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Review article

Mechanisms and treatments of myocardial injury in patients with corona virus disease 2019

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ABSTRACT

The infection epidemic event of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was formally declared a pandemic by World Health Organization on March 11th, 2020. Corona Virus Disease 2019 (COVID-19) is caused by SARS-CoV-2, a new type of coronavirus, which has high contagion and mainly causes respiratory symptoms. With the increase in confirmed cases, however, the infection symptoms turn to be diverse with secondary or first clinical symptoms relating to damage of the cardiovascular system and changes of myocardial enzyme spectrum, cardiac troponin I, electrocardiogram, cardiac function. The occurrence of extrapulmonary manifestations, including immediately and long-term damage, means that the overall health burden caused by SARS-CoV-2 infection may be under-estimated because COVID-19 patients developed cardiovascular system injury are more likely to become serious. The factors such as directly pathogen-mediated damage to cardiomyocytes, down-regulated angiotensin-converting enzyme 2 (ACE2) expression, excessive inflammatory response, hypoxia and adverse drug reaction, are closely related to the occurrence and development of the course of COVID-19. In combination with recently published medical data of patients having SARS-CoV-2 infection and the latest studies, the manifestations of damage to cardiovascular system by COVID-19, possible pathogenic mechanisms and advances of the treatment are proposed in this article.

1. Introduction

On February 11, 2020, the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (ICTV-CSG) announced that the novel coronavirus (2019-nCoV) had been officially classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) declared that the novel coronavirus infection was named coronavirus disease 2019 (COVID-19) [1]. By March 11, 2020, more than 118,000 confirmed cases (including 4291 deaths in 114 geographical territories) had been reported, and the WHO made the assessment that the COVID-19 outbreak can be characterized as a pandemic.

SARS-CoV-2 belongs to the Betacoronavirus genus; it is an enveloped, single-stranded RNA virus with a diameter of 50–200 nm, and it is the seventh coronavirus that can infect humans to date [2]. The full genome sequences of SARS-CoV-2 share 79.6% sequence identity to SARS-CoV [3]. In a comparative analysis of genomic data between SARS-CoV-2 and other coronaviruses in nature, Andersen et al. observed two notable SARS-CoV-2 spike protein features, including the optimized receptor-binding dimain (RBD) and polybasic cleavage site, which suggested that SARS-CoV-2 is not a product of purposeful manipulation [4]. Tang et al. found that SARS-CoV-2 strains had 149 mutation sites. They also proposed that SARS-CoV-2 has evolved into two subtypes, L type and S type, which account for 70% and 30% of the viral population, respectively [5].

In general, SARS-CoV-2 first causes pneumonia via the respiratory tract. The main symptoms are fever, dry cough, fatigue or myalgia. Chest X-ray shows extensive inflammatory infiltrates of the lungs. While most patients with COVID-19 present with respiratory symptoms as the primary clinical manifestations, some patients present with cardiovascular symptoms, including palpitations and chest tightness, as the initial symptoms. Therefore, it is essential to investigate SARS-CoV-2–related cardiovascular symptoms and potential mechanisms and search for potential treatment targets and practical treatment strategies

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to facilitate epidemic prevention and control.

2. SARS-CoV-2-related cardiac injury

2.1. Acute cardiac injury

With the increase in confirmed cases, acute cardiac injury is not rare. Early COVID-19 case reports suggested that 5 of the first 41 confirmed COVID-19 patients (12%) had acute myocardial injury, characterized by high-sensitivity cardiac troponin I (hs-cTnI) > 28 pg/mL; of these patients, 4 had severe forms of the disease [6]. Later, in another clinical cohort of COVID-19, CK and lactate dehydrogenase (LDH) were increased in 13% and 76% of patients, respectively [7]. Wang et al. analyzed 138 hospital patients and found that 10 (7.2%) had acute cardiac injury. In addition, critically ill patients had significantly higher levels of myocardial markers, such as CK-MB and hs-cTnI, suggesting that severe patients were more susceptible to acute myocardial injury [8].

Tachycardia, bradycardia and arrhythmia are common in SARS. For example, in a study of 121 SARS patients, tachycardia was observed in 87 patients (71.9%), transient bradycardia in 18 patients (4.9%) and atrial fibrillation in 1 patient, suggesting transient heart injury [9]. It was shown that in addition to sinus tachycardia, SARS-CoV can also cause supraventricular arrhythmia, ventricular arrhythmia, first-degree atrioventricular block, and ST-T segment changes [10]. Similarly, 23 (16.7%) of 138 COVID-19 patients had arrhythmia [8]. Furthermore, Guan et al. found that severe and critical patients were more likely to present with fever-independent tachycardia, which may be associated with exacerbation [11].

