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Review Article

Coronavirus disease 2019 and cardiovascular disease

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus behind the coronavirus disease 2019 (COVID-19) pandemic, is a type of RNA virus that is nonsegmented. Cardiovascular diseases (CVDs) increase the mortality risk of patients. In this review article, we overview the existing evidence regarding the potential mechanisms of myocardial damage in coronavirus disease 2019 (COVID-19) patients. Having a comprehensive knowledge of the cardiovascular damage caused by SARS-CoV-2 and its underlying mechanisms is essential for providing prompt and efficient treatment, ultimately leading to a reduction in mortality rates. Severe COVID-19 causes acute respiratory distress syndrome and shock in patients. In addition, awareness regarding COVID-19 cardiovascular manifestations has increased, including the adverse impact on prognosis with cardiovascular involvement. Angiotensin-converting enzyme 2 receptor may play a role in acute myocardial injury caused by SARS-CoV-2 infection. COVID-19 patients experiencing heart failure may have their condition exacerbated by various contributing factors and mechanisms. Increased oxygen demand, myocarditis, stress cardiomyopathy, elevated pulmonary pressures, and venous thrombosis are potential health issues. The combination of these factors may lead to COVID-19-related cardiogenic shock, resulting in acute systolic heart failure. Extracorporeal membrane oxygenation (ECMO) and left ventricular assist devices (LVADs) are treatment options when inotropic support fails for effective circulatory support. To ensure effective COVID-19-related cardiovascular disease (CVD) surveillance, it is crucial to closely monitor the future host adaptation, viral evolution, and transmissibility of SARS-CoV-2, given the virus's pandemic potential.

Keywords: *Angiotensin-converting enzyme 2 receptor, Cardiovascular disease, Coronavirus disease 2019*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in December 2019 and rapidly spread worldwide, causing coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-2, a member of the Coronaviridae family, is an enveloped virus with a nonsegmented, positive-sense RNA genome [2]. SARS-CoV-2 causes respiratory illness that ranges from asymptomatic or mild symptoms to severe acute respiratory distress syndrome (ARDS) and multi-organ failure [3]. In the current pandemic, there is an urgent need for biomarkers that can help in stratifying patients based on their risk and actively monitoring the severity of illness. This can aid in optimizing patient care and allocation of resources [4]. Patients with underlying cardiovascular diseases (CVDs) may have a

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higher risk of mortality, hence highlighting the importance of risk stratification and early intervention in this vulnerable population [5].

Taiwanese studies indicate a higher risk of severe illness and mortality among COVID-19 patients with preexisting cardiovascular problems. As per a study in the *Journal of the Chinese Medical Association*, COVID-19 is a respiratory disease that is contagious and can manifest with a wide range of symptoms. These symptoms can vary from being asymptomatic to severe pneumonia and even lead to multiple organ failure. Evidence shows extrapulmonary involvement in the nervous, cardiovascular, gastrointestinal, hepatic, renal, endocrine, and dermatologic systems. Cardiovascular comorbidities worsen outcomes, while complications correlate with poor survival. Frequent occurrences of gastrointestinal symptoms and impaired liver function, along with acute kidney injury in critically ill patients, have been reported in COVID-19. In addition, COVID-19 may exacerbate hyperglycemia and lead to various skin lesions [6].

For individuals with preexisting cardiovascular conditions, it is crucial to take extra precautions to prevent contracting COVID-19. These measures include social distancing, mask wearing, and good hand hygiene. They should also stay in close communication with their health-care provider to manage their condition and monitor any potential symptoms of COVID-19.

As medical professionals, it is essential to understand the possible mechanisms of COVID-19-induced myocardial injury. Therefore, we present an overview of the available evidence on this topic. Understanding SARS-CoV-2's impact on the cardiovascular system and its mechanisms is critical for timely and effective treatment to reduce mortality.

