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# The effects of novel coronavirus (SARS-CoV-2) infection on cardiovascular diseases and cardiopulmonary injuries

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ABSTRACT

COVID-19 caused by a novel coronavirus named SARS-CoV-2, can elites severe acute respiratory syndrome, severe lung injury, cardiac injury, and even death and became a worldwide pandemic. SARS-CoV-2 infection may result in cardiac injury via several mechanisms, including the expression of angiotensin-converting enzyme 2 (ACE2) receptor and leading to a cytokine storm, can elicit an exaggerated host immune response. This response contributes to multi-organ dysfunction. As an emerging infectious disease, there are limited data on the effects of this infection on patients with underlying cardiovascular comorbidities. In this review, we summarize the early-stage clinical experiences with COVID-19, with particular focus on patients with cardiovascular diseases and cardiopulmonary injuries, and explores potential available evidence regarding the association between COVID-19, and cardiovascular complications.

## 1. Introduction

COVID-19, a novel betacoronavirus, causes severe acute respiratory syndrome. It was first isolated from some patients with pneumonia in Wuhan of China in December of 2019. Since it causes similar symptoms to the previous SARS virus, it was originally called SARS-CoV-2. The novel coronavirus is a coronavirus of the beta genus, characterized by a capsule and round or oval shape. The incubation period in the patients ranges from 1 to 14 days, with most around 3 to 7 days (Huang et al., 2020). In the following months, COVID-19 had become a worldwide pandemic, with about 78,326,033 documented cases globally as of Dec 23, 2020. It quickly became a major threat to global public health and no very effective treatment exists currently due to the novel nature of COVID-19. Extensive public-health measures to reduce person-to-person transmission of COVID-19 have been implemented globally to curb the spread of disease, reduce the burden on healthcare systems, and protect vulnerable populations, including the elderly and those with underlying medical comorbidities, especially associated with cardiovascular diseases, and the myocardial damage caused by SARS-CoV-2 has received great attention in clinic.

According to the novel coronavirus pneumonia diagnosis and treatment plan, the main clinical manifestations of COVID-19 are fever, dry cough, and fatigue. Some patients present with nasal congestion, runny nose, sore throat, myalgia, diarrhea, and other symptoms. Patients with mild disease only showed low fever, mild fatigue, and no pneumonia. In the course of the disease, severely affected patients may have moderate or low fever, or even no obvious fever (Wang et al., 2020); whose patients usually have dyspnea and/or hypoxemia one week after the onset of the disease. These patients can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation dysfunction, and multiple organ failure. COVID-19 causes viral pneumonia with additional extrapulmonary manifestations and major complications, including acute myocardial injury, acute myopericarditis, arrhythmia and shock. It is revealed that global cardiovascular disease, hypertension and diabetes mellitus are the most prevalent comorbidities associated with the severity of COVID-19, from a meta-analysis of 46,248 cases. ARDS and acute cardiac injury may represent the main complications for the recovery of patients (Hu et al., 2020; Su et al., 2020). Fifteen percent of patients developed cardiovascular disease, who became infected have cardiovascular disease previously (Lake, 2020). Patients with COVID-19 are highly susceptible to death due to endothelial dysfunction and endogenous heart failure (Del Turco et al., 2020). Global cardiovascular disease were significantly associated with mortality in COVID-19 patients (Shamshirian et al.,

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2020).

At the time of this review, data on the effects of this infection on patients with cardiovascular disease were limited. We focused on cardiovascular risk factors such as ACE2 and cytokine storm so as to understand the role of SARS-CoV-2 on the cardiovascular system (Su et al., 2020). We also summarized the early experience of COVID-19 with particular focus on patients with cardiovascular disease. We provided evidence for further understanding of the pathogenesis of COVID-19 so as to provide a basis for designing cardiac-protective strategies.

## 2. Virological characteristic of novel coronavirus pneumonia patients with various clinical classifications

The clinical classification of novel coronavirus infection is mainly light, normal, heavy and severe. There may be various manifestations of cardiac injuries in different clinical types. Mild and ordinary patients usually have a lower probability of cardiac injury (Angeli et al., 2020). ECG changes occur in individual cases. 2%–4% of mild patients have myocardial necrosis markers damage, while severe patients have a higher risk of cardiac injury, which is 22.2%–31%. The risk of cardiac injury in dead patients is higher than that in survivors, which is 28%–88.9% (Bhatla et al., 2020). In addition, the follow-up chronic damage caused by virus infection is also worthy of attention. Many cases including high-grade artioventricular block, artial filbrillation, polymorphic ventricular trachycardia, cardiogenic shock and pulseless electrical activity arrest were highlight the spectrum of arrhythmias observed in patients with COVID-19 infection (Bhatla et al., 2020). The prognosis of covid-19 patients should be followed up in time. When making decisions regarding choice of antiarrhythmics, ionotropes, and vasopressors, clinicians need to keep in mind potential proarrhythmic effects of antimalarial and antibiotic therapies currently being investigated as therapeutic agents against COVID-19 (Jeremic et al., 2015). We classified and summarized the cardiac manifestations of patients with different clinical types after infection. Shown in Table 1.

### 2.1. Initial diagnosis method

Early diagnosis and treatment are critical to prevent the spread of the disease and to improve the cure rate. These includes nucleic acid detection and serological diagnosis technologies (Huang et al., 2020). The SARS-CoV-2 infection in suspected cases is currently confirmed according to the following evidence: 1) real-time fluorescence RT-PCR detection of SARS-CoV-2 nucleic acid, with clinical symptoms and epidemiological features (Hirotsu et al., 2020), including oral swabs, throat swabs, nasal swabs, saliva, bronchoalveolar lavage fluid, blood, urine and fecal or rectal swabs. The SARS-CoV-2 nucleic acid diagnostic kit include a fluorescent PCR method, a joint probe anchoring polymerization sequencing method and an isothermal amplification method (Perng et al., 2020); 2) viral gene sequencing, highly homologous with the new coronavirus; 3) serological positivity of specific IgM antibody and IgG antibody to SARS-CoV-2. Common methods include immunoassay, colloidal gold strip, indirect immunofluorescence and pathogen isolation, electrochemiluminescence ELISA (Kourilov and Steinitz, 2002),4) SARS-CoV-2 specific IgG antibody turned increased from negative to 4-fold acute phase levels. 5) High-resolution computed tomography (CT) of the chest has been considered a complementary diagnostic modality (Pan et al., 2020). Thin-slice CT of the is simple and fast; combined with epidemiological history and clinical manifestations, it aids early isolation and intervention of suspected or confirmed cases. CT also evaluate the severity of the disease and dynamically monitor the disease process, so as to guide timely decision-making and provide prognostic information. The appearance of lungs on CT are described in various stages: stage I (0–4 d), stage II (5–9 d), stage III (10–14 d), and stage IV (>14 d). In patients with COVID-19, bilateral lung involvement occurs in all stages (I, III, IV: 100.00%, II: 87.50%); the lesions are mainly peripherally distributed (subpleural distribution) (stage I: 50.00%, stage II: 62.50%, stage III: 60.00%, and stage IV: 90.00%), most commonly among those with stage IV.

