emerge. In order to protect the wider population, antibody testing and effective vaccines will be needed to make a history of COVID-19. And some treatment related issues need attention.

Firstly, the use of ACEI / ARB drugs was controversial in the earlier phase of COVID-19 epidemic. But recently published studies suggested that there is no need for patients with hypertension to stop using ACEI / ARB or switch to other antihypertensive medicine [60,61,209]. Some conjectures [210] based on the disease mechanism in the early stage of the outbreak that ACEI / ARB may increase the infection of new coronavirus and the aggravation of COVID-19 by increasing the expression of ACE2 have been denied by more and more clinical evidence. We see that the continuous treatment of COVID-19 patients with hypertension with ACEI / ARB will not only cause the deterioration of the condition, but also continue to exert cardiovascular protection and even improve the prognosis [60,61,209].

Secondly, we should pay attention to the application of hydroxychloroquine [200–203] and azithromycin [204–207] for their side effects of prolonging the QT interval. Other drugs used to treat the COVID-19 patients, such as antiviral drugs (lopinavir, ritonavir), antibiotics (moxifloxacin, levofloxacin), antifungal drugs, glucocorticoids and some antiarrhythmic drugs, can cause the QT interval prolongation and should attract more attention. Reference by Sapp et al. would help to minimize risk of drug-induced ventricular arrhythmia during treatment of COVID-19 [211].

Thirdly, A recent study from JAMA reported that the mortality rate of patients with mechanical ventilation treatment was 88.1 % [212]. Multiple studies around the world have shown that the mortality rate of COVID-19 patients using ventilator was still high [213–215]. And it was believed that the ventilator should be used more cautiously in patients with COVID-19, which can reduce the mortality of patients using the ventilator by more than 50 % [216]. New guidelines should be established for when to use a ventilator for patients with COVID-19. We advocate the application of staged breathing support methods to delay the use of ventilator. Simple oxygen treatment like nasal oxygen supply may be safer and more effective.

Fourth, methylprednisolone are the classical immunosuppressive drugs, which are important to stop or delay the progress of the pneumonia, and have been proved to be effective for the treatment of acute respiratory distress syndrome (ARDS). In recent study [217], Wu et al. found that the administration of methylprednisolone appeared to reduce the risk of death in COVID-19 patients with ARDS. However, of those who received methylprednisolone treatment, 23 of 50 patients died. This is a rather high mortality of ~50 %. The indication, timing, dosage and duration, the application of methylprednisolone needs further investigation.

Fifth, the early report showed that remdesivir was highly effective in the control of SARS-CoV-2 infection in vitro [218]. But recent study published in Lancet showed that remdesivir did not reduce the mortality of COVID-19 patients [219]. However, another clinical trial showed that remdesivir accelerates recovery from advanced COVID-19

[220]. Another clinical trial showed that there was no significant difference in clinical outcome between the 5-day and 10-day course of remdesivir [221]. These data suggested remdesivir does not reduce the mortality of COVID-19 patients, but have an effect on shortening the course of disease in mild patients. And early medication may be better. The application of remdesivir needs further researches.

8. Conclusion

Clinical data indicate that comorbid cardiovascular disease will aggravate the severity of coronavirus infection, leading to a poor prognosis. Coronavirus may cause myocardial injury, and the prognosis of patients with complicated myocardial injury is poor. The mechanism of coronavirus causing myocardial injury and drug treatment options remain to be further studied.

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Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work

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