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# COVID-19 Myocarditis Clinical Presentation, Diagnosis and Management: A Narrative Review

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## Abstract

*Objective:* The purpose of this article is to review the cases of myocarditis in COVID-19 patients and synthesize the current understanding regarding the presentation, diagnosis, and management of myocarditis in the setting of COVID-19 disease.

*Background:* The novel coronavirus disease has shown serious implications for the cardiovascular system, including acute myocardial injury, arrhythmias, venous thromboembolism, and myocarditis. Several cases of myocarditis in COVID-19 patients have been reported since the disease's emergence at the end of 2019. The diagnostic approach and management have been variable. The purpose of this narrative review is to gather the most reliable published material regarding myocarditis in COVID-19 and present it as an overview to simplify the current understanding we have of this disease.

*Methods:* We screened PubMed, Scopus, and Embase. We then selected peer-reviewed and pre-print articles published in English that were related to the involvement of the cardiovascular system in COVID-19, with a focus on myocarditis. We included case reports describing myocarditis in COVID-19 patients and summarized their clinical presentation, diagnosis, and management. References of the selected articles were also screened, and some were included when relevant.

*Discussion:* This article is subdivided into sections that discuss the clinical presentation of COVID-19 myocarditis and move on to various diagnostic approaches and management options. Each subsection presents a brief literature review followed by a summary and interpretation of what was found in the reported cases.

Conclusion: After noticing the involvement of the cardiovascular system in COVID-19 patients, specifically through myocarditis, we present this narrative review to provide the medical community with a unified

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article regarding the current understanding of myocarditis in COVID-19 patients. This article further stresses the necessity of establishing proper treatment guidelines for COVID-19 myocarditis.

*Keywords: COVID-19, coronavirus, myocarditis, case report, cardiovascular, clinical manifestations, diagnosis, imaging, cardiac magnetic resonance, echocardiography, endomyocardial biopsy, management*

## Introduction

A novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan City infected clusters in December 2019 and caused an outbreak of SARS-like respiratory illness worldwide with associated human-to-human transmission [1]. The new coronavirus disease 2019 (COVID-19) outbreak was declared a Public Health Emergency of International Concern by the World Health Organization on January 30, 2020 [2] and upgraded to a pandemic on March 11, 2020 [3].

Although COVID-19 mainly manifests with respiratory symptoms, cardiac complications have also been reported in these patients. A study showed that up to 19% of COVID-19 hospitalized patients demonstrated cardiac injury [4]. The mechanism of cardiac disease is thought to be multifactorial, involving (1) the entry of the SARS-CoV-2 virus into cardiomyocytes, which induces direct cardiotoxicity, and (2) the viral driven inflammatory process with cytokine release, which leads to myocarditis, hypercoagulability, vascular inflammation, and plaque instability [5].

While different cardiac manifestations have been reported in COVID-19, such as ACS, arrhythmias, myocardial injury, and thromboembolism, early studies in China reported that 7-20% of patients diagnosed with COVID-19 had viral myocarditis [6]. Viral myocarditis caused by the SARS-CoV-2 has also been documented as a cause of dilated cardiomyopathy, albeit in rare case reports [1, 7]. Although many of these early studies did not include echocardiography or Magnetic Resonance Imaging (MRI) data to assert whether the typical myocarditis features were present in these patients, the number of reports of COVID-19 myocarditis published warrants a necessity to review this topic.

## Methods

We screened databases including PubMed, Scopus, and Embase and selected peer-reviewed articles published in English that were related to the cardiovascular system's involvement in COVID-19, with a focus on myocarditis. To look for case reports of myocarditis in COVID-19 patients, we performed the search on the PubMed database using the combination of the following keywords: COVID-19, myocarditis, and case report and found 44 results. All the articles found up to July 29, 2020, were screened, and we ended up with 27 case reports describing 29 patients with confirmed COVID-19 who were diagnosed with myocarditis. We summarized their clinical presentations, laboratory findings, diagnostic approach, and treatment, regardless of the country from which these cases were reported. We compared the results to the existing literature regarding myocarditis by screening the databases above using combinations of keywords, including myocarditis, clinical manifestations, diagnosis, imaging, cardiac magnetic resonance, and others. References of the selected articles were screened and included when relevant.

## Discussion

### 1. Clinical Presentation

Patients with acute myocarditis can be asymptomatic and often present with non-specific symptoms such as chest pain, dyspnea, and palpitations. Those who develop acute heart failure develop dyspnea, fatigue, and exercise intolerance, often with paroxysmal nocturnal dyspnea and orthopnea [1, 8-10]. To note, a viral prodrome with fever, myalgias, and respiratory or gastrointestinal symptoms may be related to myocarditis, though this remains variable [10].

We described patient demographics, including age, sex, ethnicity or nationality, and comorbidities within the supplementary material. As shown in Table 1, we identified the presenting signs and symptoms of the 29 reported cases of COVID-19 myocarditis. We found the clinical presentation to be variable and non-specific. Many patients presented with fever (62.1%), cough (37.9%), and dyspnea (51.7%), which are the typical symptoms in most cases of COVID-