Some coronavirus infections may seriously affect the heart. For instance, in rabbits, coronavirus may induce cardiomyopathy that may result in cardiac chamber dilatation and impairment of systolic function [12]. Chen et al. found that patients, even without underlying cardiovascular diseases, can also suffer from severe heart failure in the wake of SARS-CoV-2 infection and eventually die of sudden cardiac death [7]. Likewise, Hu et al. reported a case of coronavirus infection presenting fulminant myocarditis [13], and Gnecchi et al. reported a case of acute myocarditis in a 16-year-old boy positive for SARS-CoV-2 [14]. The patient, complaining of chest pain, did not have any of the signs or symptoms typically reported in COVID-19, indicating the possibility that cardiovascular involvement may exclusively be due to COVID-19 and not a comorbidity. As SARS-CoV-2 and SARS-CoV both belong to the Betacoronavirus genus, electrocardiographic changes and troponin elevation may signal underlying heart injury, and echocardiography frequently demonstrates subclinical left ventricular diastolic impairment in COVID-19 patients.

2.2. Chronic cardiac damage

The clinical effects of pneumonia have been associated with an increased risk of cardiovascular disease up to a 10-year follow-up [15]. Long-term follow-up data concerning 25 recovered SARS patients showed that 68% of survivors had hyperlipidemia, 44% had cardiovascular system abnormalities and 60% had glucose metabolism disorders [16]. Among them, the most significant metabolic disruptions were the comprehensive increase in phosphatidylinositol and lysophosphatidylcholine levels. However, the mechanisms by which SARS-CoV leads to dyslipidemia and long-term cardiovascular damage are still unclear. It is worth paying attention to whether SARS-CoV-2 causes chronic damage to the cardiovascular system. Recently, Puntmann et al. demonstrated that patients who recovered from COVID-19 had ongoing cardiac involvement, indicating that the virus may have a long-term effect on the heart [17,18].

2.3. SARS-CoV-2 infection with underlying cardiovascular disease

Some SARS-CoV-2 patients have chronic underlying diseases, especially cardiovascular disease and diabetes, and these patients are more susceptible to severe conditions after infection [8]. The Chinese Centers for Disease Control and Prevention released a report of more than 70,000 COVID-19 cases that showed that mortality was significantly higher in patients with comorbidities, with overall mortality rates of approximately 10.5% in patients with cardiovascular disease and 6.0% in patients with hypertension [19]. An analysis of 1099 clinical patients suggested that COVID-19 patients with previous cardiovascular diseases, such as hypertension and coronary heart disease, were at higher risk for cardiovascular system damage or mortality [11]. Chronic cardiovascular diseases reduce the natural cardiac reserve and impair the patient's ability to fight severe pneumonia. As a result, these patients are more susceptible to acute cardiovascular events after infection. For example, the systemic inflammatory response and its procoagulant effects may lead to plaque rupture, thrombosis and myocardial infarction in patients with coronary heart disease [20]. In Shanghai, the first death related to SARS-CoV-2 pneumonia was an 88-year-old patient with severe hypertension and cardiac insufficiency. Further analysis showed that the SARS-CoV-2 infection only induced heart failure and systemic multiorgan dysfunction in the patient [21].

3. SARS-CoV-2 possible mechanisms for heart damage

3.1. Direct cardiac infection by SARS-CoV-2

Some COVID-19 patients have chest pain and other cardiovascular symptoms as the main symptoms, and the serological markers of cardiac injury are significantly increased, suggesting the possibility that SARS-CoV-2 may be a cardiotropic virus. Previous research has documented that SARS-CoV can directly attack human cardiomyocytes by binding angiotensin-converting enzyme 2 (ACE2) [22,23]. SARS-CoV-2 has similar gene sequences and clinical manifestations and the same cell receptor on its envelope. ACE2 is expressed in the heart, including in endothelial cells and cardiomyocytes [24]. More recently, emerging evidence has shown the presence of SARS-CoV-2 in the myocardial tissue of autopsy cadavers [25]. The virus mainly exists in endothelial cells, which may affect heart microcirculation and lead to abnormal myocardial zymograms. However, we cannot rule out the possibility of the virus directly attacking cardiomyocytes, since the expression level of ACE2 in endothelial cells is higher than that in cardiomyocytes and the patients who underwent autopsy did not show symptoms of myocarditis during the illness.

