

REVIEW

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Systematic review of case reports on COVID-19 associated myocarditis: a discussion on treatments

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Abstract

Although COVID-19 is a disease consisting of mostly upper and lower respiratory symptoms, a subset of patients develop cardiac sequelae including myocarditis and pericarditis. For these patients, a standardized set of diagnostic imaging techniques and treatments has not been established. While there have been numerous case reports on this topic, there are few reviews that evaluate the effectiveness of different treatment modalities with a significant number of cases. We reviewed 146 cases of patients (ages ranging from 2 months old to mid 80 s) obtained from searches on PubMed, Google Scholar, and several case report journals. ECG abnormalities, elevated inflammatory markers, and reduced left ventricular ejection fraction were most associated with COVID-19 myocarditis. While classic symptoms of COVID-19 include upper respiratory symptoms, a subset of patients diagnosed with COVID-19 displayed no signs of respiratory disease at all. In 22% of cases, cardiac sequelae was not present until after the patient recovered from COVID-19. Steroids were given in 57.5% of cases. Cardiac MRI was used in 40.4% of cases for diagnosis of myocarditis. Of all the patients who were treated with ECMO, 82.1% of these patients were able to fully recover. The use of cardiac MRI and transthoracic echocardiogram for diagnosis of COVID-19 myocarditis should be heavily considered in any patient with COVID-19 infection. ECMO, IVIG, steroids, and anticoagulants should also be heavily considered. A randomized controlled trial should be conducted to better associate treatments with outcomes.

Keywords Myocarditis, COVID-19, Clinical presentations of COVID-19 associated myocarditis, Treatments for myocarditis

Introduction

In March 2020, the World Health Organization (WHO) declared a pandemic caused by SARS-CoV-2, the virus that causes COVID-19. COVID-19 initially emerged in December 2019 when individuals in Wuhan, China suffered from pneumonia of unidentified origin. These patients presented with common symptoms such as

cough, fever, and shortness of breath. It was initially thought that these were the only symptoms COVID-19 produced, but it was later discovered that COVID-19 has a much broader range of presentations, including gastrointestinal symptoms, headache, myalgia, and even asymptomatic presentations.

Although it is predominantly a respiratory infection, there have been several reports of short and long term consequences of cardiac sequelae caused by COVID-19 induced inflammatory responses. One of the most diagnosed cardiac injuries in hospitalized patients with COVID-19 is myocarditis. According to the CDC, there is on average a 16× higher risk of myocarditis among patients diagnosed with COVID-19 compared

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to those who do not contract COVID-19 [1]. Current guidelines in diagnosing, managing, and treating patients with COVID-19 are constantly changing, warranting frequent systematic reviews that discuss the most recently published data. While there have been numerous case reports on this topic, there are few reviews that evaluate the effectiveness of different treatment modalities with a significant number of cases. This systematic review aims to discuss current treatments and outcomes of patients diagnosed with COVID-19 induced myocarditis.

Methods

A systematic medical literature review was conducted in the English language. A search of PubMed and several case report journals were completed with key terms “COVID-19 myocarditis.” A total of 146 case reports were identified and used for this review. A thorough screening of all case reports was completed to ensure that included reports covered COVID-19 related myocarditis only. Cases that discussed other cardiac injuries, such as takotsubo cardiomyopathy, MISC-A, pericarditis, and cardiac tamponade, were excluded. Cases that hypothesized COVID-19 vaccination as a potential cause of myocarditis were excluded. For each case, patient demographics were collected including gender and age. Additionally, comprehensive information of clinical presenting symptoms, diagnostic results (including imaging and biopsy finding), ECG findings, and laboratory values were obtained. Furthermore, we included the variety of treatments that were administered to patients including steroids, antiviral medications, NSAIDs, surgical interventions, and immune and cardiac medications (Table 1).