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***Table 1:*** *Table showing the presenting signs and symptoms of the 29 reported cases of myocarditis in COVID-19 patients*

| | | Presenting Signs and Symptoms | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Chest pain | Dyspnea | Cough | Fatigue | Fever | Vomiting Diarrhea | Myalgias | Other |
| Sala, Simone et al. [8] | | ✓ | ✓ | | | | | | |
| Inciardi, Riccardo M et al. [11] | | | | ✓ | ✓ | ✓ | | | |
| Kim, In-Cheol et al. [12] | | | ✓ | ✓ | | ✓ | ✓ | | |
| Warchoł, Izabela, et al. [13] | | | | | | | | | ✓ |
| Hu, Hongde et al. [14] | | ✓ | ✓ | | | | ✓ | | |
| Paul, Jean-François et al. [15] | | ✓ | | | ✓ | | | | |
| Doyen, Denis et al. [16] | | | ✓ | ✓ | ✓ | | ✓ | | |
| Zeng, Jia-Hui et al. [17] | | ✓ | ✓ | ✓ | | ✓ | | | |
| Coyle, Justin et al. [18] | | | ✓ | ✓ | | ✓ | ✓ | ✓ | |
| Cizgici, Ahmet Yasar et al. [19] | | ✓ | ✓ | | | | | | ✓ |
| Yuan, Wei-Feng et al. [20] | | ✓ | | | | ✓ | | ✓ | |
| Irabien-Ortiz, Angela. [21] | | ✓ | | | | ✓ | | | |
| Radbel, Jared et al. [22] | | | ✓ | ✓ | | ✓ | | | |
| Beşler, Muhammed Said, and Halil Arslan [23] | | ✓ | | | | ✓ | | | |
| Luetkens, Julian Alexander et al. [24] | | | ✓ | | ✓ | | | | |
| Hua, Alina et al. [25] | | ✓ | ✓ | ✓ | | ✓ | | | |
| Rehman, Mahin et al. [26] | | ✓ | | | | | | | |
| Craver, Randall et al. [27] | | | | | | | ✓ | | ✓ |
| Khalid, Nauman et al. [28] | | ✓ | | | | ✓ | | ✓ | |
| Gill, Gauravpal S et al. [29] | Case 1 | ✓ | ✓ | | | | | | |
| | Case 2 | ✓ | ✓ | | | ✓ | | | ✓ |
| Khatri, Akshay, and Frances Wallach [30] | | | ✓ | ✓ | ✓ | ✓ | | | ✓ |
| Oberweis, Marie-Laure et al. [31] | | | | ✓ | ✓ | ✓ | | | ✓ |
| Gnecchi, Massimiliano et al. [32] | | ✓ | | | | ✓ | | | |
| Pavon, Anna Giulia et al. [33] | | ✓ | ✓ | | | ✓ | | | |
| Giacomet, Vania et al. [34] | | | | | | ✓ | ✓ | | |
| Hussain, Hussain et al. [35] | | | ✓ | ✓ | ✓ | ✓ | | | |
| Caballeros Lam, Meylin et al. [36] | Case 1 | ✓ | | | | | | | |
| | Case 2 | | | ✓ | | ✓ | ✓ | | ✓ |

19. Although none of the articles reported patients presenting with paroxysmal nocturnal dyspnea or orthopnea, dyspnea itself was commonly associated with chest pain, with 8 of 29 cases reporting both symptoms combined (27.6%). Both of these are non-specific symptoms of acute myocarditis. Chest pain was reported in 55.2% of cases independently. Many reported cases additionally had fatigue (24.1%), gastrointestinal symptoms such as vomiting and/or diarrhea (24.1%), and myalgias (10.3%), which are non-specific symptoms of viral infections that may be present in viral myocarditis unrelated to COVID-19 as well as in COVID-19 patients without myocarditis. Other less common symptoms such as headaches, dizziness, weight loss, weakness, and odynophagia were reported, each in 1 of the 29

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patients. These occurred combined with one or more of the previously discussed symptoms. Three patients reported syncope and/or near syncope episodes, which is considered one of the clinical syndromes associated with with acute myocarditis, as will be discussed later in the classification section. Two reported cases were already diagnosed with COVID-19. They were suspected of having developed acute viral myocarditis after identification of electrocardiography (ECG) changes. One patient developed a hemodynamically unstable new-onset ventricular tachycardia and another one developing ST-segment elevation on ECG. A number of these patients were considered as fulminant myocarditis (17.2% of the cases) and developed cardiogenic shock (13.8% of the cases).

## 2. Pathogenesis

Myocarditis is an inflammatory cardiomyopathy with several clinical and histological presentations [9]. Acute and chronic myocarditis can involve changes in the number and function of lymphocytes and macrophages as well as antibody-mediated injury [9]. This, in turn, causes a cascade of structural and functional changes in cardiomyocytes and ultimately regional or global contractile impairment, conduction system abnormalities, or chamber stiffening.

## 3. Classification

Classification of myocarditis can be either by etiology, histology, immunohistology, or clinicopathological and clinical criteria [9].

Clinical classification seems to be the most practical as many clinical facilities cannot perform endomyocardial biopsy (EMB). The classification is based on increasing diagnostic certainty and includes three categories as per Table 2 [9].

Looking at this classification, we noticed that out of the 29 patients, only one patient had undergone an endomyocardial biopsy, and 1 underwent autopsy and histopathological evaluation after death. Both of these showed positive histological studies confirming a diagnosis of definite myocarditis. Other cases were reported as myocarditis despite commonly falling under probable acute myocarditis.

## 4. Diagnostic Testing

### a) ECG Findings

Most patients with myocarditis have non-specific changes on ECG, including sinus tachycardia, ST-wave and T-wave abnormalities like ST-segment elevation or depression, pathologic Q waves, and occasionally atrioventricular or bundle branch block [9, 10]. A widened QRS and Q waves are associated with poor prognosis in acute myocarditis [9]. Pericarditis often manifests with PR depression and diffuse ST-segment elevation [9]. The sensitivity of ECG for myocarditis is low (47%) [9].