Pathophysiology

The mode of entry of SARS-CoV2, a coronavirus with a single-stranded RNA [7], into human cells, is primarily through binding with the angiotensin-converting enzyme 2 (ACE2) receptor [8]. This receptor is highly expressed in multiple human cells, including lung alveolar cells, cardiac myocytes, and vascular endothelium [5]. The primary mode of transmission of SARS-CoV2 is through inhaling viral particles that enter the respiratory tract [5]. COVID-19 can exacerbate heart failure due to various factors [9]. Diffuse endothelial inflammation was demonstrated due to SARS-CoV-2 directly infecting endothelial cells. Although the virus primarily infects the host's pneumocytes in the epithelial alveolar lining using the ACE2 receptor, causing lung injury, this receptor is also found on endothelial cells in multiple organs [10].

Severe acute respiratory syndrome coronavirus 2 entry pathway into endothelial cells

When SARS-CoV-2 binds to the cell membrane ACE2 receptor, its surface spike (S) glycoprotein must be cleaved by host cell proteases at two different sites. The cleavage by furin and/or transmembrane protease serine 2 (TMPRSS-2) triggers the ACE2-dependent entry at the cell membrane. The virus uses host proteases TMPRSS-2 and ADAM metallopeptidase domain 17 (ADAM17) [11]. The priming action of the host protease furin on the S protein leads to the activation of the S1 receptor-binding site, which promotes viral ingress. After entering the host cell, this will downregulate host cell ACE2 expression; meanwhile, it also upregulates angiotensin II. By interacting with the angiotensin I receptor, Ang II can modify the expression of various inflammatory cytokines through nuclear factor-kappa B signaling, thus activating macrophages and promoting the production of inflammatory cytokines. This process has the potential to cause macrophage activation syndrome or ARDS [12].

ADAM17 is responsible for shedding the ACE-2 ectodomain, which results in the downregulation of these proteins. The virus-ACE-2 complexes produced by shedding are soluble and can prevent virus entry in vulnerable cells. Therapeutic benefits for COVID-19 patients may be provided by some protease inhibitors that downregulate TMPRSS2 and ADAM17 [13]. The activation of the S protein intracellularly is mediated by furin in the trans-Golgi network or cathepsins in lysosomes [14]. The synthetic furin inhibitor could potentially inhibit SARS-CoV-2 replication [15].

ADAM17 and other metalloproteases can release pro-inflammatory cytokines and ACE2 receptors, leading to their solubility and loss of protective function on the cell surface. This shedding process may worsen SARS-CoV-2 infection progress [16]. SARS-CoV-2 infection induces pro-inflammatory cytokine and chemokine production by monocytes and macrophages, causing tissue inflammation and cytokine storm, which are major contributors to COVID-19 complications such as ARDS [12].

SARS-CoV-2 binds to ACE2 receptors on the host cell membrane and invades with the aid of proteases TMPRSS-2 or ADAM17 [11]. The receptor-binding domain of the S protein will attach to the ACE2 receptor. The binding of CyPA to the S protein of SARS-CoV-2 S and the CD147 complex can augment the internalization of the virus, while the translocation of GRP78 from the ER to the plasma membrane is associated with various pathological conditions and cellular stress. Once SARS-CoV-2 enters endothelial cells, the membrane fusion function of the S protein is activated by cathepsin L. The cleavage site was identified in the same region where the subunit responsible for binding to the receptor is separated from the subunit responsible for fusion with the membrane in coronaviruses that have furin-activated spikes [17] [Figure 1].

Proposed functions of host vascular endothelial cell molecules for severe acute respiratory syndrome coronavirus 2 interaction

The hemostatic system can be disrupted by inflammatory mediators through various mechanisms, including endothelial cell dysfunction [18]. The inflamed endothelium stimulates platelet and leukocyte aggregation and increases von Willebrand factor release, mediating platelet adhesion and aggregation at endothelial damage sites and carrying factor VIII in circulation [19]. Conversely, the inflamed vascular smooth muscle cell stimulates oxidative stress and

vascular fibrosis [20]. Meanwhile, cytokine release increases permeability, causing apoptosis and cell death [Figure 2].

Proposed host cardiac muscle cell molecule functions for severe acute respiratory syndrome coronavirus 2 interaction

Patients infected with SARS-CoV-2 frequently experience diverse cardiovascular symptoms such as acute myocarditis, acute coronary disease, myocardial ischemia, arrhythmias, heart failure, stress-induced cardiomyopathy, acute pericarditis, and thromboembolic complications [1]. Systemic inflammation causing direct cardiomyocyte damage is a cardiac injury mechanism. In the inflammatory process, transforming growth factor-β signaling induces interstitial fibrosis. When T helper cells, specifically Th1 and Th2, trigger a cytokine response, it can lead to fibrosis development. Fibrosis can lead to fatal complications by causing organ remodeling despite its beneficial role in inflammation and wound healing [21] [Figure 3].