Table 1 Demographics

Sex*	Total	% (number of cases/total cases)
Male	100	69
Female	45	31
Age		
0–18 yr	31	21
18–29 yr	24	16
30–49 yr	48	33
50–64 yr	28	19
65+	15	10

* Total reported for sex is 145. One article did not specify sex

Results

During the period spanning from 2020 to 2022, we identified 146 (145 noted in our figure because one case did not report the sex) individual cases of myocarditis that occurred after or during active COVID-19 infection. We conducted an analysis of the population demographics for each case, encompassing a cohort of 146 patients who were diagnosed with myocarditis secondary to a COVID-19 infection. Our data collection efforts successfully included patients across a wide range of ages, allowing for a comprehensive understanding of the impacts of COVID-19-induced myocarditis across different age groups. Our analysis revealed a notable male predominance among the cases, accounting for 69% of the total patients. One case did not report the sex of the affected individual and therefore could not be categorized into either group. There were no significant differences in age in each sex group. Most of the cases (84%) were able to successfully recover from myocarditis secondary to COVID-19 infection, while a minority of patients (14%) died. The outcomes for 2% of the cases were not reported (Fig. 1).

Clinical presentations exhibited a range of findings, indicating variability in symptoms. The most frequently reported presenting symptoms were shortness of breath (43%) and chest pain (29%). Additional presenting symptoms are summarized in Table 2. There is also a subset of patients with delayed cardiac presentations (22%) and no signs of respiratory disease (25%). We did not see any significant differences in presentation of symptoms based on demographics.

In terms of diagnostic tools, 67.9% of these case studies reported reduced left ventricular ejection fraction (LVEF) on echocardiogram findings. Electrocardiogram (ECG) findings were variable and showed classic findings of

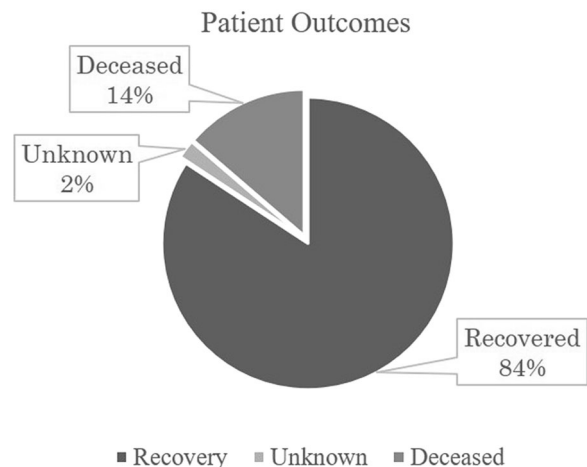


Fig. 1 Percentage of cases that reported a patient recovery or mortality following the illness reported

Table 2 Presenting symptoms

Presenting symptoms	Total	% (number of cases/total cases)
Chest pain	42	29
Palpitations	6	4
Shortness of breath	62	43
Cough	33	23
Sore throat	3	2
Fever	68	47
Upper respiratory tract symptoms (cough mainly)	10	7
Myalgia	14	10
Fatigue	23	16
Syncope	7	5
No Signs of Respiratory Disease	36	25
Delayed cardiac presentations	32	22
Gastrointestinal symptoms	39	27
Other	29	20

myocarditis: 24.4% exhibited ST elevation, 15% showed diffuse ST elevation, and 29.1% had sinus tachycardia. A large majority of patients had elevated troponin levels (90.1%) and a slight majority had elevated C-reactive protein (58.5%). There was no significant difference in imaging presentation related to sex or age of patients (Tables 3 and 4).

A range of therapeutic interventions were employed, including steroids (47.3%), antivirals (20.5%), NSAIDs (41.7%), immunosuppressive drugs (41.1%), anticoagulants (28.8%), inotropes (25.3%), vasopressors (31.5%), and antibiotics (40.4%). Patients with severe cases of myocarditis required lifesaving measures such as extracorporeal membrane oxygenation (ECMO) (28%).

