

Correlation between Coronavirus Disease 2019 and Heart Failure: A Review

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to the coronavirus disease 2019 (COVID-19) pandemic, which has resulted in devastating conditions worldwide. In addition to affecting the respiratory system, COVID-19 affects other systemic organs, and in particular, cardiovascular failure is related to the worsening of symptoms and death. Among these, cardiac insufficiency seems to be an important prognostic factor.

Methods and Findings: We reviewed the association between COVID-19 and heart failure by searching Google Scholar and PubMed for reports related to COVID-19 and heart failure and selected those qualitatively and quantitatively established. The presence of heart failure may cause increased susceptibility to SARS-CoV-2 due to an abnormal immune response, which may aggravate COVID-19. In addition, myocardial injury, cytokine storm, endothelial dysfunction, blood coagulation abnormality, and hypoxemia due to respiratory injury may lead to worsening heart failure.

Conclusions: Heart failure and COVID-19 are closely related, and their mechanisms are diverse. Multidisciplinary treatment is required to control the progression of cardiac insufficiency, which complicates COVID-19. Further elucidation of the pathology and establishment of efficacious therapy is desirable.

Keywords: COVID-19; Heart Failure; Mechanism; Management

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has brought about devastating conditions worldwide, with Johns Hopkins University reporting >170 million infected and >3,530,000 deaths globally as of May 31, 2021, with infection continuing to spread [1]. Many critically ill patients have a comorbid cardiovascular disease, and people with heart failure have a particularly high risk of suffering from serious conditions of the disease [2-4]. In patients with chronic heart failure, the cardiac workload increases due to fever,

tachycardia, and hypoxia caused by the infection, exacerbating heart failure [5]. In COVID-19, cardiac events can also occur due to the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the cardiovascular and coagulation systems [6-9]. This review aimed to describe the relationship between COVID-19 and heart failure, the mechanisms of COVID-19-induced heart failure, and the clinical course and management of concomitant heart failure.

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Morbidity risk of COVID-19 in patients with heart failure

In addition to age, chronic comorbidities increase the risk of severe COVID-19 infection and mortality. In particular, the mortality rate is believed to exceed 10% in patients with pre-existing cardiovascular diseases [10]. In an early Chinese study of 416 patients with COVID-19, 19% patients had signs of previous cardiac injury and showed a significantly higher mortality rate (51.2% vs. 4.5%; $p < 0.001$) [11]. In a large global observational study of approximately 9000 patients with coronary artery disease and congestive heart failure conducted in 169 hospitals on three continents [12], the mortality rates were 15.3% and 5.6% in patients with and without heart failure, respectively (CI, 1.62–3.79). Hence, heart failure was found to be an independent predictor of in-hospital mortality [12]. Individuals with heart failure may be at increased risk of severe infections due to compromised immunity, common frailty, and compromised hemodynamic capacity [13]. Monocytes have been reported to produce more TNF- α and less IL-10 in patients with heart failure than in healthy subjects [14]. These cytokine production abnormalities may be associated with the systemic inflammatory response and inability to respond to elevated cardiac output demand observed in severe COVID-19. In addition, reduced angiotensin-converting enzyme (ACE) 2 expression found in chronic heart failure may exacerbate inflammation [15], leading to a runaway immune response (cytokine storm).

A previous report on influenza epidemics suggest that viral infection may exacerbate pre-existing heart failure, and increased readmissions for heart failure have been observed during seasonal influenza epidemics [16]. It is assumed that more aggressive SARS-CoV-2 infections may increase the risk of acute exacerbations in patients with heart failure.

Mechanisms of onset and exacerbation of heart failure induced by COVID-19

The mechanisms of heart failure onset and exacerbation by SARS-CoV-2 infection may involve inflammation, coagulopathy, direct myocardial injury due to the virus, and hypoxemia due to pulmonary injury [17].

In a report of 61 patients who died of COVID-19, SARS-CoV-2 infection was observed in both the lungs and heart [12, 13]. SARS-CoV-2 infection forms viral inclusions and induces monocytes/macrophages, neutrophils, and lymphocytes. Infiltration of inflammatory cells due to the virus leads to edema, which may adversely affect heart function and lead to the development of heart failure. Indeed, the cellular autoimmune response elicited by the virus leads to myocarditis [18].

Cytokines adversely affect cardiac function by promoting myocardial infiltration by monocytes/macrophages, neutrophils, and lymphocytes. In addition, cytokines may directly affect cardiac function. Cytokines associated with COVID-19 include interleukin-1 β and tumor necrosis factor- α (TNF- α). Interleukin-1 β increases cellular growth and differentiation and may be involved in myocardial layer thickening associated with cardiomyopathy [19]. TNF- α is secreted by many cells, including macrophages, neutrophils, mast cells, and even cardiomyocytes, and it is involved in various inflammatory processes such as cellular proliferation and fever [20,21].