Xu et al. discovered that compared with that of SARS-CoV, which emerged in 2003, the spike protein of SARS-CoV-2 has a similar structure and high affinity with ACE2, suggesting that SARS-CoV-2 may infect humans in a manner similar to SARS-CoV, in which the spike protein binds to ACE2 in the lungs, and the complex is then internalized into alveolar cells [2]. Moreover, one study found that epithelial cells infected with SARS-CoV-2 can lead to an increase in ACE2 expression on adjacent cells by activating the interferon pathway, which may provide SARS-CoV-2 with more invasive sites [26].

ACE2 is also expressed in the heart, indicating that SARS-CoV-2 is likely to attack cells of the myocardium [27]. The viral load in vivo increases and lasts for more than 1 week, suggesting that the virus could directly attack cardiomyocytes and cause viral myocarditis [28]. However, additional pathological evidence is needed to confirm the direction of cardiomyocyte infection by SARS-CoV-2.

3.2. Downregulation of ACE2 in cardiac tissues

ACE2 was identified as an angiotensin-converting enzyme (ACE) homologue in 2000, and its sequence is 42% homologous to that of ACE. It is a member of the zinc metalloprotease family and is a type I

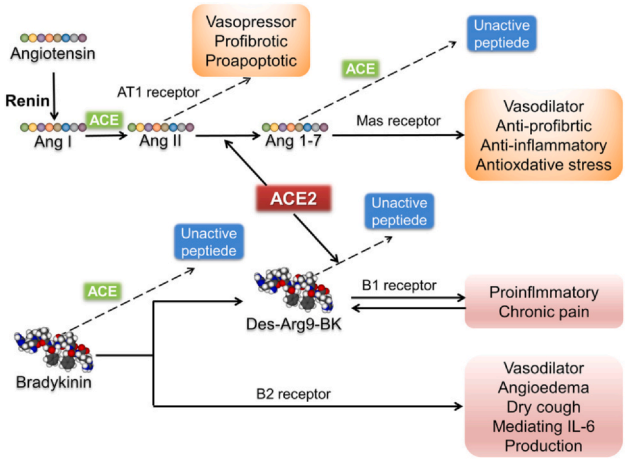

Fig. 1. Schematic of the proposed mechanism underlying ACE2 and ACE effects.

membrane protein encoded by a gene on the X chromosome. ACE2 has 805 amino acids, including an N-terminal signal peptide, a catalytic extracellular domain, a transmembrane domain, and a C-terminal intracellular domain [29]. Both ACE2 and ACE belong to the renin-angiotensin system (RAS) family, but they differ in their roles. ACE2 can hydrolyze angiotensin (Ang I) to produce Ang 1–9, which is then hydrolyzed by ACE or another peptidase to produce the vasodilator peptide Ang 1–7. ACE2 can also directly act on angiotensin II (Ang II) to produce Ang 1–7, which is far more efficient than hydrolyzing Ang I. Ang 1–7 exerts vasodilatory, antiproliferative, and antioxidative stress effects by binding to the Mas receptor [30]. It is a potent negative regulator of RAS and provides protective effects for the cardiovascular system (Fig. 1). (See Table 1.)

Crackower et al. showed that ACE2 knockout has a severe impact on mouse cardiac contraction, increases Ang II levels and upregulates hypoxia-induced genes in the heart, indicating that ACE2 is vital for cardiac function [31]. Oudit et al. showed that in mice with SARS-CoV lung infection, the expression of ACE2 mRNA and protein was downregulated in myocardial tissues [23]. In one possible pathway, a decrease in ACE2 could cause a decrease in cardioprotective Ang 1–7, probably resulting in an imbalance between the ACE/Ang II/AT 1R axis and the ACE2/Ang 1–7/Mas axis. This is followed by elevated levels of Ang II, which could accelerate the occurrence and development of cardiovascular diseases. On the other hand, studies have shown that ACE2 degrades Des-Arg9-bradykinin [32]. When ACE2 is decreased following myocardial injury, the Des-Arg9-bradykinin/bradykinin (BK) 1 receptor pathway may be overactivated, thereby promoting inflammatory responses (Fig. 1).

Ang I, angiotensin; Ang II, angiotensin II; ACE, angiotensin converting enzyme; ACE2 , angiotensin converting enzyme 2; AT 1R , angiotensin type I receptor. B1 receptor, Bradykinin 1 receptor, B2 receptor , Bradykinin 2 receptor. ①The predominant physiological function of ACE is in cardiovascular homeostasis through hydrolyzing Ang I to produce the potent vasoconstrictor, angiotensin II, which can

Table 1
Treatment plan of corona virus disease 2019 (COVID-19).

