Review Article

A Clinical Review of COVID-19 Associated Myocarditis

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Abstract

The Coronavirus 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2(SARS COV-2) which can cause multi-organ dysfunction with noteworthy ramifications for patients' cardiovascular consideration. Complications like myocarditis, myocardial injury, acute-onset heart failure, acute coronary syndrome, arrhythmia have been reported. However, a limited number of case reports, retrospective studies, and impairing factors, including the lack of proper diagnostic modalities for COVID-19 associated myocarditis, have made the exact incidence of myocarditis from COVID-19 unclear. In this paper, we have analyzed peer-reviewed articles to highlight COVID-19 myocarditis and outline the associated risk factors, pathophysiology, symptoms, diagnosis, and management of such patients. This is to ensure rapid triage, so their treatment is not compromised and thereby averting fatal complications from it.

Keyword: COVID-19; Myocarditis; Cardiovascular; Infectious disease; Myocardial injury

Abbreviations

ACS: Acute coronary syndrome; AHA: American Heart Association; CMR: Cardiac magnetic resonance; CT: Computerized tomography; MHC: Major histocompatibility complex; SCMR: Society for Cardiovascular Magnetic Resonance; TNF: Tumor necrosis factor; WHO: World Health Organization.

Introduction

The ongoing pandemic of Coronavirus Disease 2019 (COVID-19) was first described in Wuhan, China, and has rapidly spread across the globe [1–3]. In March 2020, it was declared a public health emergency by the World Health Organization (WHO) [1–3]. With the rapidly increasing number of confirmed cases every day, knowledge and the clinical presentation of COVID-19 infection have changed markedly. In addition to the common clinical presentation of respiratory involvement ranging from mild respiratory symptoms to respiratory failure caused by COVID-19, the cardiovascular manifestations prompted by this viral disease has raised significant concern as a part of multiorgan involvement [3–6].

COVID-19 infection with associated cardiac manifestations has been reported with a wide spectrum of cardiovascular complications, including acute coronary syndrome (ACS), myocardial injury, arrhythmias, acute-onset heart failure, myocarditis, and cardiac arrest [6–8]. Myocardial injury is considered relatively common in COVID-19 patients. Further, myocarditis was considered as a cause of death in few COVID-19 patients. However, the prevalence of myocarditis in COVID-19 cases is not clear, limited evidence exists that myocarditis can be the cause of myocardial injury, and our knowledge on COVID-19 is still limited. We, therefore, reviewed current literature on the present pandemic to provide insights into the current understanding of the pathophysiology, clinical manifestations, and possible management of myocarditis related to COVID-19.

Incidence of COVID-19-Related Myocarditis

Among the long-term impacts of COVID-19, cardiac dysfunction is relatively not among the most common symptoms. However, cardiovascular manifestations, along with cardiac injury induced by COVID-19, has been reported in a considerable number of confirmed cases [6,9]. Several studies showed that cardiovascular manifestations (mostly acute myocardial injury) have been observed in less than 10% of confirmed COVID-19 cases [10–12]. More recently, Shi et al. reported that as much as 20% of COVID-19 patients in their study experienced cardiac injury [6].

Due to the limited number of case reports and retrospective studies, the exact incidence of myocarditis due to COVID-19 infection is unclear. Moreover, myocarditis could be associated with several factors including lack of proper diagnostic criteria and modalities.

Myocardial injury can be defined as a persistently elevated serum troponin level, where myocardial ischemia is clinically evident. Driggin et al. reported 7% of COVID-19-related deaths were attributed to myocardial damage with associated circulatory failure without a definitive diagnosis of myocarditis [13]. Another study of critically ill COVID-19 patients demonstrated that 33% (n = 7) of patients

developed cardiomyopathy [14]. Other reports have described autopsy findings of inflammatory mononuclear infiltrate in myocardial tissue without the presence of SARS-CoV-2,whichCOVID-19, in the myocardium in the setting of acute death due to fulminant myocarditis with high viral load and even without respiratory symptoms [4,9,15–18].

Risk Factors of Developing COVID-19-Related Myocarditis

Cardiac involvement including myocarditis can be subclinical or can present with overt manifestations even without respiratory symptoms [5,17]. Several studies have identified various risk factors for developing cardiovascular involvement of COVID-19 along with myocarditis [3,4,11,18,19]. The most described risk factors include older age, hypertension, diabetes, chronic heart failure, and pre-existing coronary artery diseases [3,4,11,18,19]. Patients with more serious comorbidities are also at greater risk of mortality [3,18].

Disproportionate mortality rates have been seen among certain ethnic groups which may be due to different pre-existing health-related factors. For example, the African American population, who also had an increased number of cardiac risk factors, have shown higher death rates due to COVID-19 compared to other ethnicities in many American states [20].