The ECGs of the reported cases of COVID-19 myocarditis showed a variety of changes (Table 3). Of the 29 cases reported, 6 did not include the ECG findings of the patient, and 1 case was reported as having a normal ECG. Several patients showed ST-segment elevation; however, some were diffuse [11, 19, 35] while others were localized to specific leads. Due to the ST-segment elevation in some cases,

***Table 2:*** *Classification of Myocarditis*

| | |
|---|---|
| *Possible subclinical acute myocarditis* | *Asymptomatic patient with no other causes of acute cardiac disease and with a recent cause for myocarditis*<br><br>*Biomarkers of cardiac injury raised, ECG findings suggestive of cardiac injury, or Abnormal cardiac function in echocardiogram or cardiac MRI* |
| *Probable acute myocarditis* | *An individual with all the criteria for possible subclinical myocarditis but also has one of four clinical syndromes consistent with acute myocarditis:*<br><br>*Acute heart failure, chest pain, presyncope or syncope, or myopericarditis* |
| *Definite myocarditis* | *The patient has positive histological studies regardless of any clinical syndrome* |

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suspicion of myocardial ischemia was raised, and many patients underwent a conventional coronary angiography or a coronary computed tomography angiography to rule out coronary stenosis. In all cases, there was no coronary narrowing [14, 16, 19, 33] except for one case which had mild luminal irregularities [29]. Other patients' ECGs showed non-specific ischemic changes such as T-wave inversions [11, 26]. Tachyarrhythmias, mainly sinus tachycardia, was

***Table 3:*** *ECG findings in the reported cases of myocarditis in COVID-19 patients*

| | | ECG Findings |
|---|---|---|
| *Sala, Simone et al.* [8] | | *Mild ST-segment elevation in leads V1–V2 and aVR, reciprocal ST depression in V4–V6, and QTc 452 ms with diffuse U-waves* |
| *Inciardi, Riccardo M et al.* [11] | | *Low voltage in the limb leads, minimal diffuse ST-segment elevation (more prominent in the inferior and lateral leads), and an ST-segment depression with T-wave inversion in lead V1 and aVR* |
| *Kim, In-Cheol et al.* [12] | | *Non-specific intraventricular conduction delay and multiple premature ventricular complexes* |
| *Warchoł, Izabela, et al.* [13] | | *Not reported* |
| *Hu, Hongde et al.* [14] | | *ST-segment elevation in leads III, aVF* |
| *Paul, Jean-François et al.* [15] | | *repolarization changes in the precordial ECG leads* |
| *Doyen, Denis et al.* [16] | | *Left ventricular hypertrophy (LVH) and diffuse inverted T waves - a previous ECG showed inverted T waves in anterior leads only* |
| *Zeng, Jia-Hui et al.* [17] | | *Sinus tachycardia and no ST-segment elevation* |
| *Coyle, Justin et al.* [18] | | *Sinus tachycardia without ST-T wave changes* |
| *Cizgici, Ahmet Yasar et al.* [19] | | *Atrial fibrillation with 150 beat/min and concave ST elevation except for aVR lead* |
| *Yuan, Wei-Feng et al.* [20] | | *Ventricular tachycardia* |
| *Irabien-Ortiz, Angela.* [21] | | *Concave ST-segment elevation and PR-segment depression, as well as low voltages* |
| *Radbel, Jared et al.* [22] | | *ST segment depression in leads V4-V6 on ECG, mild global hypokinesis* |
| *Beşler, Muhammed Said, and Halil Arslan* [23] | | *Not reported* |
| *Luetkens, Julian Alexander et al.* [24] | | *Not reported* |
| *Hua, Alina et al.* [25] | | *Concave ST elevation in infero-lateral leads and sinus tachycardia* |
| *Rehman, Mahin et al.* [26] | | *1 to 2 mm ST elevations in lead I and aVL, ST depression in aVR, mild J-point elevation, and T-wave inversion in leads II, III and aVF* |
| *Craver, Randall et al.* [27] | | *Not reported* |
| *Khalid, Nauman et al.* [28] | | *Sinus tachycardia with low-amplitude QRS in the precordial and limb leads, and poor R-wave progression in the anterior leads* |
| *Gill, Gauravpal S et al.* [29] | *Case 1* | *ST-segment elevations in leads I, II, III and aVF with ST-segment depressions in leads V1-4* |
| | *Case 2* | *Significant reduction in voltage and subtle PR-segment depressions in leads II, III and aVF* |
| *Khatri, Akshay, and Frances Wallach* [30] | | *Sinus tachycardia, ST-elevation in leads II, III, aVF and ST-depression in I, aVL* |
| *Oberweis, Marie-Laure et al.* [31] | | *Discrete ST elevation in V3 consistent with pericarditis* |
| *Gnecchi, Massimiliano et al.* [32] | | *Inferolateral ST-segment elevation* |
| *Pavon, Anna Giulia et al.* [33] | | *Not reported* |
| *Giacomet, Vania et al.* [34] | | *Sinus tachycardia without other clear pathologic alterations* |
| *Hussain, Hussain et al.* [35] | | *Diffuse ST elevation* |
| *Caballeros Lam, Meylin et al.* [36] | *Case 1* | *Normal ECG* |
| | *Case 2* | *Not reported* |

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noted [17, 18, 25, 28, 30, 34], as well as ventricular tachycardia and atrial fibrillation [2, 19].

### b) Laboratory Blood Tests

Serum biomarkers are elevated in a minority of patients with acute myocarditis. Troponin I has a high specificity (89%) but a low sensitivity (34%) in the diagnosis of myocarditis [10]. Increased troponin I is more common than high levels of creatine kinase myocardial band CKMB [10]. Other serum markers of inflammation that are non-specific, such as C-reactive protein, erythrocyte sedimentation rate, and leucocyte count, can be elevated in patients with suspected myocarditis but these markers are of limited value due to their low specificity [9].