Patient	Clinical types	Clinical manifestations	Therapeutic measures
COVID-19 patients	Light or common COVID-19 patients	Manifestations accord with the appropriate criteria of *The Diagnosis and Treatment plan of Corona Virus Disease 2019 (Tentative Seventh Edition)* [46]	General treatment: 1.Support therapy 2.Monitoring life signs 3.Oxygen therapy 4. Antiviral drugs 5.Antibiotics when necessary
	Severe or critical COVID-19 patients		1.General treatment 2.Respiratory support: mechanical ventilation, extracorporeal membrane oxygenation(ECMO) for acute respiratory distress syndrome patients
		Patient with renal failure symptoms	1. General and symptomatic treatment 2. Etiological therapy 3. Continuous renal replacement therapy
		Patient with disease progressed quickly	1. General and symptomatic treatment 2. Rehabilitee plasma therapy
		Patient with cytokine storm	1. General and symptomatic treatment 2. Blood purification: plasma exchange, adsorption, perfusion i.e.
		Patient with the increase of serum IL-6	1. General and symptomatic treatment 2. Immunotherapy: trastuzumab (IL-6 mAb)
		Patient with excessive inflammatory response, severe respiratory distress and so on	1. General and symptomatic treatment 2. Glucocorticoid 3. Xuebijing injection (a traditional Chinese medicine): intravenous 100 ml/day, twice a day 4. Microecological preparation prevents secondary bacterial infection
COVID-19 patient complicated with cardiovascular system injury	COVID-19 patient with acute cardiac injury [75]	The increase of myocardial enzyme spectrum or cTnI	1. Medications to protect myocardium and improve cardiac function: Co-enzyme Q, Vitamin C, sodium creatine phosphate
	COVID-19 patient with arrhythmia	Electrocardiogram abnormal, clinic symptoms such as palpitation, chest stuffiness	1. Antiarrhythmics 2. Anticoagulant 3. Intervention therapy
	COVID-19 patient with heart failure [73]	Patient with the increase of BNP,or the occurrence of dyspnea, edema	1. Etiological therapy 2. Anti-heart failure 3. EOMO when necessary
	COVID-19 patient with acute coronary syndrome [73]	Acute chest pain,the changes of cTnI, electrocardiogram abnormal. i.e.	1. Thrombolysis 2. Percutaneous coronary intervention (PCI) when necessary

COVID-19, Corona Virus Disease 2019; ECMO, extracorporeal membrane oxygenation; IL-6 mAb, interleukin 6 monoclonal antibody; cTnI, cardiac troponin I, which can reflect myocardial infarction; BNP, brain natriuretic peptide, a marker of heart failure.

promote vasoconstriction, fibrosis and apoptosis by binding to AT 1R.ACE also inactivates the vasodilator Ang 1–7, bradykinin, by the sequential cleavage of two C-terminal dipeptides. ② ACE2 can hydrolyze a number of physiologically relevant peptides including both angiotensin I and angiotensin II. Ang 1–7 exerts vasodilatory, anti-proliferative, and anti-oxidative stress effects by binding to the Mas receptor, indicating ACE2 is a negative regulator of renin-angiotensin system. ③ACE2 also can inactivate des-Arg9-bradykinin. The decrease of ACE2 induces the increase of des-Arg9-bradykinin, which has an inflammatory effect. ACE link renin-angiotensin system and kinin-kallilrein system by cleaving bradykinin. The decrease of ACE can produce the increase of bradykinin, which exerts positive effect of vasodilation, angioedema, but also negative effect of mediating the production of interleukin-6.

3.3. Cytokine storms and autoimmune response

Many severe patients among the first confirmed SARS-CoV-2 patients developed cytokine storms [6,8]. Cytokine storm, also known as cytokine release syndrome, refers to the rapid production of a large amount of various cytokines, including tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), and interferon-γ (IFN-γ), in body fluids following microbial infection. It is an important cause of acute lung injury, acute respiratory distress syndrome (ARDS) and multiorgan disorders in patients with viral infections [33]. As mentioned above, ACE2 has an inhibitory action on the RAS. Liu et al. found that the plasma Ang II level of COVID-19 patients was significantly higher than that of healthy controls [28]. Moreover, Ang II levels in COVID-19 patients are closely correlated with viral titer and lung injury, suggesting that SARS-CoV-2 may lead to acute lung injury due to an imbalance in the renin-angiotensin system in patients and that ACE2-associated pathways may be involved in the inflammatory storm.