### 2.2. Pathophysiology

According to the limited autopsy and biopsy histopathological findings, the following pathophysiology is a summary.

Pathophysiology on the heart and blood vessels**:** Degeneration and necrosis were seen in myocardial cells, and a few mononuclear cells, lymphocytes and/or neutrophils were seen in the stroma. There was some vascular endothelium exfoliation, intimal inflammation and thrombosis. It is reported that patients with congenital heart disease could be considered at higher risk for complications from COVID-19 (Fang et al., 2020). Certain congenital heart disease patients in adults are likely at higher risk than others; includes the following conditions: double-outlet ventricle cyanotic heart defects, double-outlet ventricle, Fontan procedure, interrupted aortic arch, mitral atresia, single ventricle, pulmonary stresia, transposition of the great arteries, truncus arteriosus, other abnormalities of atrioventricular and ventriculoarterial connection. These symptoms could be considered high risk for complications related to COVID-19 infection on the basis of decreased functional reserve.

Pathophysiology on the lung: The lung shows consolidation to varying degrees. Serous, fibrinous exudate and hyaline membrane were found in alveolar cavities. Focal hemorrhage and necrosis of lung tissue have been found, and hemorrhagic infarctions. Some alveolar exudates appear organized, associated with interstitial fibrosis (Jin et al., 2020). Under electron microscope, coronavirus particles were found in the cytoplasm of bronchial mucosa epithelium and type II alveolar epithelial cells. The novel coronavirus antigen novel coronavirus antigen was positive in some alveolar epithelial cells and macrophages, and RT-PCR detected positive for new coronavirus DNA.

Pathophysiology on other organs including spleen, hilar lymph nodes and bone marrow, kidney, brain etc. The spleen was obviously reduced. The number of lymphocytes was significantly reduced, focal hemorrhage and necrosis, macrophages proliferation and phagocytosis were observed in spleen, while the number of lymphocytes in lymph nodes was less and necrosis was seen. The number of three lineage cells in bone marrow decreased. The liver might dark red, the gallbladder is highly filled. Liver cell degeneration, focal necrosis with neutrophil infiltration, congestion of hepatic sinuses, infiltration of lymphocytes and monocytes in portal area, and microthrombosis. With the kidney, protein exudate was found in the glomerular balloon cavity, and the renal tubular epithelium degenerated and fell off, and transparent tubular type was seen. Interstitial congestion, microthrombosis and focal fibrosis were observed. The brain tissue was congested and edematous, and some neurons degenerated. Focal necrosis of adrenal gland was found. The mucosal epithelium of esophagus, stomach and intestine was denatured, necrotic and exfoliated.

### 2.3. Transmission routes (human-to-human transmission)

Respiratory droplets and close contact are currently the known transmission routes. In relatively closed environments, the virus propagates through aerosols at high concentrations for long periods of time (Patel et al., 2020). Because SARS-CoV-2 can be isolated from feces and urine, attention should be paid to the spread of aerosols or contacts caused by environmental pollution by feces and urine. The transmission of tears and mother-to-child transmission remains to be confirmed (Vivanti et al., 2020). There are no effective drugs and vaccines, and active participation of the entire population in self-protection and self-isolation has become the key to cutting off transmission routes and effectively controlling the epidemic.

**Table 1**
Viral effects on the heart and on patients with cardiovascular conditions.

| | Type | Clinical features | Incidence of heart injury/control strategies | Reference |
|---|---|---|---|---|
| **Clinical classification** | Light | The clinical symptoms were mild and no pneumonia was found on imaging. | 2%–4% | (Huang et al., 2019; Angeli et al., 2020) |
| | Common type | With fever, respiratory tract and other symptoms, imaging showed pneumonia. | | |
| | Heavy | Shortness of breath, RR $\geq$ 30 times /min; Under resting state, oxygen saturation $\leq$ 93%; $PaO_2$ / $FiO_2$ $\leq$ 300 mmHg(1 mmHg = 0.133 kPa); Significantly progressed from lung imaging within 24–48 h(>50% patients:severe cases). | 22.2% − 31% | |
| | Dangerous and heavy | Respiratory failure and need mechanical ventilation;2. Shock;3. Patients with other organ failure need ICU monitoring and treatment. | 28% − 88.9% | |
| **Types of heart damage** | Acute myocardial injury | Acute right or left heart failure or total heart failure | Vasoactive drugs or mechanical circulation support;ECMO | (Zaninotto et al., 2020; Ama et al., 2020; Eastin and Eastin, 2020; Zunyou and McGogan, 2020) |
| | | Cardiogenic shock | IABP and ECMO | |
| | | Various types of arrhythmias, serious ventricular tachycardia, ventricular fibrillation | Depending on the type of arrhythmia and the hemodynamic status of patients with fulminant myocarditis | |
| | | Fulminant myocarditis | Vasoactive drugs and invasive mechanical ventilation. | |
| | | Acute myocardial infarction | STEMI isolated ward on the spot. Thrombolytic therapy (without thrombolytic contraindications); PCI or CABG (with thrombolytic contraindications). | (Franco et al., 2020; Abbasifard and Khorramdelazad, 2020; Chousterman et al., 2017) |
| | | Acute Myopericarditis | Pericardiocentesis, Surgery | |
| | | Acute aortic dissection | Surgery, control blood pressure | |
| | | Blood pressure | Control blood pressure | |
| | Underlying cardiovascular disease complicated with COVID-19 infection aggravates the injury | Acute myocardial infarction, coronary heart disease | STEMI; PCI or CABG. | (Vivanti et al., 2020; Wrapp et al., 2020; Zayet et al., 2020) |
| | | Myocarditis | Early use of steroid drugs, immunoglobulin, antiviral treatment (suspected myocarditis), breathing apparatus and circulatory support system | |
| | | Heart failure | Diuretics, vasodilators etc, the use of guideline-recommended medications be maintained in patients with preserved hemodynamics and blood pressure. | |
| | | Palpitation | Myocardial protective and nutritional drugs:coenzyme Q10, creatine phosphate, vitamin C, polarizing liquid and deep sea fish oil. | |
| | Chronic myocardial injury | Stage A (no abnormal cardiac structure and no clinical symptoms of heart failure, high risk of heart failure in the future); Stage B (with abnormal cardiac structure, but no clinical symptoms of heart failure); Stage C and Stage D (with clinical stage, abnormal cardiac structure and clinical heart failure symptoms) | Statins, beta blockers, angiotensin-converting enzyme inhibitors, aspirin and other drugs | (Shi et al., 2020; Perrotta et al., 2020) |

Notes: PCI:Percutaneous coronary intervention; CABG:coronary artery bypass grafting