Three of the cases did not report any laboratory blood test results [20, 22, 27]. In the rest of the cases, the most reported laboratory blood tests included different combinations of troponin T, Troponin I, N-terminal pro b-type natriuretic peptide (NT-proBNP), and C-Reactive Protein (CRP), all of which, when done, were consistently elevated. Some cases also reported CK-MB levels as high [11, 14, 23, 30, 35]. One case reported an elevated serum myoglobin level [17]. Serum creatine kinase, also known as creatine phosphokinase, was reported as high in two cases [10, 32]. In addition, inflammatory markers like erythrocyte sedimentation rate (ESR), procalcitonin, lactate, and ferritin were reported as high in some cases, and at times they were reported as unremarkable. D-dimers, when reported were found to be elevated [13, 21, 26, 30, 31, 33, 36]. Interleukin 6 (IL-6) was reported as elevated in two cases [31, 34]. Complete blood count and electrolytes were not consistently reported and were not included in Table 4.

### c) Imaging Studies

#### 1. Echocardiography

Acute myocarditis does not have any specific features. The most important role of transthoracic echocardiogram (TTE) on the assessment of acute myocarditis is to rule out primary valvular disease, congenital disease, or pericardial constriction [9]. Hence, imaging is used to rule out other causes of heart failure [10]. Many reported cases of myocarditis in COVID-19 patients had normal findings on echocardiography [15, 26, 36]. One patient had no changes compared to his previous echocardiography results; he was already known to have left ventricular hypertrophy due to his chronic hypertension and there were no findings otherwise [16]. Of the 29 cases summarized in this narrative review, 9 cases did not report echocardiography results or reported not having performed an echocardiography due to COVID-19 restrictions [13, 19, 20, 22-24, 27, 29, 36]. These cases will be excluded when calculating percentages and the total number of cases will be considered as 20.

Any new regional or global wall motion abnormality that is not correlated with a coronary distribution has confirmatory and prognostic value in acute myocarditis [9]. Many cases relied on this finding to confirm the diagnosis of acute myocarditis with 15% reporting diffuse hypokinesia or dyskinesia [11, 17, 18], and 10% reporting regional hypokinesis on echocardiography [32, 34]. In fulminant myocarditis, there is a possibility of wall thickening and increased ventricular sphericity [9]. Such findings were not reported in the selected case reports. Left ventricular dysfunction may be found, and 55% of cases were reported to have a left systolic dysfunction [8, 11, 12, 14, 17, 18, 28, 30, 31, 34, 35]. However, the strongest predictor of death or need for cardiac transplantation was a loss of right ventricular function [9,10].

In the 29 cases reported, only 2 were found to have right ventricular dysfunction [29, 30]. Both cases were in cardiogenic shock and on inotropic and vasoactive support. The first case underwent pericardiocentesis yielding around 300 mL of serous fluid, but with worsening status, she was escalated to veno-arterial extracorporeal membrane oxygenation (VA-ECMO). She later recovered and was discharged successfully [29]. The second case also had to undergo pericardiocentesis which yielded 600 mL of serosanguinous fluid.

She was also on vasopressor and inotropic support and cardiothoracic surgeons were consulted to initiate ECMO therapy, however, it was not started due to multi-organ failure, and the patient died on day 4 of hospitalization despite maximal supportive care [30] (Table 5).

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***Table 4:*** *Laboratory tests results in the reported cases of myocarditis in COVID-19 patients*

| | | HS-Troponin T | Troponin T | Troponin I | NT-proBNP | CK-MB | CRP | Other |
|---|---|---|---|---|---|---|---|---|
| *Sala, Simone et al.* [8] | | ↑ | | | ↑ | | ↑ | |
| *Inciardi, Riccardo M et al.* [11] | | ↑ | | | ↑ | ↑ | ↑ | |
| *Kim, In-Cheol et al.* [12] | | | | ↑ | ↑ | | | |
| *Warchoł, Izabela, et al.* [13] | | ↑ | | | ↑ | | ↑ | LDH ↑; d-Dimers ↑; AST ↑; ALT ↑; Procalcitonin ↔ |
| *Hu, Hongde et al.* [14] | | | ↑ | | ↑ | ↑ | | |
| *Paul, Jean-François et al.* [15] | | | | ↑ | | | | |
| *Doyen, Denis et al.* [16] | | | | ↑ | | | | |
| *Zeng, Jia-Hui et al.* [17] | | | | ↑ | ↑ | | | Myoglobin ↑ |
| *Coyle, Justin et al.* [18] | | | | ↑ | ↑ | | ↑ | LDH ↑ |
| *Cizgici, Ahmet Yasar et al.* [19] | | | ↑ | | | | ↑ | |
| *Irabien-Ortiz, Angela.* [21] | | | ↑ | | ↑ | | ↑ | D-dimer ↑ |
| *Beşler, Muhammed Said, and Halil Arslan* [23] | | | | ↑ | ↑ | ↑ | ↑ | |
| *Luetkens, Julian Alexander et al.* [24] | | ↑ | | | ↔ ; ↑ | | ↑ | |
| *Hua, Alina et al.* [25] | | | ↑ | | | | | |
| *Rehman, Mahin et al.* [26] | | | ↑ | ↑ | ↑ | | ↑ | D-dimer ↑; LDH ↑; ESR ↑; Procalcitonin ↔ |
| *Khalid, Nauman et al.* [28] | *C1* | | | ↑ | | | | High Sensitivity CRP ↑; ESR↑; D-dimer ↑ |
| | *C2* | | | ↑ | ↑ | | | High Sensitivity CRP ↔; ESR↔; Lactate ↑ |
| *Gill, Gauravpal S et al.* [29] | *C1* | | | ↑ | | | | High Sensitivity CRP ↑; D-dimer ↑; LDH ↑; Lactate ↔ |
| | *C2* | | | ↑ | | | | High Sensitivity CRP ↔; d-dimer ↔; LDH ↔; Lactate ↑ |
| *Khatri, Akshay, and Frances Wallach* [30] | | ↑ | | | | ↑ | ↑ | LDH ↑; Lactate ↑; AST/ALT ↑; Procalcitonin ↑ ; D-dimer ↑ ; ESR ↑; Ferritin ↑ |
| *Oberweis, Marie-Laure et al.* [31] | *Peds* | ↑ | | | ↑ | | ↑ | D-dimer ↑; Il-6 ↑ |
| *Gnecchi, Massimiliano et al.* [32] | *Peds* | | | ↑ | | | ↑ | LDH ↑; CPK ↑ |
| *Pavon, Anna Giulia et al.* [33] | | ↑ | | | | | | D-dimer ↑ |
| *Giacomet, Vania et al.* [34] | *Peds* | | ↑ | | ↑ | | ↔ | Procalcitonin ↔; Il-6 ↑ |
| *Hussain, Hussain et al.* [35] | | | ↑ | | ↑ | ↑ | | |
| *Caballeros Lam, Meylin et al.* [36] | *C1* | | ↑ | | | | | |
| | *C2/Peds* | | ↑ | | ↑ | | ↑ | D-dimer ↑; Ferritin ↑ |