Early studies showed that in SARS patients, elevated serum pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, IFN-γ, interferon-inducible protein 10 (IP10), and monocyte chemoattractant protein 1 (MCP1), were related to pulmonary inflammation and lung injury [34]. Similarly, Huang et al. analyzed 41 COVID-19 patients and found significantly elevated IL-1β, IFN-γ, IP10, and MCP1, which may lead to T helper type 1 (Th1)/Th2 imbalance and cause T cell-mediated immune injury [6]. One study indicated that SARS-CoV-2 can cause intense multifactorial immune responses, and early adaptive immune responses may be associated with better prognosis [35]. Moreover, the levels of granulocyte colony-stimulating factor (GCSF), IP10, MCP1, macrophage inflammatory protein 1 alpha (MIP1α), and TNF-α were significantly elevated in ICU patients, which suggests that cytokine storms are positively correlated with the severity of the disease [6].

One retrospective study found that increases in COVID-19 patient serum hs-cTnI, CK-MB, IL-6, C-reactive protein, and procalcitonin were associated with a decrease in lymphocyte counts and CD4/CD8 ratios, suggesting that SARS-CoV-2 infections may lead to heart damage through excessive inflammatory responses [36]. Previous studies reported that inflammatory factors such as IL-1β, IL-6, interleukin 8 (IL-8) and TNF-α can promote coagulation and even thrombosis via multiple pathways, increasing the risk of thromboembolism [37]. Moreover, a study proposed three characteristics of poor prognosis in COVID-19 patients, including older age, higher sequential organ failure assessment (SOFA), and obviously elevated levels of D-dimer (> 1 μg/L). In particular, the increase in D-dimer reflected a persistent state of inflammatory response, which may exacerbate myocardial injury [38]. The first minimally invasive autopsy of a SARS-CoV-2 patient showed markedly elevated pro-inflammatory cells, such as CC chemokine receptor 4-positive (CCR4 +), CC chemokine receptor 6-positive (CCR6 +) and helper T 17 (Th17) cells, which may partially explain the severe lung immune injury. Additionally, the autopsy showed inflammatory infiltration of a small number of mononuclear cells in the myocardial stroma, implying cardiac inflammation [39]. Together, these data suggest that cytokine storms may be one of the mechanisms of myocardial injury.

3.4. Other mechanisms

Hypoxemia caused by viral infection is another important mechanism of cardiac damage since it can induce some adverse responses, such as mitochondrial injury and oxidative stress. Acidosis and the generation of oxygen free radicals during hypoxia and hypoxia-reperfusion can aggravate myocardial injury, while hypoxia can also induce inflammatory responses, thereby further aggravating cardiac tissue damage [40]. In addition, symptoms such as fever, inflammation, and tachycardia, etc. in COVID-19 patients may further exacerbate the imbalance in oxygen supply and demand.

The side effects of antiviral drugs cannot be underestimated during the treatment of COVID-19. The *Diagnosis and Treatment Plan of Coronavirus Disease 2019 (Tentative seventh version)* recommends the use of lopinavir and/or ritonavir, both of which are protease inhibitors and should not be used in combination with statins or for patients with coronary heart disease [41]. Chloroquine can cause cardiac arrhythmias and even cardiac arrest, the most serious adverse reaction [42]. For COVID-19 patients, azithromycin and hydroxychloroquine can increase the risk of different arrhythmias, such as prolonged QT intervals, torsade de pointes and sudden cardiac death [43]. In addition, Arbidol is associated with an increase in the heart failure rate when used in combination with drugs such as azithromycin and quinolones [44]. Interferons may affect the cardiac conduction system, causing cardiac arrhythmia as well as local myocardial ischemia and cardiomyopathy [45].

In addition, for COVID-19 patients, excessive anxiety, tension, and physical and mental stress may induce the release of a large amount of catecholamine, resulting in myocardial toxicity, microcirculation disturbances, vasospasm, and arrhythmia, all of which impair cardiac function and may even cause stress cardiomyopathy.