## 3. SARS-CoV-2 caused cardiopulmonary injuries and strategies for prevention and treatment

Novel coronavirus infection is typically characterized by respiratory symptoms, and some patients have viral infection related heart injuries. Cardiac function may be the decisive factor affecting the development of severe infection with cardiovascular disease. At the same time, it was found that the prognosis of patients with cardiovascular disease was more serious than that of common patients. We divided SARS-CoV-2 caused cardiopulmonary injuries into two situations: 1) The cardiovascular injuries caused by COVID-19; 2)underlying cardiovascular disease complicated with COVID-19 infection aggravates the injury. One is cardiovascular injuries caused by SARS-CoV-2. It might cause cardiovascular injures in COVID-19 patients by targeting many genes specific to endothelium in the heart, lungs and vessels, which can increase vulnerability to cardiac injury via inhibition of cardioprotective proteins or activate pathways for systemic immune-mediated cardiovascular injuries. One of the proposed mechanisms might direct injury to myocardial cells due to viral invasion of the vascular endothelium and myocardium. The second presumption is the impact of tissue hypoxia, destabilization of coronary plaque, and micro-thrombogenesis caused by the systematic inflammation associated with cytokine storm. The other situation is that cardiovascular basic diseases may accelerate the progress of COVID-19 disease. Case fatality rate of COVID-19 patients without associated disease is relatively low. While if the COVID-19 patients are underlying cardiovascular disease complicated, it can be classified as high risk patients, and the clinical prognosis of these patients is worse than that of ordinary patients. The gross mortality of patients with underlying diseases is much higher, with crude fatality rate was 10.5%.The fatality is even higher than those with cancer, those with diabetes, chronic respiratory diseases, and hypertension.

Zhong Nanshan team sampled 1099 patients with covid-19 from 30 provinces and cities in China, of which 14.9% were complicated with hypertension, and hypertension patients were more likely to develop into severe cases, with a high incidence of composite endpoint events. 2.5% of patients with coronary heart disease were also more likely to develop into severe cases. 5 (12%) of the 41 patients with covid-19 were diagnosed with virus-related heart injury, mainly manifested as the increase of high-sensitivity troponin (>28 ng/L) (Chen et al., 2020). Four of the five patients were admitted to intensive care unit (ICU), accounting for 31% of the total number of ICU patients. 2 patients had no cardiovascular basic diseases, but obvious cardiac injury occurred in the process of disease progression. One case showed persistent abnormal myocardial enzyme spectrum and ST segment change of ECG, and one case showed sudden progressive decrease of heart rate and no heart sound was heard. It was also reported that 2% of patients had chest pain during hospitalization.

The levels of serum myocardial necrosis markers were increased in both mild and severe patients, but the risk of cardiac injury was higher in severe patients (22.2%–31%) and mild patients (2%–4%). The risk of cardiac injury in dead patients was higher than that in survivors (28%–88.9%). In addition, chronic damage is worthy of attention. The prognosis of covid-19 patients should be followed up in time. The novel coronavirus infection induced acute myocardial injury, and chronic myocardial damage caused by new coronavirus infection., and the covid-19 patients whose combined with underlying cardiovascular diseases usually aggravated intrinsic myocardial injury, which might getting worse. In addition to active antiviral therapy, attention should be paid to the control and treatment of cardiovascular disease for such patients.

### 3.1. SARS-CoV-2 and myocardial injury

Many studies have found abnormal myocardial enzymes and myocardial injury markers in patients with COVID-19. Myocardial infarction is more common in these patients. This outcome is closely related to the severity of the disease and the increased risk of death in the hospital (Liu et al., 2020). The abnormal degree of myocardial injury markers is related to the severity of the patient's condition. In 22%-58.1% of severe SARS-CoV-2 patients, the myocardial damage markers are elevated (Driggin et al., 2020). Studies also found that the levels of troponin, C-reactive protein, and procalcitonin in patients with COVID-19 were also significantly elevated (Shi et al., 2020). It is suggested that for older patients with COVID-19 (especially men) with abnormal myocardial enzymes, myocardial injury markers and imaging indicators, caregivers should pay more attention to heart injury, so as to make interventional treatment decisions and improve outcomes (Chen et al., 2020; Guo et al., 2020). However, there remain many problems and bottlenecks in the current understanding, research, and treatment of COVID-19, including whether abnormal increases in levels of myocardial enzyme and myocardial damage markers are caused by viral infection, by septic shock, liver Injury, kidney injury, or by other comorbidities; more basic research and autopsy studies are needed.

### 3.2. SARS-CoV-2 and myocarditis

Myocarditis is increasingly recognized as a complication of COVID-19 and may result from direct viral injury or from exaggerated host immune response. Myocardial injury in patients with COVID-19 can be diagnosed by increasing the number of dynamic or routine ECG examinations and the examination of myocardial enzymes and inflammatory factors. For patients with suspected myocarditis, there should be early use of sufficient doses of steroids and intravenous immunoglobulin, and antiviral therapy, as well as ventilatory and circulatory support. It showed that C-reactive protein and procalcitonin increased in all children, which were higher than 94 mg/L and 1.6 ng/mL, respectively.. Patients with COVID-19 and acute myocarditis need to be diagnosed early after infection and be referred to expert centers for treatment.

In April 2020, of four children and adolescents who were admitted to the intensive care due to multiple system inflammatory syndrome and Kawasaki disease-like features associated with the SARS-CoV-2 were found to have acute myocarditis symptoms within one week of admission (Blondiaux et al., 2020). SARS-CoV-2 was negative for qPCR in nasopharyngeal, respiratory tract and fecal specimens; however, there was positive serology. Cardiac MRI showed symptoms of diffuse myocardial edema.Endomyocardial biopsy may be performed if the diagnosis remains uncertain. These modalities are helpful for the diagnosis of myocarditis after SARS-CoV-2 infection in children and adolescents (Blondiaux et al., 2020). Vasoactive drugs and invasive mechanical ventilation are current management. In the setting of cardiogenic shock and refractory, life-threatening arrhythmias that persist despite medical therapy, advanced mechanical circulatory support devices should be considered. Besides, it is mainly supportive with the potential addition of interventions recommended for severe COVID-19 disease, such as remdesivir, steroids, and convalescent plasma.