Abbreviations: C1: Case 1; C2: Case 2; Peds: Pediatrics Population; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase. ↑: Elevated; ↔ Normal; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HS-Troponin T: High Sensitivity Troponin T; CK-MB: Creatine kinase-MB; NT-proBNP: N-terminal (NT)-pro hormone BNP

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***Table 5:*** *Echocardiographic findings in the reported cases of myocarditis in COVID-19 patients*

| | **Echocardiography Findings** |
|---|---|
| *Sala, Simone et al.* [8] | • *Mild left ventricular systolic dysfunction (LVEF 43%)*<br>• *Inferolateral wall hypokynesis* |
| *Inciardi, Riccardo M et al.* [11] | • *Normal LV dimensions with increased wall thickness and diffuse echo-bright appearance of the myocardium.*<br>• *Diffuse hypokinesis*<br>• *Estimated LV ejection fraction (LVEF) of 40%.*<br>• *Left ventricular diastolic function mildly impaired with mitral inflow patterns.*<br>• *Circumferential pericardial effusion most notable around the right cardiac chambers* |
| *Kim, In-Cheol et al.* [12] | • *Severe left ventricular (LV) systolic dysfunction* |
| *Hu, Hongde et al.* [14] | • *Enlarged heart and a marked decrease in ventricular systolic function, LVEF 27%*<br>• *Trace pericardial effusion (2mm)* |
| *Paul, Jean-François et al.* [15] | • *Normal systolic function*<br>• *No pericardial effusion* |
| *Doyen, Denis et al.* [16] | • *Mild LVH (patient known to have LVH attributed to chronic HTN)*<br>• *LVEF and wall motion within normal* |
| *Zeng, Jia-Hui et al.* [17] | • *Enlarged left ventricle*<br>• *Diffuse myocardial dyskinesia*<br>• *Low LVEF (32%), pulmonary hypertension (44 mmHg), normal right cardiac function.*<br>• *No pericardial effusion* |
| *Coyle, Justin et al.* [18] | • *Moderate diffuse hypokinesis (relative apical sparing)*<br>• *LVEF of 35% to 40%*<br>• *No ventricular dilation or pericardial effusion* |
| *Irabien-Ortiz, Angela.* [21] | • *Moderate concentric hypertrophy*<br>• *Diminished intraventricular volumes with preserved LVEF*<br>• *Moderate pericardial effusion*<br>*2 hours after admission*<br>• *Severe biventricular failure and diffuse myocardial edema* |
| *Hua, Alina et al.* [25] | • *Normal left ventricular function*<br>• *Global pericardial effusion with a maximum depth of 1.1 cm and no tamponade* |
| *Rehman, Mahin et al.* [26] | • *No wall motion abnormalities*<br>• *Completely normal ejection fraction at 55%-60%*<br>• *No evidence of pericarditis or pericardial effusion.* |
| *Khalid, Nauman et al.* [28] | • *Severe left ventricular systolic dysfunction (EF = 25%)*<br>• *Large pericardial effusion with signs of pericardial tamponade* |
| *Gill, Gauravpal S Case 2 et al.* [29] | • *Large pericardial effusion with right ventricular diastolic collapse*<br>• *Severe global biventricular systolic dysfunction with an LVEF of 20%.* |
| *Khatri, Akshay, and Frances Wallach* [30] | • *Severe global LV systolic dysfunction, RV enlargement, and RV systolic dysfunction*<br>• *Moderate-to-large pericardial effusion anterior to the RV with organizing material (suggesting an inflammatory process)*<br>• *Evidence of intermittent RV impaired filling and collapse, suggestive of tamponade physiology* |
| *Oberweis, Marie-Laure et al.* [31] | • *Normal cardiac anatomy with impaired left ventricular function and trace mitral insufficiency*<br>• *Small pericardial effusion with neither evidence of left ventricular dilatation nor myocardial hypertrophy or significant pulmonary hypertension* |
| *Gnecchi, Massimiliano et al.* [32] | • *Transthoracic echocardiography showed hypokinesia of the inferior and inferolateral segments of the LV*<br>• *Preserved ejection fraction of 52%*<br>• *No pericardial effusion* |
| *Pavon, Anna Giulia et al.* [33] | *72 hours after the CMR*<br>• *LVEF at 47%.* |
| *Giacomet, Vania et al.* [34] | • *Hypokinesia of the inferior left ventricular wall and the inferior interventricular septum*<br>• *Mild decrease in the LVEF (57–58% in parasternal short-axis view, 52.7% in biplane Simpson's method)*<br>*On day 4:*<br>• *Ejection fraction recovery with normal left ventricular dimensions*<br>• *Persisting mild dyskinesia of the inferior LV wall and the inferior interventricular septum* |
| *Hussain, Hussain et al.* [35] | • *Enlarged heart with a marked decrease in ventricular systolic function*<br>• *Ejection fraction of 20%.* |
| *Caballeros Lam, Meylin et al.* [36] Case 1 | *Normal* |

Abbreviations: LV: Left Ventricular, RV: Right Ventricular, LVH: Left Ventricular Hypertrophy, LVEF: Left Ventricular Ejection Fraction, EF: Ejection Fraction, HTN: hypertension, CMR: Cardiac Magnetic Resonance

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While chest X-Rays performed on COVID 19 patients with myocarditis did not elicit a diagnostic pattern, transthoracic echocardiography revealed a drop in the ejection fraction ranging from mild all the way to severe in patients with no prior history of heart failure. In the cases we reviewed, the lowest ejection fraction reported was 20% [35].