4. Treatment of cardiovascular injury associated with SARS-CoV-2 infection

4.1. Antiviral therapy

The Diagnosis and Treatment Plan of Coronavirus 2019 (Tentative seventh version) recommends the use of antiviral drugs, including α-IFN, lopinavir/ritonavir, ribavirin (combined with one of the above medications), chloroquine and Arbidol [46]. Beyond that, many medications have been included in clinical trials. Previously, the Ministry of Science and Technology of the People's Republic of China officially announced that both favipiravir and remdesivir were scheduled for clinical trial. The results of the “Clinical Study on the Safety and Efficacy of Favipiravir in the Treatment of Patients with Coronavirus Disease 2019 (COVID-19)” (Registration Number: ChiCTR2000029600) suggested that favipiravir may be effective in reducing the clearance time of SARS-CoV-2. Compassionate use of remdesivir for severe COVID-19 patients may have certain benefits [47]. Nevertheless, the current data are limited, and further research confirming the clinical benefits of remdesivir for COVID-19 patients is warranted. In addition, researchers found that early treatment with the triple antiviral therapy combination of interferon beta-1b (IFN β-1b), lopinavir/ritonavir, and ribavirin may help patients with mild to moderate COVID-19 recover [48]. Aside from antiviral drugs, a recombinant adenovirus type-5 vectored COVID-19 vaccine, a subunit vaccine created by Chen Wei et al., has been approved for clinical trials, and the data from the first phase of trials of the vaccine showed that it is safe, tolerable, and immunogenic in healthy adults [49]. However, one study found that lopinavir/ritonavir treatment is no better than standard care in hospitalized adult patients with severe COVID-19 [50].

4.2. ACE2 as a potential target during the treatment of SARS-CoV-2 infection

SARS-CoV-2 mainly invades alveolar epithelial cells via ACE2 and causes pulmonary inflammation. However, as the number of infections has increased, some patients have presented with virus-associated cardiovascular injury, which may result from direct myocardial injury via ACE2 or a range of pathophysiological changes owing to ACE2 downregulation. Thus, ACE2 can be regarded as a potential therapeutic target for SARS-CoV-2 infection. These possibilities include blocking the binding between ACE2 and SARS-CoV-2, suppressing ACE, and using recombinant human ACE2 protein for pulmonary protection.

4.2.1. Blocking the binding between SARS-CoV-2 and ACE2

Zhou et al. found that the ACE2 expressed in mammalian cells has more glycosylation sites in its extracellular domain. They believed that these glycosylation modifications may affect the binding between the SARS-CoV-2 spike protein and ACE2 [51]. Some researchers have investigated the structure of the SARS-CoV-2-human ACE2 complex and first revealed the interaction between the spike protein of SARS-CoV-2 and ACE2 at the molecular level [52,53], providing clues to guide the development of targeted drugs and vaccines. SARS-CoV-2 must bind to the ACE2 expressed on the cell surface to infect cells, so modifying the ACE2 binding site or changing its configuration may be potential approaches. Chloroquine inhibits viral infection by increasing the pH of the viral inclusion bodies required for virus-cell fusion and interfering with glycosylation at the ACE2 terminal [54]. Chloroquine phosphate has been proven to effectively inhibit SARS-CoV-2 in vitro and is scheduled for large clinical trials [55]. It was suggested that type II transmembrane serine proteases (TMSPSS2) can activate SARS-CoV-2 S proteins to bind with ACE2 and enter host cells, so TMSPSS2 inhibitors prevented the SARS-CoV-2 Spike proteins from binding to ACE2 [56].

In addition, vaccines against SARS-CoV-2 are a classic and traditional choice. Currently, researchers around the world are working together to develop an effective vaccine. To date, there are 169 vaccines in the trial phase, 30 of which are in the clinical trial phase, with 6 in phase III, including a nonreplicating viral vector (ChAdOx1–5) from the University of Oxford (ISRCTN89951424), an RNA vaccine (LNP-encapsulated mRNA) from Moderna (NCT04470427), an RNA vaccine (LNP-mRNA) from BioNTech (NCT04368728), an inactivated vaccine from Sinovac (NCT04456595), and 2 inactivated vaccines from Sinopharm (ChiCTR2000034780). Additionally, Chen et al. announced the completion of the phase II clinical trial of Ad5-nCoV (ChiCTR2000031781) and are waiting to enter phase III.

4.2.2. ACE inhibitors (ACEIs)

SARS-related studies have shown that after SARS-CoV infection, ACE2 was downregulated in the lungs, causing ACE/ACE2 imbalance. Moreover, the increase in Ang II may result in overactivation of the AT 1 receptor and acute lung injury [57]. Decreased ACE2 combined with elevated Ang II is a potential mechanism of lung injury, which also indicates that ACEIs and angiotensin II receptor blockers (ARBs) may inhibit such injury. In animal studies, the administration of enalapril in mice with acute lung injury quickly reduced Ang II levels [58], while the administration of captopril reduced IFN-γ, prostaglandin E2 (PGE2), and TGF-β1 levels and increased interleukin 4 (IL-4) levels, thereby regulating the Th1/Th2 balance [59] and reducing pulmonary inflammation and lung injury. A retrospective study showed that continuous in-hospital administration of ACE inhibitors can reduce mortality and intubation rates in non-SARS patients [60].