Discussion

Although classic presentations of COVID-19 typically involve respiratory symptoms, it is important for clinicians to be prepared for cardiac manifestations of the disease. The occurrence of myocarditis after COVID-19 infection does not depend on the initial health or pre-existing cardiovascular problems. Myocarditis secondary to COVID-19 can have a silent progression, as it can develop unexpectedly over the course of disease. The severity and complexity of symptoms often depends on the extent of myocardial involvement. Without treatment, complications may occur such as arrhythmia, cardiomyopathy, intracardiac thrombosis, and even death. Based on the data collected, we see that there are several patients who presented with cardiac symptoms alone with a confirmed infection of COVID-19. The

Table 3 Diagnostic results

Diagnostic testing	Total	% (number of cases/total cases)
<i>Echocardiogram results</i>		
Reduced left ventricular ejection fraction (LVEF)	95	68
Pericardial effusion	35	25
Ventricular Hypertrophy	17	12
Valve Regurgitation	13	9
Dilated cardiomyopathy	8	6
Hypokinesia	56	40
Thrombus	9	6
Normal	19	14
Use of Cardiac MRI	59	40
Use of Coronary angiography	28	19
Use of Endomyocardial Biopsy	18	12
<i>EKG Findings</i>		
ST elevation	31	24
ST elevation; diffuse	19	15
ST depression	11	9
T-wave inversion	23	18
Sinus tachycardia	37	29
Normal	13	10
<i>Elevated lab values</i>		
Troponin	128	90
D-dimer	57	40
Pro B-type natriuretic peptide	65	46
C-reactive Protein	83	59
Normal	4	3

exact pathophysiology is unknown, but it is hypothesized that the virus damages the myocardium by attaching to angiotensin-converting enzymes 2 receptors (ACE2) and increases inflammatory cytokine production [2]. Furthermore, myocarditis may arise because of inflammation associated with cytokine storms, autoimmune damage, and inflammation of coronary endothelial cells [3].

ACE2 receptor is a membrane bound protein found in cardiac epithelium and allows SARS-CoV-2 entry into the cell, where it replicates and antagonizes stress granule formation, further promoting cell damage. Systemic inflammation may also contribute to the development of myocarditis. The cytokine IL-6 has been implicated in the pathophysiology of myocarditis by attracting inflammatory cells to the myocardium. It is a key mediator of cytokine storm, a life threatening condition that involves excessive production of proinflammatory cytokines and an uncontrolled immune response, which can further damage the myocardium [4]. Even though the clear pathogenesis of cardiac involvement is still

Table 4 Treatments

Treatments	Total	% (number of cases/ total cases)
<i>Steroids</i>		
Methylprednisolone	40	27.4
Dexamethasone	15	10.3
Prednisone	14	9.6
<i>Anti-virals</i>		
Remdesivir	11	7.5
Chloroquine/ hydroxychloroquine	19	13
<i>NSAIDs</i>		
Colchicine	21	14.4
Aspirin	31	21.2
Ibuprofen	9	6.1
<i>Surgical</i>		
Use of ECMO	28	19.2
Implantable devices	14	9.6
Catheterization	5	3.4
Pericardiocentesis	6	4.1
<i>Immune drugs</i>		
Intravenous immunoglobulin	38	26
Tocilizumab	12	8.2
Interferon	1	0.7
Anakinra	9	6.2
<i>Cardiac drugs</i>		
Use of anticoagulants	42	28.8
Inotropes	37	25.3
Vasopressors	46	31.5
Angiotensin-II receptor blocker	1	0.7
ACE Inhibitor	13	8.9
Beta-blocker	23	15.8
Anti-Arrhythmic	11	7.5
<i>Other</i>		
Diuretics	22	15.1
Unspecified anti-inflammatory	5	3.4
Antibiotics	59	40.4
Unspecified Steroids	15	10.3
Unspecified anti-virals	13	8.9
Hydrocortisone	3	2.1
Acetaminophen	4	2.7
Mineralocorticoid antagonist	2	1.4

ECMO: Extracorporeal membrane oxygenation

unknown, it is proposed that SARS-CoV-2 has the ability to disseminate through blood or lymphatics of the respiratory tract, leading to inflammation and pericardial effusion [5].