### 3.3. SARS-CoV-2 and heart failure

Studies found that heart failure was one of the main causes of death in patients with COVID-19. A wide range of factors can result in HF including coronary artery disease (CAD), hypertension, cardiomyopathy, atrial fifibrillation, or HF due to obesity. It is possibly related to renin-angiotensin-system (RAS) and ACE2 receptors (Zhang et al., 2020); besides in patients who are more susceptible to heart failure, such as obese patients, the systemic inflflammation that results from COVID-19 infection may further increase the risk for heart failure. RAS is closely related to the occurrence and development of cardiovascular diseases; it plays an important role in regulating and maintaining the balance of blood pressure, water and electrolyte balance, and homeostasis (Min et al., 2017). ACE2 has high homology to ACE. ACE2 converts extracellular Ang I and Ang II into Ang-(1–7). Both ACE2 and Ang-(1–7) inhibit cardiomyocyte hypertrophy, inflammatory reactions, and

oxidative stress caused by Ang II (Mercure et al., 2008). Relevant animal studies showed that ACE2 and Ang-(1–7) inhibited ventricular remodeling (Huentelman et al., 2005; Grobe et al., 2007). Crackower et al. reported that ACE2 gene knockout mice had elevated levels of Ang II, decreased levels of Ang-(1–7) expression, and severe heart failure (Kassiri et al., 2009; Verdecchia et al., 2020). The results of these animal experiments show that, after knocking out the expression of ACE2 in rat myocardium, the response of inflammatory factors and oxidative stress was enhanced, resulting in enhanced myocardial damage. It is speculated that the pathogenic mechanism in patients with COVID-19 may involve the binding of SARS-CoV-2 virus to ACE2, resulting in decreased ACE2 expression and increased Ang II expression in plasma and myocardial tissues. Decreased expression levels of Ang-(1–7), inflammatory responses and oxidative stress induce myocardial damage that turn leads to decreased myocardial contractility and heart failure (Chen et al., 2020). SARS-CoV-2 infection can result in oxidative stress, fibrosis, diastolic dysfunction, and subsequent systolic heart failure, mainly due to increased ROS production, low baseline levels of cytoprotective autocoids, uncoupling of mitochondrial enzymes etc.

### *3.4. The cardiovascular burden of COVID-19 with a focus on congenital heart disease*

Currently, there are emerging data of the effect of COVID-19 on patients with congenital heart disease, Adults with congenital heart disease represent a growing and complex population of patients who requires protection from SARS CoV-2 and a proactive, tailored treatment in case of COVID-19 infection. Many patients with CHD are also afflicted with residual haemodynamic lesions, such as valve dysfunction, diminished ventricular function, arrhythmias, or cyanosis, have extracardiac comorbidities, and face additional challenges regarding pregnancy. Patients with residual pulmonary hypertension, central cyanosis, and the absence of a sub pulmonary ventricle were considered at the greatest risk of adverse COVID-19 outcomes. However, many aspects including risk stratification and treatment considerations, remain unclear. In another group, many studies on COVID-19 in children with congenital heart disease have been reported. Children are usually less prone to acquiring COVID-19, if infected often exhibit mild disease ranging from flu-like to no symptoms. However, Children with CHD, may develop serious COVID-19 related cardiovascular complication, which are more likely to require ICU admission and artificial respiratory support, especially those with cyanotic defects. Additionally, pediatric COVID-19 patients with complex cardiac comorbid conditions may likely develop severe and critical, for example depressed myocardial contractility, pulmonary hypertension. Experts should provide meticulous care to this at-risk population. All current management strategies for children are extrapolated from what is known about the effect of COVID-19 on adult patients with cardiovascular disease (Tan and Aboulhosn, 2020).

### *3.5. The effect of SARS-CoV-2 on lung and treatment*

The clinical manifestations of patients with COVID-19 are primarily fever and cough. From CT imaging, the lesions in each stage with different types of lung injuries are characterized by ground glass opacities, consolidation, and mixed density lesions (paving stone-like changes). Of these, the mixed density lesions at each stage are more common. Compared with stages II–IV, ground glass opacities in stage I is more common (50.00%). Compared with stage I, the lesions showed consolidations more often in stages II–IV, of which the third stage had the largest proportion (50.00%). Striated lesions appeared more often in stages II–IV, of which stages III and IV had the largest proportions (100.00%). No patients had pleural effusions or mediastinal lymphadenopathy (Xie et al., 2020; Xiang et al., 2020). Once a patient with underlying disease is more easier to be infected, the lungs show obvious signs, and the proportion of cough symptoms increases (Fu et al., 2020a, 2020b). Patients with underlying diseases are more likely to evolve critical illness. The proportion of symptoms of chest tightness and shortness of breath was 32.14%, which is higher than that of the group without underlying diseases (Wang et al., 2020).The pathophysiology of SARS-CoV-2 causing lung injury includes its binding to ACE2, resulting in a series of lung injuries. This also includes cytokine storms. The cytokines involved to “cytokine storms” include interferons, interleukins, chemokines, and tumor necrosis factors. The virus may activate nuclear transcription factor, activator protein-1 and activator-2 (Marazuela and Giustina, 2020). It can cause the recruitment of specific inflammatory cytokines and neutrophils, and it can also lead to the excessive production of chemokines, all of which ultimately lead to respiratory failure and death.

All patients with COVID-19 should be treated with various antiviral drugs (such as α-interferon, lopinavir/ritonavir, ribavirin, chloroquine phosphate, and ridacive) to improve lung function. Simultaneously, attention should be paid to the adverse reactions of drugs, contraindications, and interactions with other drugs. There should be treatments with appropriate combinations of antibacterial drugs (Wu et al., 2006). For patients with ARDS, more in-depth treatment plans should be adopted. Many hospitals regard noninvasive positive pressure ventilation (NPPV) as the main treatment for patients with ARDS. Nevertheless, the effect is not ideal, and some patients die of respiratory failure; therefore, NPPV should be used with caution. In addition, we must pay close attention to the patient’s respiratory rate, tidal volume, oxygen saturation and other indicators (Tuffet et al., 2020; Rocker et al., 1999). If the patient’s respiratory distress does not improve after NPPV treatment, then regardless of oxygen saturation, noninvasive ventilation should be terminated and changed to endotracheal intubation. NPPV should also be monitored in terms of patient tolerance. If the patient develops anxiety, abdominal distension, difficulty sleeping, or even consciousness disturbances during the treatment, failure of NPPV should be considered, and tracheal intubation may be an option (Chawla et al., 2020). Extracorporeal membrane oxygenation is often used as a rescue measure to treat critically ill patients and is regarded as a guarantee for lung-protective ventilation (Lotz et al., 2016).

## 4. COVID-19 may result in cardiac injury via several mechanisms

As described above, the cardiac injuries associated with COVID-19 includes a variety of clinical presentations of acute cardiac injury, cardiomyopathy, and hemodynamic instability etc. Myocardial injury, arrhythmias, cardiac arrests, heart failure, and coagulation abnormality were reported with COVID-19 in China. We summarized the proposed mechanisms of cardiovascular injury in COVID-19 are as follows: The most frequently mentioned mechanism is related to angiotensin-converting enzyme 2(ACE-2) receptors. It is reported that SARS-CoV-2 has high affinity for ACE2 and infects cells by binding with the ACE2 receptor, the affinity between S protein and ACE2 of SARS-CoV-2 was 10–20 times higher than that of SARS-CoV, suggesting that the virus was more infectious (Wrapp et al., 2020). The ACE-2 receptors are used for cellular entry by SARS-CoV-2 are expressed in the lung as well as in various organs, including the heart and endothelial cells. SARS-CoV-2 has been shown to trigger an exaggerated systemic inflammatory response that, in addition to acute lung injury and ARDS, may ultimately lead to multiple cardiovascular complications, including acute myocardial infarction, unstable angina, tachycardia, heart failure, and stroke (Zayet et al., 2020). SARS-CoV-2 promoted an aberrant release of pro-inflammatory cytokines and chemokines by alveolar epithelial cells, vascular endothelial cells, activated monocytes and lymphocytes, all of which express ACE2 on their surfaces. Secondly, another mechanism was related to cytokine storm, which is associated with vascular leakage, activation of the coagulation cascade, and cardiomyopathy. The cytokine storm and profound inflammation seen in patients with severe COVID-19 are associated with macrophage and endothelial activation