However, Ferrario et al. showed that while the administration of ACEIs and ARBs to rats reduced blood pressure, it caused ACE2 levels to increase 4.7 times and 2.8 times, respectively [61]. The increase in ACE2 levels may make it easier for the virus to enter cells. In addition, Liu et al. suggested that ACE inhibitors increase the level of bradykinin, which binds to bradykinin B2 receptor (B2R) to dilate vessels and reduce blood pressure but may also increase vascular permeability and aggravate pulmonary edema. Bradykinin also mediates IL-6 production via the B2R/Erk 1/2 pathway and thus aggravates inflammation. Therefore, Liu et al. recommended that COVID-19 patients with hypertension discontinue the antihypertensive ACEIs and ARBs (if applicable) and switch to calcium channel blockers (CCBs). However, the European Society of Hypertension (ESH) emphasized that there is no evidence that ACEIs and ARBs can increase the risk of SARS-CoV-2 infection or cause deterioration of COVID-19 patients [62], so ACEIs and ARBs should not be discontinued easily for COVID-19 patients with pre-existing cardiovascular disease. For stable patients, the use of ACEIs and ARBs should be executed according to the recommendations in the 2018 ESC/ESH guidelines 1 [63]. Currently, researchers are still debating the use of ACEIs, and further clinical data are needed to verify the conclusions.

4.2.3. Use of recombinant human ACE2 (rhuACE2)

Animal studies have shown that treating ACE2-knockout mice with rhuACE2 injections reduced acute lung injury resulting from acid aspiration or sepsis and improved pulmonary edema [57]. In a phase II clinical study, the use of rhuACE2 in 10 patients with ARDS rapidly reduced Ang II while increasing Ang 1–7, suggesting that ACE2 injections in humans may regulate the ACE2/ACE balance in the lungs and help to treat acute lung injury [64]. Recently, Monteil et al. found that human recombinant soluble ACE2 can prevent SARS-CoV-2 from infecting engineered human blood vessels and kidneys [65].

4.3. Treatment of cytokine storms associated with SARS-CoV-2 infection

As mentioned previously, SARS-CoV-2 infection could induce overactivation of the immune system, resulting in cytokine storms, multiple organ dysfunction syndrome (MODS), and even death. Therefore, the combination of blocking cytokine storms, regulating homeostasis, and protecting organ function is a promising approach to treat SARS-CoV-2 infection and reduce mortality. Currently, most targeted drugs for COVID-19 are still being tested in preclinical studies, and symptomatic treatment remains the primary therapy. It is essential to promptly and effectively block the occurrence and development of the inflammatory response to improve patient outcomes. The expert panel of the Chinese Society of Immunology recommended the following treatments for cytokine storms: antishock therapy, supportive and symptomatic treatment, proper steroid treatment at an appropriate dose level, and neutralizing antibodies [66]. *The Diagnosis and Treatment plan of Corona Virus Disease 2019 (Tentative Seventh Edition)* recommends that patients with an excessive inflammatory response receive short-term (3 to 5 days) steroid therapy [46]. It should be noted that high-dose steroid therapy may delay viral clearance. Moreover, blood purification therapy may be considered if possible to remove cytokines and correct pH and electrolyte disorders [46]. In addition, melatonin, a well-known anti-inflammatory and antioxidative molecule, is protective against ALI/ARDS caused by viruses and other pathogens, which suggests avenues for new potential therapeutic targets [67].

Studies have shown that compared with those of nonsevere patients, IL-6 levels are obviously increased in severe COVID-19 patients, suggesting that IL-6 monoclonal antibodies (mAbs) may be used to treat cytokine storms associated with SARS-CoV-2 infection [68]. Zhou et al. found that granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-6 play a pivotal role in the inflammatory storm caused by SARS-CoV-2 [69]. Zhou introduced the use of a new effective regimen of tocilizumab (IL-6 mAb) + conventional therapy for 14 severe patients at the First Hospital, University of Science and Technology of China. To further evaluate the efficacy and safety of tocilizumab in COVID-19 pneumonia, a prospective, multicenter, randomized controlled study (ChiCTR2000029765) was registered on the official website of the Chinese Clinical Trial Registry [70]. The *Diagnosis and*