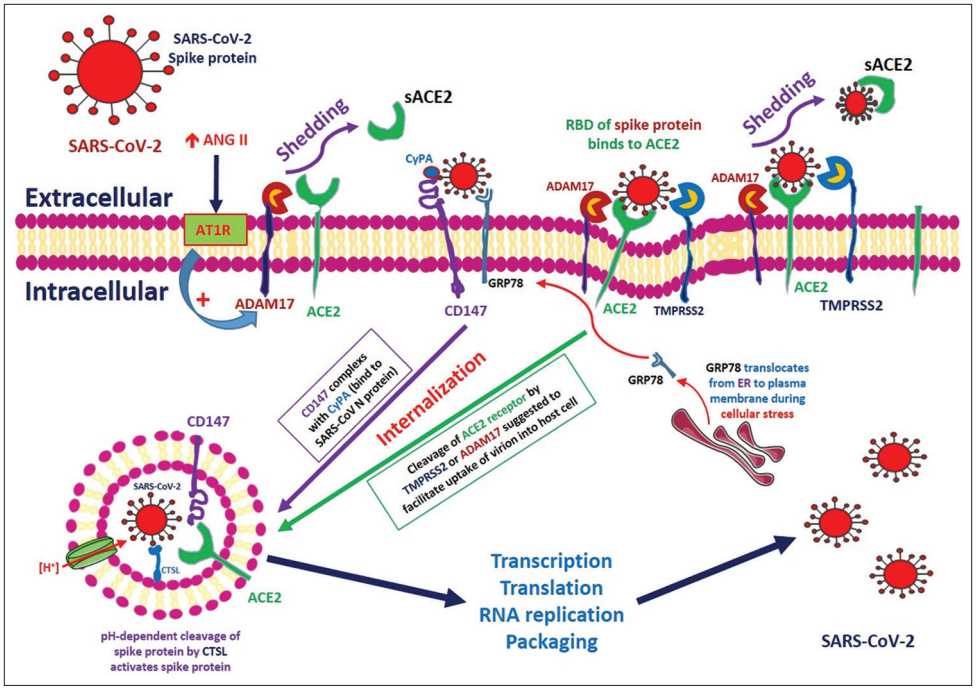

Figure 1: Proposed functions of host cell molecules for interaction with SARS-CoV-2. SARS-CoV-2 enters cells by binding its spike proteins to ACE2 receptors and priming with TMPRSS2 proteases. CyPA and SARS-CoV-2 N protein can promote entry via CD147. GRP78, normally a chaperone in the ER, can promote entry when transported to the cell membrane. The acidic environment in intracellular vesicles facilitates viral replication. CyPA regulates inflammation and cardiovascular processes. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, ACE2: Angiotensin-converting enzyme 2, TMPRSS2: Transmembrane serine protease 2, ER: Endoplasmic reticulum