### 2. Cardiac Magnetic Resonance

Cardiac MRI is being increasingly used as a routine and non-invasive imaging tool for the diagnosis of suspected acute myocarditis and as a means to localize sites for EMB [9, 10]. In the 29 reported cases of myocarditis in patients diagnosed with COVID-19, 14 did not report or perform a cardiac MRI [14, 17, 19, 21, 22, 25-30, 34, 35].

Among patients with nonischemic dilated cardiomyopathy (DCM) and myocarditis, the correct diagnosis was obtained through cardiac MRI alone in 80% of cases [9]. A combination of T2 weighted MRI and post-gadolinium early and late T1 weighted MRI provided the highest sensitivity (67%) and specificity (91 %) for diagnosis [9]. In the reported cases of COVID-19 myocarditis, the combination of increased signal intensity on T2WI along with late gadolinium enhancement often confirmed the diagnosis of several cases by fulfilling the Lake Louise criteria [11, 23, 24]. In other cases, the findings on cardiac magnetic resonance did not completely meet the criteria and so the patient was considered to have an atypical myocarditis [20].

The Lake Louise criteria are based on regional or global myocardial signal intensity increase in T2 weighted images, increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle, and late gadolinium enhancement.

#### d) Histopathology: Endomyocardial Biopsy (EMB)

The gold standard for the diagnosis of myocarditis is histological or immumohistological evidence of an inflammatory cell infiltrate with or without myocyte damage [9]. Endomyocardial Biopsy (EMB) should be used in a risk vs. benefit approach when there is more prognostic and therapeutic information gained from the biopsy [9]. The American Heart Association/American College of Cardiology/ European Society of Cardiology (AHA/ACC/ESC) joint scientific statement class 1 recommendations include performing EMB in patients with heart failure with:

*"(1) Normal or dilated dimensions of the LV, symptoms for a maximum of 2 weeks duration, and hemodynamic compromise*

*(2) A dilated ventricle, symptoms lasting from 2 weeks to 3 months, new onset of ventricular arrhythmias, Mobitz type 2 second- or third-degree block, or a failure to respond to care withing 1–2 weeks" [9]*

In other clinical scenarios, the use of endomyocardial biopsy remains debatable [10]. However, those with an indication for an EMB should be sent to a medical center with biopsy capability and expertise [10]. To confirm the diagnosis of myocarditis in the reported cases of COVID-19, only one case underwent an endomyocardial biopsy [8]. The medical team refrained from performing a biopsy in the rest of the cases due to several reasons, of which they mentioned: no evidence of heart failure or arrythmias, hemodynamic instability along with significant coagulopathy, rapid and favorable improvement, and establishment of a diagnosis based on the Cardiac Magnetic Resonance (CMR) findings and clinical context. In the case that underwent an EMB, the pathology demonstrated a diffuse infiltrate of T-lymphocytes (with a CD3+ > 7/mm$^2$) and described a huge area of interstitial edema as well as limited foci of necrosis. There was no replacement fibrosis which suggested the acute nature of the inflammatory process. No SARS-CoV-2 genome was detected in the myocardium. No microvascular abnormalities or contraction band necrosis were reported [8].

Another case also had a histopathologic confirmation of the diagnosis, however it was not through an EMB, rather on autopsy, as the patient reported in the case was found pulseless and resuscitation was unsuccessful [27]. Macroscopically, the heart weighed 500g (reference for age 262-295 g), was soft, rubbery, mottled, and there were 80 mL of pericardial fluid. Microscopically, diffuse inflammatory infiltrates were described, with lymphocytes, macrophages, and prominent eosinophils. These were mainly in the interstitium. Multiple foci of myocyte necrosis were found in the RV and LV. There was no evidence of perivascular infiltrates,

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***Table 6:*** *CMR findings in the reported cases of myocarditis in COVID-19 patients*