Treatment Plan of Corona Virus Disease (Tentative Seventh Edition) recommends the use of plasma therapy during the recovery stage in patients with rapid progression and severe or critical conditions [46]. Some researchers further proposed that in addition to tocilizumab, specific SARS-CoV-2 antibodies from convalescent patients may be added to the plasma to treat patients during the recovery stage. Zhang et al. successfully isolated monoclonal antibodies from the B lymphocytes of convalescent patients and found that two of those antibodies showed a strong ability to prevent SARS-CoV-2 from binding the ACE2 receptor [71]. Recently, Cao et al. identified SARS-CoV-2-neutralizing antibodies by high-throughput single B cell sequencing of antigen-enriched B cells from 60 convalescent patients, and they found that BD-368-2, the most potent one of these antibodies, showed high therapeutic and prophylactic efficacy in SARS-CoV-2-infected mice [72]. While clinical trials are ongoing, the use of plasma during the recovery stage has potential unknown risks and ethical issues. It is unlikely to be developed and mass-produced in the near future. Therefore, specific antibodies and vaccines are the main methods for treating and preventing COVID-19.

4.4. Treatment of SARS-CoV-2 infection with underlying cardiovascular diseases

Current data show that all age groups are at risk of SARS-CoV-2 infection, and the condition is generally more severe in elderly patients and those with underlying diseases [73]. Fifty percent of COVID-19 patients had complications, of which hypertension was the most common comorbidity, followed by diabetes and coronary heart disease, that led to high mortality [38]. Therefore, COVID-19 patients with pre-existing cardiovascular disease should be closely monitored for any symptoms and signs of cardiovascular dysfunction. Recently, the American College of Cardiology (ACC) released a clinical bulletin [74] that proposed that elderly patients should be closely monitored for cough or shortness of breath and indicated that a personalized regimen that helps stabilize plaques (involving treatments such as statins, β-blockers, ACE inhibitors, aspirin) and provides additional protection for cardiovascular patients should be administered. When acute myocardial injury occurs, medication to improve myocardial energy metabolism can significantly protect and improve cardiac function, and when heart failure occurs, etiological treatment is the optimal choice. In addition to routine anti-heart failure treatment, extracorporeal membrane oxygenation (ECMO) should be implemented as early as possible. Moreover, for COVID-19 patients comorbid with chronic underlying cardiovascular disease, the primary cardiovascular disease must be managed, and organ protection and homeostasis maintenance must be ensured during antiviral therapy. If a critical cardiovascular condition occurs in a COVID-19 patient, the treatment principles include treatment of the viral infection first, followed by risk assessment, conservative treatment (preferred), and self-protection. Thrombolysis is preferred for patients with non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) without relevant contraindications; emergency percutaneous coronary intervention (PCI) may be performed under close monitoring in patients with acute STEMI with hemodynamic instability and patients with life-threatening NSTEMI [75]. In addition, oxygen support, treatments to maintain electrolyte balance and improve myocardial metabolism, and mental health intervention and counseling are also essential for effective treatment.

5. Preventive measures

It is necessary and important for citizens to take precautions such as wearing a face mask or respirator, wash hands frequently and ventilating rooms regularly. After all, 86% of all infections were undocumented before the 23 January 2020 travel restrictions, and those were the major cause of the rapid spread of SARS-CoV-2 in China [76]. Therefore, increasing the identification and isolation of asymptomatic patients would be important to fully control epidemics. A new study suggested that the median duration of detoxification in COVID-19 patients is 20 days, with the shortest duration being 8 days and the longest duration being 37 days [38]. This is of vital importance for both the decision of isolation and the guidance of the duration of antiviral therapy for early and effective antiviral therapy, which may improve the prognosis of patients.

6. Conclusion

The outbreak of SARS-CoV-2 infection has been defined as a pandemic that is seriously contagious and can spread through many transmission routes. Early reports show that cardiovascular injury in the wake of viral epidemics is not uncommon. In addition, patients with chronic cardiovascular disease are at an increased risk of acute cardiovascular events with poor prognosis. To effectively treat COVID-19 patients, health care professionals must be knowledgeable about the prevention and treatment of infectious diseases while paying attention to the underlying disease and organ protection. We summarized the symptoms and pathogenesis of myocardial injury, existing therapies and promising new directions of COVID-19. Although the SARS-CoV-2 information already identified in our article might only be the tip of the iceberg, we still hope this review will provide a relatively comprehensive summary and some directions for clinical treatment and new therapeutic targets of COVID-19.

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Declaration of competing interest

The authors declare that there are no conflicts of interest

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