and surges in the levels of IL-6, IL-1, IL-8, and TNF-α. The most reliable hypothetical pathogenetic mechanism for cardiovascular complications and cardiac injury in severe COVID-19 patients appears to be a sustained endothelial dysfunction, caused by the interplay of inflammation and coagulation (Serena et al., 2020).Direct SARS-CoV-2 infection of the endothelial cells along with diffuse endothelial inflammation has been reported (Serena et al., 2020).In addition, it is also reported that a hypercoagulable state in a cluster of patients with COVID-19 with a high incidence of venous thromboembolism (VTE) despite the use of prophylactic anticoagulants. Furthermore, SARS-CoV-2 induced lymphocyte death through pyroptosis, which could explain why patients COVID-19 are often lymphopenic, thereby further contributing to organ injury. We summarized detailedly the most important mechanisms of novel coronavirus-related pathology below.

### 4.1. Myocardial injury mediated by downregulation of ACE2

ACE2 is expressed in lung, heart, kidney, and the gastrointestinal tract, localized in cardiomyocytes, cardiac fibroblasts, pericytes, vascular endothelium, and vascular smooth cells (Zaninotto et al., 2020). Zou et al. analyzed the distribution of ACE2 in human respiratory, cardiovascular, digestive and urinary systems using single cell RNA sequencing data (Zou et al., 2020). They found that ACE2 was expressed not only in type II alveolar epithelial cells and lower respiratory tract epithelial cells, but also in cardiac muscle, vascular endothelium, esophageal epithelium, renal proximal convoluted tubule, and bladder epithelial cells. These findings suggest that these organs should be regarded as high-risk organs for SARS-CoV-2 infection. The cardiovascular system is a potential target organ of cardiovascular SARS-CoV-2 (Oudit and Pfeffer, 2020; Guo et al., 2019). The ACE2-related signaling pathway may play a key role in myocardial injury. SARS-CoV-2 can affect the regulation of the renin angiotensin system (RAS) system by downregulating the expression of ACE2, thereby causing or aggravating cardiac damage (Ganatra et al., 2020; Oudit et al., 2007). RAS is one of the most important body fluid regulation systems. It can regulate blood pressure, water and electrolyte balance, and maintain homeostasis, playing important roles in the regulation of cardiovascular activities. Under physiological conditions, the ACE angiotensin II and ACE2 ang (1–7) axes maintain dynamic balance (Santos et al., 2018, 2003). However, in COVID-19 patients, expression of ACE2 is downregulated, leading to decreased Ang (1–7) levels, thereby weakening vasodilation and blood pressure reduction, as well as anti-inflammatory, anti-proliferation, anti-fibrotic, and anti-apoptotic effects in alveolar epithelial cells. The abnormal increase of AngII levels aggravates vasoconstriction, blood pressure, inflammatory reactions, apoptosis and pathogen proliferation, resulting in de novo heart damage or aggravation of pre-existing chronic cardiovascular disease (Fig. 1).

As for the treatment plan for this mechanism, the key to prevention and improvement of cardiac injury is to inhibit the damage of cardiac myocytes and microenvironment induced by SARS-CoV-2. Viral spindles bind to ACE2 via their receptor binding domain; therefore, these regions are considered to be the main targets for prevention of viral entry. As ACE2 is expressed in many tissues including vascular endothelium and cardiac tissue, there have been some suggestions that ACE-inhibitors and angiotensin receptor 1 blockers may have an effect on the course of COVID-19. Novel vaccines are also hot topics in the control of COVID-19.

### 4.2. Cytokine storm

Over-production of inflammatory cytokines and chemokines was common in COVID-19 patients, when acute heart and lung injury was diagnosed. Further investigations are required to elucidate the potential role of the cytokine storm in the pathogenesis of cardiovascular complications following SARS CoV-2 infection and to understand the potential mechanistic relationships between cardiovascular diseases and COVID-19 outcomes. Cytokine storm is an important cause of morbidity and mortality, caused by imbalances of T-helper 1 and T-helper 2 cells that lead to disease progression and myocardial damage, which were associated with the severity of COVID-19, ranging from mild to severe and multiple organ failure. In the context of severe infection caused by SARS-CoV-2 infection, negative and positive feedback regulation of this system is accelerated, and the immune regulation network becomes unbalanced, resulting in sharp increases in levels of various cytokines, leading to stronger immune responses. Cytokine storm can aggravate diffuse damage of pulmonary capillary endothelial cells and alveolar epithelial cells, resulting in a large amount of lung exudation; it can also act on vascular endothelial cells, thereby producing platelet

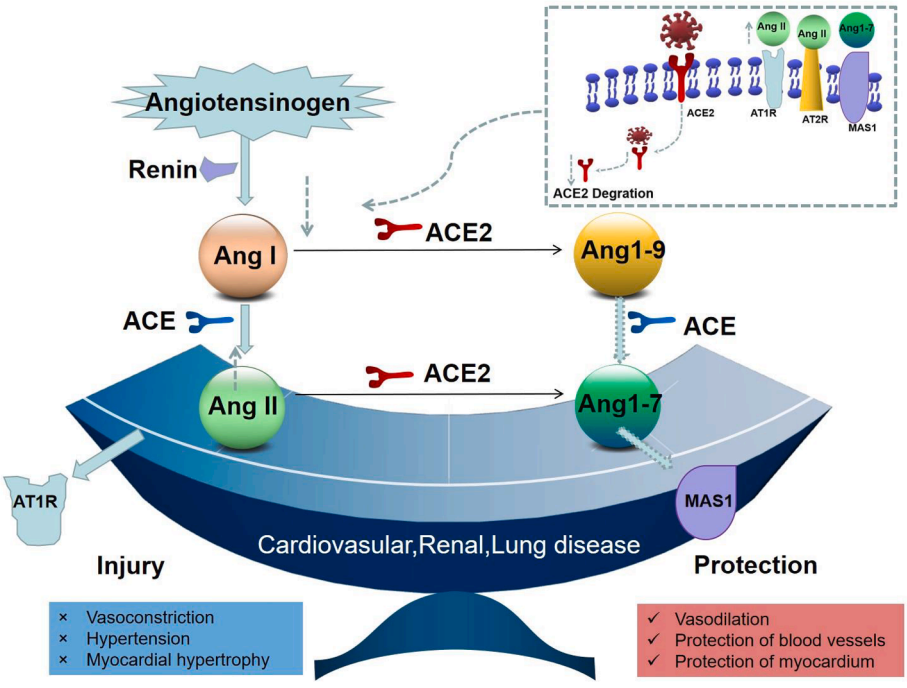


**Fig. 1.** The role of renin-angiotensin system and myocardial injury caused by SARS-CoV-2 affecting ACE2. The combination of SARS-CoV-2 with ACE2 resulted in the decrease of ACE2 expression, the increase of Ang II expression in plasma and myocardium, and the decrease of Ang(1–7) expression. Inflammatory reaction and oxidative stress induced myocardial injury, which led to decreased myocardial contractility and heart failure. MAS angiopoietin 1–7 receptor, ACE:angiotensin-converting enzyme, AT angiotensin II receptor, Angangiotensin.