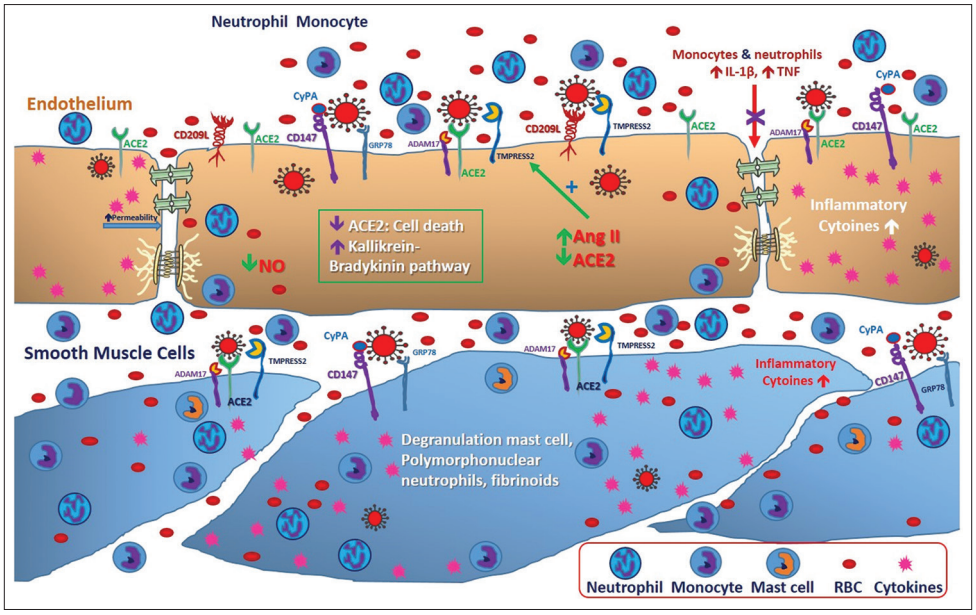

Figure 2: Endothelial cell damage, thromboinflammation, and VSMC injury in COVID-19. VSMC: Vascular smooth muscle cell, COVID-19: Coronavirus disease 2019

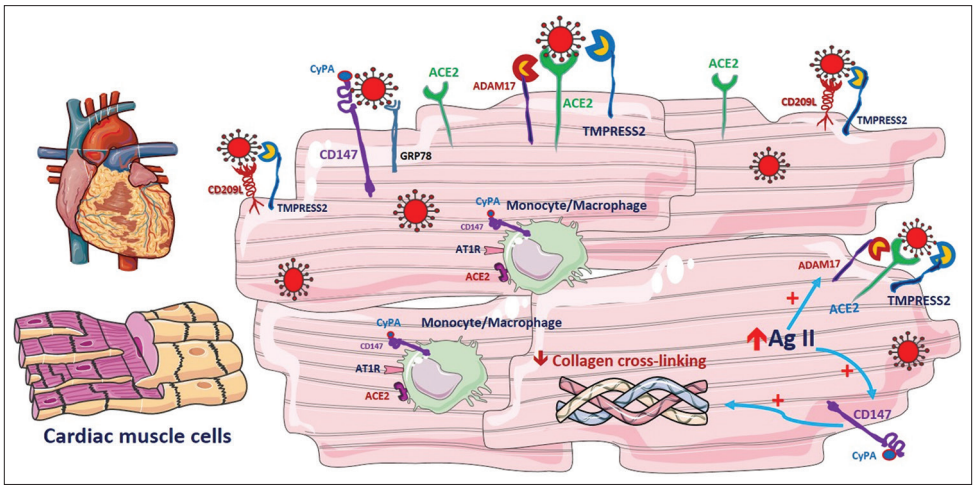

Figure 3: Possible mechanisms of myocardial injury in COVID-19. SARS-CoV-2 infection of the myocardium depends on ACE-2 receptors and leads to cardiomyopathy, dysfunction, and heart failure. Viral RNA is detected in autopsied heart samples, with significant macrophage infiltration. ACE-2 downregulation impairs cardioprotective effects, leading to TNF-α production and myocardial damage. Elevated inflammatory markers and troponin levels support the idea of a severe inflammatory response causing damage. SARS activates TGF-β signaling, inducing fibrosis and potentially causing cardiac damage. Interferon-mediated responses and exaggerated cytokine response from T-cells contribute to myocardial dysfunction. CD147 may provide an alternative route for SARS-CoV-2 entry besides ACE2. CD147 expression is regulated by reactive oxygen species and cytokines and is associated with hypertension, obesity, and cardiomyopathy. Cyclophilins, such as CyPA, may also promote entry through CD147. Other alternative receptors include CD209 L and CD209. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, ACE2: Angiotensin-converting enzyme 2, TMPRSS2: Transmembrane serine protease 2, ER: Endoplasmic reticulum

Various cardiovascular presentations

ARDS and shock develop among severe COVID-19 cases. In addition, increasing awareness of COVID-19 cardiovascular manifestations was noted, including the adverse impact on prognosis with cardiovascular involvement. Distinguishing whether the symptoms are due to a cardiac or respiratory cause can be difficult, as both can primarily present with dyspnea. Recognizing when cardiac and pulmonary involvement coexists is also critical. COVID-19 can worsen preexisting heart failure, leading to mixed shock. Invasive hemodynamic monitoring may help manage cardiac shock in these cases. During the ongoing pandemic, COVID-19 infection should be considered a potential cause of a typical cardiac syndrome, even without the presence of a fever or cough. Prompt cardiogenic shock assessment is necessary for patients with COVID-19-related acute systolic heart failure, and health-care providers should have a low threshold for this evaluation. Extracorporeal membrane oxygenation (ECMO) and left ventricular assist devices (LVADs) are recommended when inotropic support fails, as they require minimal maintenance [22].