Pathophysiology of COVID-19 Associated Myocarditis

Myocarditis is an inflammatory disease of the heart muscles without any ischemia. Viral infection is the most commonly recognized cause [21,22]. T lymphocyte-mediated cytotoxicity, alongside direct cell injury, contributes to viral myocarditis and the cytokine storm syndrome has a detrimental effect on it [21]. Several animal models have provided evidence of pathological phases that begin with viral-mediated myocyte lysis. This viral-mediated injury leads to activation of the innate immune response with the release of proinflammatory cytokines [23]. Proteins released through cell lysis might display epitopes similar to the viral antigens and be presented via the major histocompatibility complex (MHC). Myosin heavy chain, a major structural protein of the heart muscle, is an example of this molecular mimicry. Adaptive immune response is mediated by activating antibodies and T cells. T-helper cells and cytotoxic T cells orchestrate their responses by triggering inflammatory cascade and cytolysis [Th1 interferon (IFN)-c, Th2 – e.g., IL-4, Th17 – IL-17, and Th22 – IL-22]. Later, macrophages migrate to the site of cardiac injury [23,24]. There may be either recovery or low levels of chronic inflammation with concomitant development of left ventricular dysfunction in the late stage [24].

Pathophysiology of acute myocarditis of SARS-CoV-2 is still elusive. Different mechanisms have been proposed which is similar to the mechanism of viral myocarditis. Several studies reported that patients contracted SARS-CoV-2 infection have high levels of interleukin-1 (IL-1) beta, IL-6, interferon (IFN) gamma, IFN-inducible protein-10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor (TNF), leading to cytokine storm through activation of T-helper-1 cell [25,26]. Zheng et al. proposed a different mechanism where this viral myocarditis could have a possible relation with angiotensin-converting enzyme 2 (ACE2)[27].

SARS-CoV-2 binds to ACE2 via its S-spike protein, using it as an entry point to the cell [28].

Although there is limited evidence that COVID-19 directly invades myocardium, the viral RNAs similar to SARS-CoV-2 (Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV) have been identified in the cardiac tissues of infected animals [25,29]. Recently, Dolhnikoff et al. detected SARS-CoV-2 RNA on a post-mortem nasopharyngeal swab and in cardiac and pulmonary tissues of a child by real-time RT-PCR [29].

It is not still certain whether the response to COVID 19 infection is related to inflammation, autoimmunity, or a blend of both since we have little proof that is specific for the COVID-19 pathophysiological mechanism.

Clinical Scenario/ Symptoms

Established myocarditis is a moderately uncommon sequela of COVID-19 infection that can cause clinical jeopardy due to presence of overlapping symptoms with primary COVID- 19 infection. Myocarditis seems to be more prevalent in male patients than in female patients, with a male/female ratio of 1.5:1. Patients with myocarditis exhibit a range of symptoms, ranging from fatigue, chest pain, and palpitations to sudden cardiac arrest [22,30]. The clinical scenario of COVID-19-related myocarditis varies in the literature. While some studies reported patients with mild chest discomfort and palpitations, other studies recorded fatigue, dyspnea, chest pain, and chest tightness are among the common presentations, which make it challenging to distinguish it from other causes in most patients [16,31–33].

However, some critical COVID-19 cases may experience fulminant myocarditis, suggesting that COVID-19 is also related to this condition. Fulminant myocarditis in those patients displayed as ventricular dysfunction and heart failure within 2-3 weeks of the viral infection. Early signs of fulminant myocarditis include low pulse pressure with a febrile presentation, sinus tachycardia, and livedo reticularis, which highly resemble early signs of sepsis [22].

Clinical symptoms
Common symptoms: Fatigue, chest pain, palpitations leading to sudden cardiac arrest, dyspnea, and chest tightness [15,30–33]. Early signs: Fever, low pulse pressure, cold or mottled extremities, and sinus tachycardia [22].
Labs
Significant serum troponin elevation indicates cardiac involvement but negative troponin result cannot exclude myocarditis [35]. Lactate elevation [37]. Inflammatory markers elevation. NT-proBNP elevation.