| | | Cardiac Magnetic Resonance |
|---|---|---|
| *Sala, Simone et al.* [8] | | *Performed on day 7*<br>• *Recovery of systolic function (to 64%; 43% on echocardiography)*<br>• *Mild hypokinesia (basal and mid left ventricular segments)*<br>• *Diffuse myocardial edema → wall pseudo-hypertrophy*<br>• *Absence of detectable myocardial scar/necrotic foci.* |
| *Inciardi, Riccardo M et al.* [11] | | • *Increased wall thickness*<br>• *Diffuse biventricular hypokinesis (especially apical)*<br>• *Severe LV dysfunction (LVEF of 35%)*<br>• *Marked biventricular myocardial interstitial edema on T2WI and STIR*<br>• *Diffuse late gadolinium enhancement (LGE) extended to the entire biventricular wall.* |
| *Kim, In-Cheol et al.* [12] | | • *Diffuse high signal intensity (SI) in the LV myocardium*<br>• *Myocardial wall thickening suggesting edema on STIR*<br>• *Extensive transmural ILGE* |
| *Warchoł, Izabela, et al.* [13] | | • *Left atrial enlargement*<br>• *Global left ventricular hypokinesia with ejection fraction of 20%.*<br>• *T2WI did not show myocardial edema*<br>• *LGE demonstrated a large, patchy, and linear nonischemic pattern of fibrosis localized subepicardially and intramurally in the basal and mid-cavity segments of the inferior and inferolateral wall and in the apical segments of the inferior wall* |
| *Paul, Jean-François et al.* [15] | | • *Late subepicardial enhancement predominating in the inferior and lateral walls* |
| *Doyen, Denis et al.* [16] | | • *Subepicardial late gadolinium enhancement of the apex and inferolateral wall).* |
| *Coyle, Justin et al.* [18] | | • *Recovery of ejection fraction to 82%*<br>• *Diffuse biventricular and bi-atrial edema*<br>• *Small area of LGE* |
| *Yuan, Wei-Feng et al.* [20] | | • *High signal intensity on T2WI in the apical region of the left ventricle → possibility of myocardial cell edema*<br>• *the signal of the corresponding segment was normal both in early gadolinium enhancement (EGE) and LGE, indicating no obvious capillary leakage, myocardial necrosis or interstitial fibrosis.*<br>• *Left ventricular systolic function was slightly decreased.* |
| *Beşler, Muhammed Said, and Halil Arslan* [23] | | *Performed after one week*<br>• *STIR sequence revealed a subepicardial high signal intensity in the mid posterolateral wall of the left ventricle which suggests myocardial wall edema.*<br>• *Subepicardial LGE of the posterolateral wall in the mid ventricle-suggestive of myocarditis at 5 and 10 min after contrast administration, respectively* |
| *Luetkens, Julian Alexander et al.* [24] | | *Performed day 10 post-admission*<br>• *Normal left ventricular size*<br>• *Mild systolic dysfunction (LVEF: 49%)*<br>• *Discrete global hypokinesis*<br>• *Normal right ventricular volume and function*<br>• *Pericardial effusion mainly around the left ventricular lateral wall*<br>• *Diffuse interstitial myocardial edema onT2WI*<br>• *Presence of diffuse myocardial inflammation was confirmed by T2 mapping*<br>• *LGE imaging was negative for focal myocardial lesions, but prolonged T1 relaxation times could be measured* |
| *Oberweis, Marie-Laure et al.* [31] | | *On day 3:*<br>• *Biventricular systolic dysfunction (LVEF: 41%, RVEF: 46%)*<br>• *Small pericardial effusion*<br>• *Mild subepicardial Gadolinium enhancement of the lateral wall*<br>• *Signs of diffuse edema* |
| *Gnecchi, Massimiliano et al.* [32] | | • *STIR sequences showed changes supporting the diagnosis of acute myocarditis.*<br>• *T2WI patchy oedema of the lateral wall.*<br>• *T2w-STIR images show subepicardial band-like high signal demonstrating the presence of oedema at the level of inferior and inferolateral walls, and patchy oedema pattern involving the whole lateral wall. T2 mapping sequences confirm the presence of oedema in the same segments.*<br>• *Late gadolinium sequences reveal high intensity signal indicating necrosis with the same distribution and localization* |
| *Pavon, Anna Giulia et al.* [33] | | • *Reduced left-ventricular (LV) systolic function (LVEF: 42%)*<br>• *Mild hypokinesia of the lateral wall*<br>• *T2-mapping sequences showed myocardial edema*<br>• *Subepicardial late gadolinium enhancement (LGE) in the anterior interventricular septum and in the inferior and inferolateral walls* |
| *Caballeros Lam, Meylin et al.* [36] | *Case 1* | • *Normal systolic function (LVEF 59%)*<br>• *No regional wall motion abnormalities*<br>• *High signal intensity on T2 maps and prolonged native T1 values in basal and mid-inferoseptal and inferior myocardial segments*<br>• *Late gadolinium enhanced (LGE) images showed mesocardial and subepicardial enhancement of those segments, representing 14.2% of the total ventricular mass.* |
| | *Case 2* | • *Normal biventricular function*<br>• *No regional wall motion abnormalities*<br>• *Slightly increased T2 and native T1 values in the ventricular septum reflecting myocardial edema*<br>• *No LGE*<br>• *Small pericardial effusion was noted.* |

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vascular thrombi, vascular inflammation, or endothelial prominence. No fibrinoid necrosis or granulomatous component was visualized. Only minimal interstitial fibrosis was seen. Although this case was reported as a case of eosinophilic myocarditis in a patient with COVID-19, the authors concluded that this eosinophilic myocarditis is not necessarily specific to the COVID-19 infection, and could instead be idiopathic or resulting from a cardiac decompensation contributed by the SARS-CoV-2.

### v. Management

The management of myocarditis generally depends on the clinical scenario. For *possible subclinical acute myocarditis***,** treatment is not known. If the ventricular function is preserved, patients are reassessed after 1 to 2 weeks for heart failure symptoms or arrhythmias [10]. However, those with an impaired left ventricular ejection fraction (less than 40%), Angiotensin-converting-enzyme inhibitors (ACEi) or Angiotensin Receptor Blocker (ARB) and possibly a β adrenergic blocker is to be given as per the AHA/ACC, Heart Failure Society of America (HFSA), and ESC guidelines for the management of stage B heart failure [10]. In the case of *probable acute myocarditis*, patients have a good response to standard heart failure treatment as well as avoidance of heavy activity for up to 6 months post infection or until ventricular recovery has been proven [10]. The use of immunosuppressive drugs is not recommended. In addition, there is not enough evidence to recommend use of IV immunoglobulin [10]. In the case of *chronic dilated cardiomyopathy*, immunosuppression with Azathioprine and prednisone showed improvement in ventricular function and quality of life. The use of antiviral therapy still requires further investigation [10]. As for mechanical circulatory support or extracorporeal membrane oxygenation, these can be used until transplantation or recovery from cardiogenic shock [10]. Survival after transplantation is the same as that of transplantation for other cardiac etiologies [10]. For *myopericarditis resembling an acute coronary syndrome, a*dministration of colchicine for around 3 months can help alleviate chest pain related to pericarditis [10]. nonsteroidal anti-inflammatory drug like indomethacin should be kept for patients with normal ventricular function [10]. In the case of *syncope from ventricular arrhythmias or heart block***,** routine management of ventricular arrhythmias due to myocarditis is recommended with hospital admission and ECG monitoring [10]. The use of implantable cardiac defibrillator has the same indications as in non-ischemic DCM but may in some cases be used earlier in giant cell myocarditis [10].