Coronavirus disease 2019 in heart failure patients

There is growing evidence to suggest that COVID-19 may cause cardiomyopathy in many patients. A US report found that 33% of 21 severe COVID-19 cases had cardiomyopathy, which was characterized by new onset of decreased left ventricular function, increased serum cardiac markers, or clinical manifestations of shock [23]. The joint statement advises continuing renin–angiotensin–aldosterone system (RAAS) antagonists for patients receiving them for cardiovascular conditions [24]. Potential therapeutic advantages could be offered by inhibiting the RAAS. Studies on the SARS epidemic revealed that mice injected with SARS-CoV-1 experienced aggravated acute lung failure, which was mitigated by blocking the RAAS [25].

Dong *et al*. recently reported four cases of end-stage heart failure patients who had contracted COVID-19, with two patients exhibiting severe symptoms and the remaining two experiencing mild symptoms. This marks the first such report of its kind [26]. Two patients died at a mean age of 62.0 years, and two patients survive at a mean age of 24.5 years. In two patients, troponin I (TNI) significantly increased a few days before death. The study revealed that the two severely ill patients had experienced a twenty-fold increase in their TNI levels, underlying myocardial damage. In addition, the levels of C-reactive protein and brain natriuretic peptide were significantly higher in the two patients who did not survive compared to the two patients who survived [26]. Although the exact mechanism behind COVID-19-induced myocardial injury is not yet fully understood, it causes myocardial injury and is strongly linked to disease progression based on research findings.

ELSO advises giving the highest ECMO priority to younger patients without comorbidities or health-care workers in settings with limited resources. ECMO should be rarely considered for older patients with significant comorbidities and multi-organ failure [27]. LVAD patients require special care during the COVID-19 outbreak. Routine care should not be interrupted, and a management algorithm should be used to diagnose and treat COVID-19 and LVAD complications. Continuous telemonitoring is essential for LVAD patients and requires a fully digitalized structure [28]. It also suggests a telemonitoring algorithm that can be implemented in any LVAD center to ensure sustainability, enforceability, and adaptability.

Coronavirus disease 2019 and endothelial cell infection and endotheliitis/myocardial injury

SARS-CoV-2 uses the ACE2 receptor expressed in multiple organs and endothelial cells to infect the host [10]. The

vascular endothelium regulates vascular tone and homeostasis as an active paracrine, endocrine, and autocrine organ [29]. In a series of COVID-19 patients, Varga *et al.* exhibited the involvement of endothelial cells in various organ vascular beds [10]. The report describes two postmortem analyses of COVID-19 patients. The first analysis was conducted on a male renal transplant recipient with preexisting conditions, revealing the accumulation of inflammatory cells and apoptotic bodies in various organs. Two cases were analyzed: one showed lymphocytic endotheliitis and cellular necrosis in multiple organs, while the other showed evidence of myocardial infarction but no lymphocytic myocarditis.

Several mechanisms have been suggested for acute cardiac injury caused by COVID-19. COVID-19 is believed to cause acute cardiac injury through direct effects on the heart and indirect systemic inflammation [30]. According to the National Health Commission of China, 11.8% of COVID-19 patients who did not have underlying CVD had significant heart damage. Elevated levels of high-sensitivity cardiac TNI (hs-cTnI) or experiencing a cardiac arrest determined this [5]. A 12-year follow-up of 25 SARS-CoV-1-recovered patients found that 68%, 44%, and 60% had hyperlipidemia, cardiovascular abnormalities, and glucose metabolism disorders, respectively [31]. Endothelial dysfunction causes microvascular dysfunction, leading to vasoconstriction, organ ischemia, inflammation with edema, and a procoagulant state [32,33].