Common presenting symptoms observed in individuals with COVID-19 related myocarditis include chest pain, palpitations, shortness of breath, cough, sore throat,

and fever. It is important for clinicians to be aware that cardiac symptoms may present alone, without respiratory symptoms, and may appear delayed to the onset of viral infection. COVID-19 related myocarditis typically occurs after the acute phase of infection [6]. A study conducted on over 150,000 US veterans revealed that individuals who have had COVID-19 faced an elevated risk of developing cardiovascular diseases, including myocarditis, 30 days post infection. They adjusted for confounding variables including demographics and comorbidities. This increase in risk was also observed even in those who did not require hospitalization during the active phase of the infection [7]. In our review, we found that 22% of patients dealt with delayed cardiac presentations after initial infection of COVID-19. As of today, the exact mechanism behind the delayed onset of symptoms in cases of fulminant myocarditis following the resolution of COVID-19 infection is not fully understood. The delayed onset suggests that there may be complex factors contributing to the development of myocarditis in some individuals, potentially involving post viral immune response or some other pathology. Thus, it is crucial to monitor and follow up on patients, especially those with comorbidities, closely to see if any cardiac manifestations arise.

Current treatments for myocarditis are mainly supportive. The American College of Cardiology published their most updated guidelines in treating COVID-19 induced myocarditis in March 2022 [8]. These guidelines, which were written before this analysis, reflect many of the same trends that are observed here, such as the use of cardiovascular magnetic resonance (CMR), ECG, and echocardiogram for diagnosis and anti-inflammatory agents for treatment. While endomyocardial biopsy is considered the gold standard for diagnosing myocarditis, it is often avoided due to its invasive nature. In our review, we see that there is a high survival rate amongst patients who followed these treatment protocols. CMR is a great diagnostic tool for detecting immune mediated myocarditis and is useful in distinguishing between various potential sources of chest pain in individuals affected by COVID-19 [9]. We see here that echocardiogram and CMR are the most commonly used diagnostic tools because they are cost efficient and minimally invasive.

As per the guidelines published by the American College of Cardiology [8], certain abnormalities observed in an electrocardiogram (ECG) and echocardiogram can indicate potential cardiac issues. These abnormalities include diffuse T-wave inversion, ST-segment elevation without reciprocal ST-segment depression, and prolongation of the QRS complex duration on ECG. In this review, the observed ST changes on ECG display a

wide range of patterns. Majority of patients exhibited elevated ST segments (24%) and sinus tachycardia (29%), however diffuse ST elevation, ST depression and T wave inversion were present as well. While elevated ST segments and sinus tachycardia can raise suspicion for fulminant myocarditis, they should be interpreted in conjunction with other clinical findings for a comprehensive assessment. Furthermore, 68% of patients were reported to have reduced left ventricular ejection fraction on echocardiogram which is consistent with findings of myocarditis [8]. There was not consistent documentation on how much the ejection fraction was reduced and how it improved over time. Early detection of echocardiogram and ECG changes indicative of myocarditis allows for timely noninvasive intervention and implementation of appropriate treatment strategies.

COVID-19 myocarditis can often lead to sudden severe complications such as heart failure, hypotension, cardiac shock, and severe arrhythmias. Extracorporeal membrane oxygenation (ECMO) serves as a simplified cardiopulmonary bypass that can be utilized for extended duration of time. ECMO provides temporary respiratory and circulatory support when the heart and lungs are unable to function adequately. In recent years, ECMO has been effectively employed as an emergency adjuvant therapy for acute circulatory and respiratory failures that arise from diverse causes [10]. Our review revealed that patients with severe cases of myocarditis arising from COVID-19 infection did require ECMO (28%). Because our sample size was relatively limited, we were unable to find any specific correlations between the severity of clinical presentation with patient demographics. While ECMO does not directly treat myocarditis, it plays a crucial role in stabilizing hemodynamics, enhancing systemic tissue perfusion, reducing the need for high-dose vasoactive medications, and effectively supporting patients during the acute phase of myocarditis [10]. Available data on the outcomes of patients on venoarterial ECMO for COVID-19 related complications is limited, but the existing literature suggests that the survival rate for patients on ECMO until hospital discharge falls within 40–45% [11]. The role of ECMO support in managing cardiopulmonary failure resulting from COVID-19 infection is continuously evolving, and a multidisciplinary approach should be used in the decision of ECMO implementation in patients with fulminant myocarditis secondary to COVID-19.