aggregation factor, prostaglandins, and leukotrienes, damaging the arterial intima, causing high cardiac output and resulting low microcirculatory resistance. The end results are myocardial ischemia, hypoxia, and necrosis (Wu et al., 2020; Panigrahy et al., 2020). Below, we discuss the role of cytokine storm induced by SARS-CoV-2, the included cytokines are small proteins synthesized and secreted by immune cells, including interleukins (IL), interferons (IFN), and tumor necrosis factor (TNF), all which are widely involved in immune responses and inflammatory response regulation. The specific mechanisms and processes are shown in Fig. 2.

The "cytokine hypothesis" for cardiac damage states that the deleterious effects of chronic cytokine release on myocardium and vascular endothelium may facilitate the onset of acute myocardial infarction or heart failure. For example, the proinflammatory cytokines interleukin-1 (IL-1), IL-6, and TNFα exert negative inotropic effects on cardiac contractility. Likewise, the sustained activation of inflammatory signaling through TNFα and IL-1β may induce massive cardiomyocyte apoptosis and lead to pathological left ventricular remodeling, which favors the onset of acute heart failure. Furthermore, cytokine storm stimulates monocytes/macrophages to release matrix metalloproteinases that boost atherosclerotic plaque growth and rupture, favoring the secretion of pro-coagulant factors and inducing hemodynamic changes, thereby increasing the probability of AMI. Huang et al. reported that plasma levels of inflammatory mediators, including IL-1β, IFNγ, IP10 (CXCL10), and MCP1 (CCL2), were upregulated in patients with COVID-19. The authors showed that cytokine levels were remarkably higher in critically ill patients. In particular, serum levels of granulocyte-colony stimulating factor (G-CSF), IP10, MCP1, MIP1A (CCL3), and TNFα were higher in patients who were admitted to the intensive care unit than in those who were not, suggesting that the cytokine storm is a clinical predictor of mortality. Zhu et al. reported that levels of hyper-sensitive cTnT and inflammatory biomarkers were significantly higher in non-surviving patients with COVID-19. The high inflammatory burden in severe COVID-19 has been further confirmed by another independent study, which reported higher levels of serum ferritin, IL-6 and C-reactive protein in patients who did not survive, likely because of fulminant myocarditis.

There are many drug method including ILs receptor antagonists, TNF-α antagonist, Anti-VEGF agents etc from the mechanism on cytokine storms. It is worth mentioning that chloroquine should not be used together with moxifloxacin. The combination of macrolides and fluoroquinolones can prolong QT interval. Cytokine Storm Induced by SARS-CoV-2 and the Drug Therapy methods are shown in Table 2 (Alvi et al., 2019; Shi et al., 2013; Yang et al., 2020; Oliviero et al., 2020; Dashti-Khavidaki and Khalili, 2020; Kong et al., 2020; Yin et al., 2020; Mangalmurti and Hunter, 2020; Franco et al., 2020; Abbasifard and Khorramdelazad, 2020; Chousterman et al., 2017; Conti et al., 2020; Rawson et al., 2020; Jamwal et al., 2020; Kai and Kai, 2020; Braga et al., 2020; Ma et al., 2019; Wen et al., 2020; Menk et al., 2015; C. China Association Of Integrative Medicine Emergency Medicine, 2019; Eliezer and Eloit, 2020; Remy et al., 2020; Kale et al., 2020; Yi et al., 2020).

### 4.3. Endothelial dysfunction

The underlying cause of respiratory failure and organ dysfunction is essentially thrombosis, inflammation and endothelial dysfunction in COVID-19 patients. Disfunction of the endothelium turns into a disastrous battlefield of the complex interaction between "cytokine and coagulative storms" can be irreparably compromised and result in systemic inflammatory complications. The molecular mechanisms of myocardial injury during COVID-19 infection are usually be summed up in several aspects:Direct injury through connection to ACE2 receptors that are expressed in the myocardium; Indirect injury due to the systemic inflammatory response syndrome (SIRS) and the cytokine storm that the infection provoke; Infection-induced vasculitis attributed either to contamination of the endothelial cells or to immunological response.

### 4.4. Oxidative stress

Severe hypoxia from acute respiratory damage caused by the virus may result in oxidative stress and myocardial injury from increased myocardial oxygen demand in the presence of severe hypoxia due to ARDS. Persistent spasm of pulmonary capillaries can cause pulmonary hypertension, in turn leading to left ventricular ejection dysfunction (Sengupta and Dutta, 2020). Myocardial cell damage and necrosis may occur in the context of long-term hypoxia, and the function of the center of gravity will be damaged. Patients with severe COVID-19 may suffer from embolism due to long-term bedrest, malnutrition, and abnormal

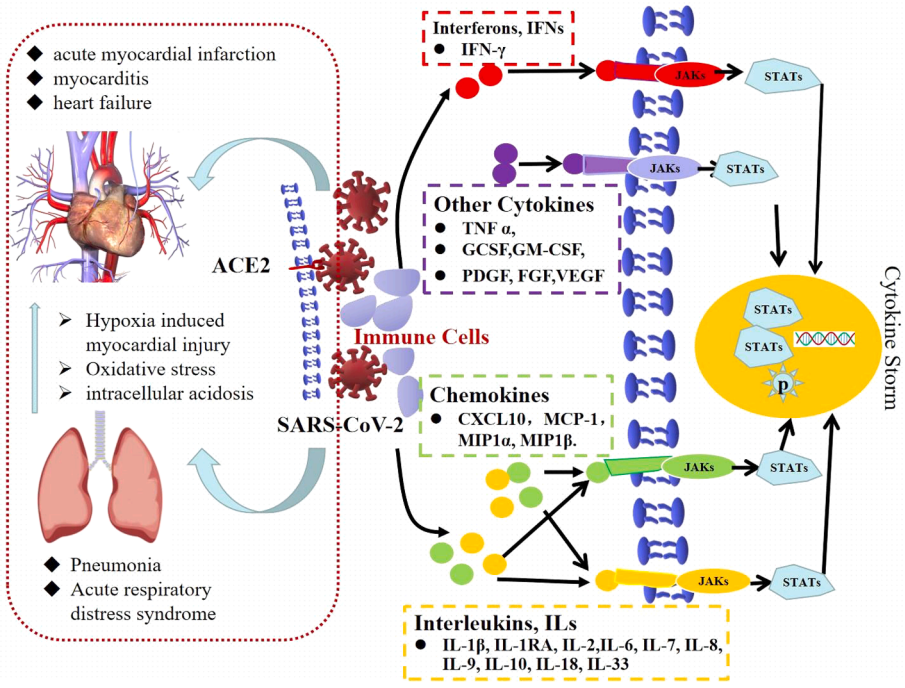


**Fig. 2.** The mechanism of cytokine storm caused by SARS-CoV-2. After human immune cells are infected with SARS-CoV-2, the immune system releases cytokines such as interferons, interleukins, and chemokines. Excessive cytokines bind to receptors on cell membranes and activate the JAK signaling pathway. The JAK signaling pathway activates the downstream STAT signaling pathway. STAT and phosphorylated STAT family members are combined with specific DNA elements in the nucleus after polymerization, and cytokine-related genes are activated. Eventually trigger a cytokine storm. JAK: Janus kinase, STAT: signal transducer and activator of transcription.