Venous thromboembolic events

COVID-19 can affect venous thromboembolism (VTE) prevention and management in various ways [7]. The virus can cause thrombotic events due to severe illness and hypoxia. Hemostatic abnormalities such as disseminated intravascular coagulation (DIC) may occur in COVID-19 patients [34]. Preexisting risk factors can increase the likelihood of thrombotic events, similar to previous outbreaks of virulent zoonotic coronaviruses [35]. There may be drug interactions between investigational COVID-19 therapies and antiplatelet agents or anticoagulants, and the pandemic's resource allocation and social distancing recommendations can impact the care of patients with thrombotic events.

Coronavirus disease 2019 and hemostasis parameters

COVID-19 infection commonly causes mild thrombocytopenia [4] and increased D-dimer levels as hemostatic abnormalities [36].

A higher risk of mortality, intensive care unit admission, and mechanical ventilation requirement is associated with these abnormalities [7]. Disease severity concerning coagulation is associated with prolonged PT and INR, and a decreased activated partial thromboplastin time [3,5]. Tang *et al*. studied 183 COVID-19 patients, with 21 deaths (11.5%). The study found that deceased patients had higher levels of D-dimer and FDP, and PT prolongation than surviving patients [37]. 71% of deceased COVID-19 patients met the DIC criteria of the International Society on Thrombosis and Haemostasis, whereas only 0.6% of survivors did [38]. These hemostatic changes indicate the presence of coagulopathy, which may increase the risk of thrombotic events.

Diagnosis of venous thromboembolism in coronavirus disease 2019 patients

COVID-19 patients commonly have high D-dimer levels [36], but routine investigation for acute VTE is not recommended unless there are other obvious clinical features. We should consider VTE in the presence of typical DVT symptoms, disproportionate hypoxemia, and/or unexplained right heart failure. Imaging studies for DVT or pulmonary embolism (PE) in COVID-19 patients may not be pursued due to transmission risk, patient instability, or severe ARDS with prone positioning. Limited access to lower extremity ultrasound can be a challenge. However, deteriorating right ventricular function justifies the need for diagnosis and treatment of PE. Echocardiography can be an option to assess worsening right ventricular dysfunction or a clot in transit but may not alter the course of critical illness [39].

Heart transplantation in coronavirus disease 2019

The cardiovascular community faces unique challenges posed by the COVID-19 pandemic, particularly for heart transplant clinicians due to the increased risk for infection and severe disease among patients on the waiting list and transplant recipients. Targeted prevention and treatment strategies are required [40].

Two heart transplant recipients in China have been reported to have COVID-19. One had a mild illness and recovered at home, while the other required hospital admission, intravenous immunoglobulin, and methylprednisolone due to progressive respiratory failure [5]. For HT patients during the pandemic, rapid COVID-19 testing, precautions, negative pressure rooms, retesting before discharge, and virtual medicine should be considered. Noninvasive monitoring with echocardiography, acute cellular rejection gene profiling, or antibody-mediated rejection-related donor-derived cell-free DNA may be used instead of right heart catheterization and endomyocardial biopsy for rejection monitoring [40].

Drugs and the renin–angiotensin system in coronavirus disease 2019

Does ACEi/ARB have a biphasic effect on COVID-19 patients' cardiovascular system? While these blockers can reduce cardiovascular injury by inhibiting Ang II, they can also upregulate ACE2 expression, leading to increased viral entry and replication, and cardiovascular injury [1]. Previous animal studies have shown that ACEi and ARBs could upregulate ACE2 expression in the heart, but this has not been confirmed in human studies or COVID-19 patients. However, there is speculation that this upregulation could increase the incidence of COVID-19 infection when taking these medications [24].

Treatments

Most COVID-19 cases are mild and can recover without hospitalization or mechanical support. Supportive care, including rest, hydration, and fever management, is typically sufficient for those with mild cases.