While the current approach to medication management for COVID-19 related myocarditis is primarily focused on providing supportive care, certain patterns have been observed in the treatment. Majority of patients among the cases cited were treated with steroids and NSAIDs, as well

as other treatments such as immunosuppressive drugs, anticoagulants, inotropes, vasopressors, and antibiotics. In our review, we observed a trend associated with positive outcomes when treated with these agents. Because glucocorticoids have strong antiinflammatory effects, they can be clinically used in management of myocarditis by potentially preventing excessive inflammation from damaging cardiac tissue. It is important to note that the efficacy of corticosteroids in treating myocarditis is controversial in the literature, with some studies suggesting it has a beneficial effect only in severe COVID-19 [12]. In our review, methylprednisolone, dexamethasone, and prednisone were the most frequently utilized drugs from the glucocorticoid family. The case study from 2022 highlights the use of glucocorticoids in the management of cytokine storm and viral myocyte damage [13]. Intravenous immunoglobulin (IVIG) infusion was the most common choice of immune drug administered to a patient. It has been suggested to potentially improve viral clearance and aid the removal of cytokines contributing to myocardial damage [14]. In viral myocarditis, IL-6 is considered the central mediator of cytokine storm, playing a crucial role in proinflammatory responses from immune cells, including T lymphocytes. Tocilizumab is an immune drug administered, which functions by preventing IL-6 from binding to IL-6 receptor and cell membrane receptor, thereby partially inhibiting the inflammatory cascade in the body [15]. Based on positive outcomes found through this systematic review of cases, administration of corticosteroid treatment and immunosuppressant medications can play a vital part in reducing the severity of inflammatory state associated with COVID-19 myocarditis. Although the use of steroids and NSAIDs were predominant in treatment of COVID-19 related myocarditis, our review also includes cases of patients who were successfully treated with other combinations of drugs such as inotropes, renin–angiotensin–aldosterone system inhibitors, and diuretics.

Limitations

The review's limitations primarily revolve around its reliance on case reports, which introduces selection bias. Due to the nature of case reports, each case's unique clinical presentation created challenges to draw broader conclusions. Additionally, another potential limitation is the risk of missed data since the case reports were not written in a standardized manner. The lack of standardized reporting protocols may have led to variations in the amount and quality of information

provided. Despite the limitations, it is important to highlight that the use of case reports in our review holds value in identifying trends and generating hypotheses. A randomized control trial is recommended to better associate treatments with outcomes.

Conclusion

COVID-19-related myocarditis is a significant cardiac manifestation that clinicians should be prepared to encounter. As of today, there are no definitive treatments available for myocarditis. Because there was a variety of treatments, it was difficult to draw associations between specific treatments to outcomes, warranting further study in this area. Diagnosis of COVID-19 myocarditis relies on various tools such as ECG, echocardiogram, and CMR. Detecting abnormalities in these tests allows for timely intervention and treatment. Based on our review, supportive care appears to serve as the primary approach to treatment of COVID-19 myocarditis, with glucocorticoids and immunosuppressive drugs showing positive outcomes in potentially reducing inflammation. The approach of using extracorporeal membrane oxygenation (ECMO) in severe cases can stabilize hemodynamics and provide critical care during the acute phase of myocarditis. Monitoring and following up on patients, especially those with comorbidities, is crucial to detect any delayed cardiac manifestations. Due to the lack of comprehensive studies on a larger scale, treatment approaches must be personalized on an individual level until further research is conducted.

Appendix

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Author contributions

VL and GT performed the initial identification and review of literature. VL, GT, and EA interpreted the case reports, were major contributors to writing the manuscript, and prepared figures. MD contributed significantly to the conception, design, and revision of this work. All authors have read and approved the final manuscript.

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