**Table 2**
Cytokine Storm Induced by SARS-CoV-2 and the Drug Therapy.

| Cytokine Storm Types | Drug Therapy | Mechanism | Reference |
|---|---|---|---|
| IL-1β, IL-1RA,IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-18, IL-33 | 1) IL-6 receptor antagonists:Trazumab2) IL-1 receptor antagonist:Anakinra3) JAK/STAT inhibitors:Fedratinib is a specific JAK2 inhibitor able to reduce IL-17 expression, as well as to repress GM-CSF biological actions.4)Else:Hydroxychloroquine, azithromycin,Glycyrrhizic acid | Trazumab: reducing neutrophil infiltration, inhibiting the activation of NF - κ B and IL-6 production, inhibiting complement system, hepatocyte apoptosis and necrosis.<br>IL-6 targeted drugs: control CRS without affecting the efficacy of car-t cells.<br>Fedratinib:JAK2 inhibitor able to reduce IL-17 expression, as well as to repress GM-CSF biological actions.<br>The therapeutic action of hydroxychloroquine can be potentiated by azithromycin, capable of reducing the proinflammatory activity of IL-6 and TNF-α. | (Alvi et al., 2019) (Franco et al., 2020) ( Abbasifard and Khorramdelazad, 2020) ( Conti et al., 2020) (Braga et al., 2020) (Ma et al., 2019) (Yi et al., 2020) |
| TNF α | TNF-α antagonist:Enbrel,Adalimumab,Etanercept | Reduce the infiltration of inflammatory cells (macrophages,neutrophils).<br>The secretion of inflammatory cytokines such as TNF-α, IL-6, IFN-γ and the expression of Toll like receptors (TLR3, TLR4 and TLR7)<br>Down regulate and inhibit the cascade proteins of nuclear factor kappa B (NF-κB, such as MyD88, trif, NF-κ B and p65),<br>Enhance the host's control over virus replication | (Shi et al., 2013) |
| IP10(CXCL10) | Nrf2 Activator PB125® | Inhibitor cytokine production,induces antioxidant and repair genes | (Yang et al., 2020; Oliviero et al., 2020) ( Chousterman et al., 2017) |
| GCSF, GM-CSF, PDGF, FGF, VEGF | Anti-VEGF agents: Bevacizumab | Inhibition of vascular leakage | (Dashti-Khavidaki and Khalili, 2020; Kong et al., 2020; Yin et al., 2020) |
| MCP-1(CCL2),, MIP1α(CCL3), MIP1β, | Inhibition of NF-κB activation Glycyrrhizic acid | Reducing neutrophil infiltration, inhibiting NF-κB activation and IL-6 formation; inhibiting hepatocyte apoptosis and necrosis. | (Conti et al., 2020) |
| IFN-γ | IFN-γ antibody therapy | Control cytokine storm. | (Remy et al., 2020; Kale et al., 2020) |
| Others methods | In vitro blood purification technology (Seraph® 100 Microbind® Affinity Blood Filter) | Seraph® 100: contains ultrahigh molecular weight polyethylene beads with heparin; approvement for the reduction of pathogens from the bloodstream. | (Chousterman et al., 2017) |
| | Recovered plasma | Virus specific antibodies neutralize the antigen. Binding to the viral spike protein to either prevent interaction with ACE-2 receptor or block the conformational changes in spike. | (Rawson et al., 2020; Jamwal et al., 2020; Kai, 2020) |
| | Xuebijing injection | Made from the extracts of 5 traditional Chinese medicine, such as safflower and red peony root. Regulate HIF-1, PI3K Akt and other signal pathways by regulating 70 proteins that can interact with ACE2. | (Wen et al., 2019; Menk et al., 2015; C. China Association Of Integrative Medicine Emergency Medicine, 2019) |
| | Glucocorticoid:Corticosteroids | Induce or inhibit the expression of inflammation related genes; antagonizing excessive inflammatory reaction, retain as much as possible lung tissue with ventilation function. | (Wen et al., 2019) |

Notes: IL-1β, Interleukin 1-β; IL-1RA, Interleukin-1 receptor antagonist; IL-2, Interleukin-2; IL-6, Interleukin-6; IL-7, Interleukin-7; IL-8, Interleukin-8; IL-9, Interleukin-9; IL-10, Interleukin-10; IL-18, Interleukin-18; IL-33, Interleukin-33; TNF α, Tumor necrosis factor α; CXCL10, CXCL10 C-X-C motif chemokine 10 or interferon gamma induced protein 10; GCSF, Granulocyte colony stimulating factor; GM-CSF, PDGF, Platelet derived growth factor; FGF, fibroblast growth factor; VEGF, Vascular Endothelial growth factor; MCP-1, monocyte chemoattractant protein-1(CCL2); MCP-1, macrophage inflammatory proteins 1.

coagulation function, all of which may have adverse effects on the heart. In addition to viral infection directly causing myocardial cell damage, virus-induced systemic inflammatory responses, and immune system disorders, imbalance of oxygen supply and demand, including hypoxemia, respiratory failure, shock, hypotension, persistent tachycardia, severe bradycardia, and anemia, can cause heart damage (Nasi et al., 2020). Drug-related myocardial injury may also occur.

## 5. SARS-CoV-2 and cardiovascular involvement

COVID-19 can cause heart damage, including acute heart injury, chronic cardiovascular system damage, and aggravation of injury caused by basic cardiovascular disease combined with SARS-CoV-2 infection. In patients with COVID-19, severe cases can develop complications other than respiratory syndromes. Reports suggest that 7.2–19.7% of patients experience acute cardiac damage, up to 40% of patients with cardiovascular and cerebrovascular diseases (Sun et al., 2020). Guan et al. retrospectively analyzed the clinical data of 1009 cases, and found that 14.9% of the patients had hypertension and 2.5% had coronary heart disease (Shi et al., 2020). A study of 72,314 patients with COVID-19 showed that, in patients with cardiovascular disease, the mortality rate was as high as 10.5% (Perrotta et al., 2020). Patients with chronic diseases such as hypertension, coronary heart disease, diabetes, heart failure, and those with advanced age develop COVID-19 faster and are often develop severe disease. Among severely affected patients, the proportions of those with hypertension and coronary heart disease were high, as were the incidences of arrhythmia, heart failure, intensive care unit transfer, mechanical ventilation, other adverse events, and death. It is speculated that this was related to several factors, including inflammatory reaction injuries, imbalances between increased oxygen consumption and hypoxic states, and unstable plaque rupture induced by blood flow change. The mortality risk of patients with myocardial injury is significantly elevated. We summarize various situations below (Shown in Table 2).