The evidence for the management of myocarditis in COVID-19 is scarce. The mainstay treatment of severe COVID-19 patients with cardiac involvement remains supportive care. General principles in the management include the avoidance of overaggressive hydration, and prevention of hypotension while targeting Mean Arterial Pressure MAP of 60-65 mmHg. Dobutamine can be considered in the setting of worsening hypotension with cardiac dysfunction, as well as epinephrine in refractory hypotension [37].

ECMO should be considered for patients with the greatest chance of recovery as well as those with refractory hypoxemia and respiratory acidosis despite advanced ventilation. Patients in cardiogenic shock can benefit from VA ECMO. However, more studies on needed on the topic to better delineate the role of ECMO in COVID-19 patients with myocarditis [37].

As for the evidence on anti-inflammatory and anti-viral therapies, a wide range of strategies has been used including but not limited to IVIG, tocilizumab, anakinra, and remdesivir/ritonavir. The data on the effect of the above drugs on cardiac outcome are mainly from case reports and more research is still needed to guide recommendations [37].

Data from our reports showed different management plans for the treated patients. Out of all the reports included in this study, 19 cases reported the management of the patients. Anti-viral therapy was initiated in 7 out of 19 cases, with lopinavir/ritonavir use mostly reported. Antibiotics were initiated in 6 cases. IVIG were used in 6 cases. In addition to that, 6 cases reported the use of Hydroxychloroquine, whereas 5 cases out of the 19 reported the use of colchicine. Steroids, mainly Intravenous methylprednisolone, was initiated in 9 cases. Tocilizumab, the drug that blocks the effect of interleukin 6 was administered in 2 cases.

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***Table 7:*** *Management of COVID-19 myocarditis patients per case report*

| | Antiviral | HCQ | Steroids | Antibiotic | Vasopressor/Inotrope | IVIG | Colchicine | ECMO | Tocilizumab |
|---|---|---|---|---|---|---|---|---|---|
| *Sala, Simone et al.* [8] | x | x | | | | | | | |
| *Inciardi, Riccardo M et al.* [11] | x | x | x | | | | | | |
| *Warchoł, Izabela, et al.* [13] | x | | | x | | | | | |
| *Hu, Hongde et al.* [14] | | | x | x | x | x | | | |
| *Doyen, Denis et al.* [16] | | | x | | | | | | |
| *Zeng, Jia-Hui et al.* [17] | x | | x | x | | x | | x | |
| *Coyle, Justin et al.* [18] | | x | x | x | x | | x | | x |
| *Irabien-Ortiz, Angela.* [21] | x | | x | | | x | | x | |
| *Beşler, Muhammed Said, and Halil Arslan* [23] | x | x | | x | | | x | | |
| *Hua, Alina et al.* [25] | | | | | x | | | | |
| *Khalid, Nauman et al.* [28] | | | x | | x | | x | x | |
| *Gill, Gauravpal S et al.* [29] | | | | | | | | x | |
| | | | x | | x | | x | x | |
| *Khatri, Akshay, and Frances Wallach* [30] | | x | | x | x | x | | x | |
| *Oberweis, Marie-Laure et al.* [31] | | | | | x | x | | | x |
| *Gnecchi, Massimiliano et al.* [32] | x | x | | | | | | | |
| *Pavon, Anna Giulia et al.* [33] | | | | | x | | | | |
| *Giacomet, Vania et al.* [34] | | | | | | x | | | |
| *Hussain, Hussain et al.* [35] | | | x | | x | | x | | |

Abbreviations: HCQ : Hydroxychloroquine

Vasopressors and inotropes were however used in 9 cases. 6 case reports placed their respective patients on ECMO (Table 7).

*Limitations*

This narrative review covers a breadth of literature regarding myocarditis in patients with COVID-19. It is however limited by its methodology as a narrative literature review which entails subjectivity in the way articles are selected and conclusions are drawn. However, within the limitations of the selection criteria and analysis conducted by the authors, we believe it brings valuable knowledge and insight regarding the clinical presentation, diagnosis and management of myocarditis in COVID-19. Further studies and systematic reviews are essential to reach conclusive evidence and establish policies regarding COVID-19 myocarditis.

## Conclusions

After reviewing 29 reported cases of COVID-19 myocarditis we conclude that its clinical presentation is variable with a predominance of fever, cough, dyspnea, and chest pain. Although the clinical classification requires an endomyocardial biopsy to confirm definite myocarditis, only one patient had undergone the histopathological evaluation as part of the diagnostic approach. The rest of the cases mostly relied on the Lake Louise Criteria. Therefore, cardiac magnetic resonance had an important role in the diagnosis of myocarditis. Other diagnostic modalities were also helpful in establishing a diagnosis. Electrocardiography was the most consistently reported modality and commonly showed ST-segment elevation which resulted in a suspicion of myocardial ischemia. Thus, conventional coronary angiography, or a coronary computed tomography angiography were often used to rule out coronary stenosis. On the other hand, serum biomarkers, when reported were found to be elevated, but this may be a bias in reporting. Echocardiography was also helpful, commonly showing wall motion abnormalities. As for the management, it was not consistent. Besides supportive management and the use of COVID-19 targeted antivirals, antibiotics, and anti-inflammatory treatments, several cases reported the use of IVIG and colchicine. This narrative review highlights our current understanding of myocarditis in COVID-19 patients and stresses on the necessity of establishing proper treatment guidelines for a better management of COVID-19 myocarditis.

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