ECG [33,43] ST elevation PR depression New-onset bundle branch block QT prolongation Pseudoinfarct pattern Premature ventricular complexes Bradyarrhythmia Atrioventricular Nodal block
Transthoracic Echocardiography (TTE)[39] Global left ventricular hypokinesis Regional wall motion abnormalities Dilated and/or hypertrophic ventricles
Cardiac Magnetic Resonance (CMR) Lake Louise criteria for CMR has a specificity of 91% and a sensitivity of 67% for diagnosing myocarditis [40–42].
Endomyocardial Biopsy (EMB) – ***Gold standard test for myocarditis*** Demonstrates nonischemic necrosis and mononuclear cell infiltrates [22]

Table 1: Clinical Presentation of COVID-19 Associated Myocarditis

Diagnosis of COVID-19-Related Myocarditis

A combination of clinical findings, biomarkers and imaging is essential for the diagnosis of myocarditis in COVID-19 patients. The myocardial injury appears to be a very likely late presentation when COVID-19 patients develop severe respiratory infection with hypoxia or Acute Respiratory Distress Syndrome (ARDS) [13]. Mild chest discomfort and palpitations might be the only clinical manifestations of COVID-19 myocarditis, making it challenging to characterize the condition in most patients. ACS is one of the major differential diagnoses of COVID-19-related myocarditis. Myocarditis is considered in the differentials when a cardiac injury is evident despite the absence of ACS. Significant serum troponin elevation indicates cardiac involvement in cases of severe COVID-19 [34]. However, myocarditis cannot be excluded with low troponin value, especially for atypical forms of myocarditis such as giant cell myocarditis or chronic myocarditis [35].

The echocardiogram (ECG) usually is commonly deployed in the diagnosis of myocarditis. Patients with myocarditis usually present echocardiogram abnormalities, such as ST elevation, PR depression. Other abnormalities seen in patients with myocarditis include new-onset bundle branch block, QT

prolongation, pseudoinfarct pattern, premature ventricular complexes, and bradyarrhythmia with atrioventricular nodal block [31,36]. ECG is, however, neither specific nor sensitive for myocarditis. Nonetheless, It is mandatory to perform ECG in all hospitalized patients with COVID-19 infection as it may help in identifying the presence and severity of myocardial injury.

Blood tests reveal that serum lactate and other inflammatory markers in the blood are often elevated when CVID-19 patients have myocarditis. Also, NT-proBNP levels are often increased in the COVID-19-related myocarditis cases and could increase secondary to myocardial stress [37].

Echocardiography, especially transthoracic echocardiography (TTE), is an important first-line non-invasive test for the diagnosis of myocarditis. It can help preclude different causes of heart failure such as myocardial infarction and valvular heart disease [38]. Global left ventricular hypokinesis, regional wall motion abnormalities, and dilated and/or hypertrophic ventricles are the mentioned findings of TTE in literature [39].

Cardiac magnetic resonance (CMR) imaging is a valuable approach in the diagnosis of myocarditis. Lake Louise criteria for CMR offer high *diagnostic* accuracy and reliability for diagnosing myocarditis, with a specificity of 91% and a sensitivity of 67% [40–42]. In several studies, researchers have fulfilled the Lake Louise criteria for the diagnosis of COVID-19 associated myocarditis with the use of CMR imaging [15,32,33,43]. Yet, CMR is precluded for unstable patients by many authors. In such critical cases, ECG-gated computerized tomography (CT) with contrast is a suitable option.

Finally, Endomyocardial biopsy (EMB) has been recognized as the gold standard diagnostic test for myocarditis. EMB findings include nonischemic necrosis and mononuclear cell infiltrates of myocytes, but not always possible in a clinical setting [22]. We did not find any evidence of direct viral particles into cardiac tissue except in a study where SARS-CoV-2 RNA was detected on post-mortem myocardium by RT-PCR [29].

Authors of Publication	**Study Design**	**Sample of Study**	**Interventions/Treatment**	**Results**	**Conclusion**
Shi et al. [6]	Cohort Study	416	Antiviral therapy, oxygen, glucocorticoids, intravenous immunoglobulin therapy, antibiotic therapy.	Abnormal ECG, Bilateral pneumonia, Ground-glass opacity, Mottling	The data and findings support cardiac injury as a complication in COVID-19 patients.

Xu et al. [5]	Case Report	50-year-old man	Interferon alfa-2b, Lopinavir, Ritonavir, Moxifloxacin, Methylprednisolone.	Multiple patchy shadows in both lungs, Infiltrate and diffuse gridding shadow in both lungs,	Clinical, pathological, and histological findings can help identify the cause of death and the link between cardiac arrest and COVID-19.
Han et al. [7]	Single-center Study	273	Monitoring of the myocardiac enzyme profiles.	High blood levels of CK-MB, MYO, Ultra-TnI, NT-proBNP indicating acute cardiac injury.	Higher concentrations of CK-MB, MYO, ultra-TnI, and NT-proBNPin venous blood signified the severity and case fatality rate (CFR) of COVID-19.
Deng et al. [8]	Retrospective Study	112	N/A	High troponin level and pulmonary hypertension indicating myocardial injury.	Myocardial injury is due to systemic consequences rather than direct injury by the 2019 novel coronavirus.
Guo et al. [10]	Retrospective single-center case	187	Antiviral therapy, antibiotics, respiratory support.	Hypertension, coronary heart disease, cardiomyopathy, elevated TnT level exhibited myocardial injury.	Myocardial injury is essentially connected with the lethal outcome
Kwenandar et al. [49]		187	Close monitoring of cardiac biomarkers such as NT-proBNP and electrocardiograms.	Patients with underlying CVD and escalation of TnT levels had the highest mortality.	SARS-CoV-2 has a devastating impact on the cardiovascular system.