### 5.1. SARS-CoV-2 and adult patients with cardiovascular disease

Some patients with cardiovascular comorbidities (including coronary artery disease, hypertension) often have a poor outcomes of SARS-CoV-2 infections, and there may be complications such as ARDS (Zhou et al., 2020). The mortality rate of patients with COVID-19 and cardiovascular complications was also significantly elevated. Patients with cardiovascular comorbidities have weak vascular functional reserves. SARS-CoV-2 infection can aggravate myocardial ischemia and necrosis, in turn worsening sequelae of myocardial infarction and leading to heart failure (Lang et al., 2020). The exact mechanisms of heart injury in patients with COVID-19 remain unclear. Some investigators believe that myocardial involvement is mediated by angiotensin converting enzyme-2 (ACE2) (Perrotta et al., 2020). A mouse model showed that lung infections in patients with SARS-CoV-2 infection also caused ACE2-dependent myocardial infection (Sun et al., 2020). Among SARS-CoV-2 patients in Toronto, 35% of autopsy results showed the presence of SARS coronavirus RNA in the heart (Zaninotto et al., 2020). Other studies showed that SARS-CoV-2-related cardiac involvement was characterized by cytokine storm mediated by an imbalance in responses between T helper cell subtypes, as well as hypoxia-induced intracellular calcium excess, leading to cardiomyocyte apoptosis. It may be that cardiovascular comorbidities are more common in the elderly, those with compromised immune systems, and those with elevated ACE2 levels, or that people with cardiovascular comorbidities are more sensitive to SARS-CoV-2 infection (Shafi et al., 2020).

### 5.2. SARS-CoV-2 and children with cardiovascular disease

Compared with adult patients with COVID-19, children appear to suffer milder illnesses. Most are moderate or mild, and there are also asymptomatic patients (Eastin and Eastin, 2020). From the reported newborns born in perinatal COVID-19 infected women, Symptoms of abnormal heart rate and pneumothorax (Zunyou and McGogan, 2020). Children appeared to be particularly vulnerable to other coronaviruses that may make them at least partially immune to SARS-CoV-2 infection (Zhu et al., 2020). The mechanisms and causes are unclear. It is speculated that the function of ACE2 protein in adults is stronger than that of children; therefore, SARS-CoV-2 is more infectious in adults (Ing et al., 2020). Other studies reported that maternal antibodies can protect infants and young children from microbes immunized by the mother, so children are completely new to all microbes that have not been immunized by the mother (van der Lubbe et al., 2017). New memory T and B cell pools can be established in the immune system of infants and young children, and reinfection of common pathogens can also be controlled. For these reasons, compared with adults, children's immune systems are typically able to respond to new microorganisms. By contrast, these functions may be weakened in adults and the elderly, and they may even be ineffective in patients over 70 years old (Carsetti et al., 2020). The team of Martin Chalumeau of the University of Paris in France analyzed the clinical features of children's Kawasaki-like multisystem inflammatory syndrome during the covid-19 pandemic in Paris (Toubiana et al., 2020). It was found that the continuous outbreak of Kawasaki-like multiple systemic inflammatory syndrome in children in Paris may be related to SARS-CoV-2. And most children have gastrointestinal symptoms and Kawasaki disease shock syndrome, most of which are of African descent (Chen et al., 2020).

More and more children novel coronavirus have been diagnosed recently, and need further attention. Children in Italy and the United Kingdom suffer from Kawasaki disease, a disease that causes swelling of blood vessels in the heart and is related to the progression of SARS-CoV-2. About 20% to 40% of affected people have problems with their blood vessels or hearts, which can lead to dyspnea and chest pain. SARS-CoV-2 qPCR and serological tests were performed in 10 of 20 children. 15 were positive, and one patient was negative for both SARS-CoV-2 qPCR and serology, however, chest CT findings were typical of SARS-CoV-2 symptoms (Wang et al., 2019). In the end, all children survived, and left ventricular function was completely restored when the patients were discharged from the pediatric intensive care unit, and there was no fever. In children, the US Centers for Disease Control defined severe COVID-19 disease as multisystem inflammatory syndrome in children (MIS-C). Children with MIS-C may have acute cardiac decompensation. Another study found that 20 children admitted to the pediatric intensive care unit in four academic tertiary care centers in Paris suffered from fever and symptoms of suspected SARS-CoV-2 infection. Therefore, a child's immune response system may have a dual function, namely to protect and to reduce immune-mediated lung tissue damage (Chen et al., 2020).

### 5.3. SARS-CoV-2 and the pregnant patient with cardiovascular disease

A study found that none of the nine pregnant women (all with caesarean section) who were infected with viruses during the second trimester passed the virus to their babies. Pregnancy suppresses the immune system, all babies had health scores higher than the Apgar scale for newborns (Chen et al., 2020). Pregnancy suppresses the immune system (so that it does not attack the fetus). Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia; and the cardiovascular system of pregnant women is unbalanced during pregnancy, in addition, pregnant women's extra demand for oxygen and blood at the end of pregnancy increases the pressure on the cardiovascular system (Li et al., 2020). Although pregnant women are more susceptible to respiratory pathogens than non-pregnant women, none of the nine women suffered from severe COVID-19. Some of the most severe symptoms of COVID-19 are due to cytokine storm, which causes immune cells and the substances they produce to spread throughout the tissue and aggravate the condition (Carsetti et al., 2020). However, pregnancy is a state of immunosuppression, possibly explaining why these women did not become severely ill (Lu et al., 2020). There is no evidence of vertical transmission in pregnant women during the third trimester. It was found that most pregnant women admitted to the hospital for SARS-CoV-2 infection were in the second trimester or the third trimester. Most patients had a good prognosis, and the transmission of SARS-CoV-2 to infants was not common. Studies have also found that there is poor perfusion in the maternal blood vessels, but it is good in the fetus, and there is no placental vascular disease after pregnancy (Knight et al., 2020).

## 6. Summary

At present, the precise mechanisms of myocardial injury caused by SARS-CoV-2 infection are not completely clear; nevertheless, the clinical and basic science studies reviewed here suggest that SARS-CoV-2 infection can lead to myocardial injury, and it is closely related to the disease progression and prognosis. We suggest that we should pay close attention to cardiovascular related indicators in patients with COVID-19, including myocardial markers and ECG changes. Lungs may not be the only target organ of SARS-CoV-2. Cardiovascular system damage should not be ignored and should be detected and treated as soon as possible. If acute heart injury occurs during treatment, cardiac protective drugs can be used as appropriate. Appropriate myocardial protection treatment may help reduce the mortality associated with COVID-19.

## Declaration of Competing Interest

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

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