While the spikes have a 76% compatibility, the protein spike in SARS-CoV-2 is different from SARS-CoV, making

drugs that target these spikes less effective against both viruses [41]. Remdesivir has shown some promise in attenuating SARS-CoV-2 infection and managing COVID-19 symptoms [42]. Remdesivir, authorized for emergency use in treating COVID-19, disrupts the virus's replication within the body's cells [43,44]. Bamlanivimab, etesevimab, and REGN-COV2 are authorized monoclonal antibody drugs for emergency use in treating mild-to-moderate COVID-19 in high-risk patients. They prevent the virus from entering healthy cells by binding to the virus spike protein. However, they should not be considered a replacement for preventative measures and must be used under the guidance of a health-care professional.

Tocilizumab is a monoclonal antibody drug for treating COVID-19 patients with severe cytokine storms [45]. Tocilizumab blocks the interleukin-6 receptor, reducing cytokine storm severity and improving outcomes in severe COVID-19 cases. Its use should only be under a health-care professional's guidance due to potential side effects and it is not a cure for COVID-19.

Chloroquine and hydroxychloroquine, commonly used as antimalarial drugs, have been proposed as possible alternatives to antiviral drugs for COVID-19. They work by altering endosomal modifications, modulating inflammatory mediators, and modifying ACE2 to prevent viral entry [46]. Recent studies indicate that chloroquine and hydroxychloroquine, which were once considered potential treatments for COVID-19, are ineffective and can cause harm. Consequently, organizations like the WHO advise against their use. Individuals must follow evidence-based treatment recommendations from their health-care provider [47].

Corticosteroids are recommended by experts for reducing inflammation in severe COVID-19 patients. Short courses of low-to-moderate doses of corticosteroids for COVID-19 pneumonia are recommended by Shang *et al.* [48]. Corticosteroids, such as dexamethasone and prednisone, are recommended for severe and critically ill COVID-19 patients. They work by reducing inflammation and suppressing the immune response. The World Health Organization recommends their use, particularly dexamethasone, as it has been shown to decrease mortality in severely ill patients. Corticosteroids should only be used under the guidance of a health-care professional and may have side effects, so not all patients are suitable [49,50].

Losartan, an ARB, has been suggested as a potential SARS-CoV-2 therapy by upregulating ACE2 receptors. Although some studies have shown that ARBs could increase ACE2 receptors [51], there is currently no concrete evidence to support their efficacy in treating COVID-19, and their use should be based on scientific evidence recommended by health-care providers or public health authorities [52,53].

Severely ill COVID-19 patients may require aggressive treatment, such as antiviral medications, corticosteroids, oxygen therapy, and mechanical ventilation. It is important to prioritize routine medical treatment and consider the potential need for mechanical support to maintain vital organ function, especially in patients with ARDS.

COVID-19 treatment should be personalized based on the patient's condition and medical history. Effective treatment requires close monitoring and communication between health-care providers and patients, particularly for those who require hospitalization or mechanical support [54,55].

Conclusions

ACE2 receptor mechanisms can induce myocardial injury during SARS-CoV-2 infection. ACE2 receptors are present in the cardiovascular system, indicating that ACE2 signaling may contribute to myocardial injury. The various factors that can worsen heart failure in COVID-19 patients through diverse pathophysiological mechanisms [9]. Consider ECMO and LVAD for COVID-19 patients with sudden systolic heart failure not responding to traditional inotropic support. Early assessment for cardiogenic shock is crucial [22]. Careful monitoring of COVID-19's host adaptation, viral evolution, and transmissibility is crucial for the surveillance of COVID-19-related CVD due to its pandemic potential.

Long COVID can cause cardiovascular symptoms in recovered acute SARS-COV-2 patients, although the exact mechanisms are not fully understood [56]. Long COVID patients may experience cardiovascular symptoms such as chest pain, palpitations, and shortness of breath. Studies suggest an increased risk of myocarditis, which can cause heart failure, arrhythmias, and other cardiovascular complications [57].

Long-term COVID-19 effects on the cardiovascular system are still being studied and not fully understood. However, health-care providers should be aware of the potential cardiovascular symptoms and complications associated with long COVID and monitor patients accordingly. Further research is needed to understand COVID-19's lasting cardiovascular implications and develop effective long COVID treatment strategies. In the meantime, patients who experience persistent cardiovascular symptoms following COVID-19 infection should seek medical attention to ensure timely diagnosis and treatment.

Data Availability Statements

The datasets generated during and/or analyzed during the current study are available from the corresponding author (Dr. Kuo-Cheng Lu) upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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