Tavazzi et al. [15]	Case Report	60-year-old patient	Intra-aortic balloon pump (IABP) was placed on top of adrenaline, noradrenaline.	Cardiogenic shock and elevated inflammatory and cardiac biomarkers.	COVID-19 can localize in organs/tissues other than the lung, especially in the heart.
Sala et al. [16]	Case Report	43-year-old woman	Lopinavir/ritonavir 500 mg b.i.d, hydroxychloroquine 200 mg b.i.d.	Bilateral opacities suggesting interstitial inflammatory lung disease.	First direct evidence of myocardial inflammation in a COVID-19 patient, undergoing both CMR and EMB characterization.
Chen et al. [25]	Retrospective Study	99	Mechanical respirators and circulatory support systems, including IABP, Impella, and ECMO	Pneumonia, abnormal CT, cardiac injury, secondary infection.	COVID-19 infection might deteriorate rapidly eventually followed by fulminant myocarditis. More attention should be paid to patients with extremely increased cardiac troponin I (cTnI) levels and new-onset arrhythmias.
Yang et al. [19]	Meta-analysis	6 studies with 1527 patients	N/A	Hypertension, cardiac-cerebrovascular disease, and diabetes.	COVID-19 might aggravate the damage to the heart.

Table 2: The connection between myocardial injury and COVID-19 as discussed in ten relevant studies.

Management of COVID-19-related Myocarditis

Evidence and cumulative clinical data from large trials have suggested low-dose dexamethasone in the management of severe COVID-19 cases on supplemental oxygen or ventilatory support although dexamethasone is not recommended for mild to moderate COVID-19 (patients not on oxygen) [44]. In the US, the FDA has approved emergency use authorization for Remdesevir for hospitalized children and severely ill COVID-19 patients. Data

from randomized trials have shown Remdesevir to have clinical benefit critically ill patients, while it offers a modest benefit for non-severe patients [44].

The outcome and prognosis of myocarditis depend on many factors. While 50% of acute cases resolve in 2-4weeks, 25% may develop persistent cardiac dysfunction and 12-25% may either die or progress to end-stage dilated cardiomyopathy and eventually need heart transplantation [22]. Despite current variability in practice, supportive therapy is still the mainstay management of myocarditis since no clear evidence supports immunosuppressants offer a clinical benefit in COVID-19 patients with myocarditis [22]. Interestingly, a number of case reports have shown successful management of COVID-19 related fulminant myocarditis using mainly systemic steroids, immune-modulators, and other supportive measures [31,47]. Although for viral myocarditis, antiviral therapies have been previously used but RCTs of these therapies have shown no clinical benefit and are thus not used as therapeutic agents anymore [48].

According to the American Heart Association (AHA) and European Society of Hypertension (ESC) suspected patients of COVID-19 associated myocarditis should be treated according to existing guideline protocol for heart failure and arrhythmia as they are common sequelae [22,42]. Both guidelines, AHA and ESC, recommend using inotropes and/or vasopressors and mechanical ventilation for patients with acute myocarditis complicated by cardiogenic shock. Extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or an intra-aortic balloon pump are most common interventions for long term management of prolonged cardiogenic shock resulting from myocarditis. Whereas Arrhythmia may require temporary cardiac pacing or antiarrhythmic drugs, no benefit of using intravenous immunoglobulin is reported in the literature [45,46].

Conclusion

Although myocarditis is a rare cause of myocardial injury related to COVID-19, it may remain underdiagnosed because of its varied clinical manifestations in critically ill COVID-19 patients. Owing to the fatal outcome it imposes, we recommend that critically ill patients with COVID-19 should be screened for myocarditis. A multidisciplinary approach should be endorsed when treating severely ill COVID-19 patients. Simple bedside tests such as serial ECG and cardiac biomarkers should be established in early evaluation since they can raise suspicion for myocarditis. Finally, we recommend that further research be conducted to more readily distinguish and comprehend the association of myocarditis and COVID-19 as well as the proper management of such patients.

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