In patients who died of COVID-19, telangiectasis with microthrombi was observed at a very early stage during the disease, with large thromboses, microangiopathies, and disseminated intravascular coagulation observed in chronic and severe cases [8,9]. Dysfunction of the vascular endothelium in individuals with COVID-19 due to coagulopathy and thrombosis may lead to myocardial infarction and heart failure, in addition to the loss of other organ functions.

Oxygen supply to the heart is reduced in patients with acute respiratory distress

syndrome and respiratory failure. Thus, lung dysfunction adversely affects cardiac function. Previous reports have shown that profound respiratory failure leads to early heart failure and is a risk factor for mortality [22-24].

COVID-19 and clinical outcomes of patients with heart failure

From the American Premier Healthcare Database, 132,312 (6.5%) of the 2,041,855 admissions had a history of heart failure, and the reasons for admission were acute heart failure in 23,843 patients (18.0%) and COVID-19 in 8383 patients (6.4%) [25]. Patients with heart failure admitted in association with COVID-19 had a higher in-hospital mortality compared with hospitalizations for acute heart failure not associated with COVID-19 (24.2% vs. 2.6%). Individuals with heart failure who were admitted with COVID-19 were at an increased risk of comorbidity, with a mortality rate of approximately 25%. Hospitalization for COVID-19 in patients with heart failure was also associated with a high use of in-hospital resources.

In a Spanish report, of 3,080 patients with COVID-19, 152 (4.9%) patients with a history of heart failure developed acute heart failure at a higher rate (11.2% vs. 2.1%; $p < 0.001$) and had higher mortality (48.7% vs. 19.0%; $p < 0.001$) than patients without such a history [26]. In addition, discontinuation of beta-blockers, mineralocorticoid antagonists, and ACE inhibitors/angiotensin receptor blockers (ARBs) was associated with higher in-hospital mortality in individuals with chronic heart failure.

Management of heart failure after definitive diagnosis of COVID-19

If COVID-19 has been definitively diagnosed, the presence or absence of concomitant acute heart failure and exacerbation of chronic heart failure should be determined. The degree of peripheral circulatory disturbance and congestion should be evaluated by clinical findings and investigations, such as plain

radiography and echocardiography. Precise determination of the volume of fluid replacement, selection of drug administration, and amount of oxygen administration are crucial. COVID-19 patients are prone to dehydration along with a systemic inflammatory response, and fluid transfer to the interstitium due to increased vascular permeability may also be observed. Therefore, the dosage must be carefully adjusted in patients receiving diuretics [27].

The drugs used for existing heart failure should be carefully examined in terms of dose reduction and discontinuation.

Recommended continuation of ACE inhibitors and ARBs

The novel coronavirus is known to enter cells via ACE2 receptors [28], which is an enzyme that degrades angiotensin II and produces Ang (1-7). An initial concern was that ACE inhibitors or ARBs may increase the risk of infection and exacerbate COVID-19 because they increase the expression of ACE2. However, several recent studies have reported that these agents do not increase the risk of infection [29] and may work protectively against COVID-19 by suppressing angiotensin II-mediated inflammatory responses and reducing mortality in COVID-19 patients with cardiovascular disease [27]. Based on the findings of these studies, continued use of ACE inhibitors and ARBs is recommended, even for preventing worsening of heart failure in patients with heart failure [27].

Ventilators and extracorporeal membrane oxygenation (ECMO)

In cases of combined cardiac insufficiency, the use of ventilators and ECMO is likely warranted due to increased severity. The commonly used VV-ECMO transfers blood between two veins. However, VA-ECMO can provide circulatory support by delivering blood to an artery in cases of concomitant cardiogenic shock and respiratory failure. These are highly efficacious treatments for maintaining life until recovery from COVID-19. However, there are concerns

that lymphopenia caused by ECMO may suppress the immune response to the virus and further activate the inflammatory response [30]. Given the finite nature of healthcare resources, careful selection of cases is mandatory in which these treatments can be more effectively and safely used.

Prevention of COVID-19 in patients with heart failure

Concomitant COVID-19 in people with chronic heart failure is associated with a high risk of fatality, and infection prevention is of paramount importance. Examination at healthcare institutions where many febrile patients are gathered may increase the risk of infection. The use of remote monitoring systems, such as implantable cardioverter defibrillators, and cardiac resynchronization therapy become important, as does self-care, such as patient-measured vital signs and body weight. Regarding prescriptions, oral medications are currently being sent by postal mail in regions where the pandemic is more serious [27].

Conclusion

Heart failure is an important prognostic factor in COVID-19, but COVID-19-induced heart failure mechanisms are diverse and often unclear. It is imperative that chronic heart failure patients carry out sufficient measures for infection prevention and ensure that worsening COVID-19 is suppressed by early countermeasures. It is necessary to perform multidisciplinary treatment using a ventilator or ECMO, as needed, for patients with new heart failure complications. The elucidation of heart failure pathology in COVID-19 is advancing, and the establishment of effective therapies is desired.

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Conflicting Interests

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