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COVID myocarditis: a review of the literature

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Abstract

Myocarditis is a potentially fatal complication of coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. COVID-19 myocarditis appears to have distinct inflammatory characteristics that distinguish it from other viral etiologies. COVID-19 myocarditis can present with symptoms ranging from dyspnea and chest pain to acute heart failure and death. It is critical to detect any cases of myocarditis, especially fulminant myocarditis, which can be characterized by signs of heart failure and arrhythmias. Serial troponins, echocardiography, and electrocardiograms should

be performed as part of the initial workup for suspected myocarditis. The second step in detecting myocarditis is cardiac magnetic resonance imaging and endomyocardial biopsy. Treatment for COVID-19 myocarditis is still debatable; however, combining intravenous immunoglobulins and corticosteroids may be effective, especially in cases of fulminant myocarditis. Overall, more research is needed to determine the incidence of COVID-19 myocarditis, and the use of intravenous immunoglobulins and corticosteroids in combination requires large randomized controlled trials to determine efficacy. The purpose of this review is to summarize current evidence on the subject.

Key words: COVID-19; SARS-CoV-2; myocarditis.

Introduction

Coronavirus Infection Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was initially identified in Wuhan city in China in December 2019 and rapidly spread worldwide [1]. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic [2]. As of August 31, 2021, there have been over 200 million confirmed cases of COVID-19 worldwide with over 4.5 million deaths [3].

The range of clinical presentations includes the symptoms such as influenza syndrome (cough, fever, fatigue, shortness of breath, anosmia, ageusia, and pharyngodynia) that may worsen in acute respiratory failure and multi-organ failure. Cardiac involvement with acute myocardial injury is a possible clinical scenario. Previous studies have shown that high troponin levels are associated with increased mortality in patients with COVID-19. However, abnormal troponin levels are not necessarily a sign of acute myocarditis [4, 5]. The purpose of this review was to critically summarize the current evidence on COVID-19-related myocarditis and address the many challenges in the early diagnosis and management of myocarditis in patients with COVID-19 infection.

Pathophysiology of COVID-19 myocarditis

The spike (S) protein of SARS-CoV-2 is critical for its ability to bind to and enter host cells. The S protein has two subunits, S1 and S2: the former enables binding to host cells, and the latter performs the fusion process between the virus membranes and the host cell [6]. Angiotensin-

converting enzyme (ACE)-2 is the receptor to which the S protein binds [7]. Once binding has occurred, the SARS-CoV-2 virus is able to fuse its membrane with the host cell, allowing it to enter in it [8]. Membrane fusion is mediated by transmembrane serine protease type 2 (TMPRSS2), a cell surface protein that cleaves ACE-2 [9]. Entry into host cells is followed by viral replication and an immune response, causing tissue damage and clinical manifestations of COVID-19.

Myocarditis is described as inflammation of the heart muscle, leading to damage in the absence of ischemia [10,11]. It has been suggested that viruses are the primary contributors to myocarditis with a wide variety of causative agents included such as adenovirus, parvovirus B19, Epstein Barr virus, and cytomegalovirus [11-14]. To date, SARS-CoV-2 also represents significant infectious virus for myocarditis. The proposed pathophysiology of viral myocarditis is a combination of direct cell damage and immune-mediated cell death [10]. Early in the development of viral myocarditis, high rates of viral replication led to direct cardiomyocyte injury [15]. The damaged cells and the proteins they release (such as cardiac myosin), activate Toll-like receptors and inflammasomes, leading to the release of pro-inflammatory cytokines [16,17]. Over time, these pro-inflammatory cytokines recruit immune cells, including natural killer cells, macrophages and T lymphocytes, to the myocardium. These cells are involved in immune-mediated myocyte damage [15]. In addition, interleukin (IL)-1 β and IL-17 cause cardiac remodeling and fibrosis, which eventually lead to dilated cardiomyopathy and heart failure [18,19]. Myocardial fibrosis leads to disruption of the conduction system, resulting in an increased risk of developing arrhythmias [20].

As mentioned earlier, SARS-CoV-2 enters human cells by binding to the ACE2 protein. While ACE2 protein is expressed on epithelial cells (type II alveolar cells) of the respiratory tract, leading to the respiratory manifestations of COVID-19, these proteins can also be found on cardiomyocytes [21-23]. A case study, using endomyocardial biopsy (EMB), revealed the presence of SARS-CoV-2 viral particles in the myocardium of a patient with COVID-19 [24]. Moreover, an alternative way in which SARS-CoV-2 can cause myocardial damage is through infection of endothelial cells in the heart [25-27]. This theory is supported by the discovery of SARS-CoV-2 in the endothelial cells of several organs, including the heart, in histological samples [28,29].

In addition, some authors have found more CD68+ cells distributed diffusely in the hearts of patients with COVID-19, compared with those with typical myocarditis and control groups [27]. Fox et al. hypothesized that the difference in immune cells on histology suggests that

COVID-19 myocarditis is a distinct inflammatory process separate from typical viral myocarditis [29].

Therefore, two theories describing the inflammatory process have been proposed. First, SARS-CoV-2 may infect endothelial cells within coronary vessels, leading to the migration of macrophages into these areas, causing complement activation and apoptosis [30]. Second, inflammation can lead to thrombus formation in coronary vessels resulting in ischemic myocardial damage [31].

Therefore, systemic inflammation may also play a role in the development of COVID-19 myocarditis. IL-6 is a cytokine implicated in the pathophysiology of myocarditis, which recruits inflammatory cells to the myocardium [30]. IL-6 is also a primary mediator of cytokine storm, a life-threatening condition observed in some patients who developed COVID-19, which is characterized by extreme increases in pro-inflammatory cytokines and an uncontrolled immune response [31-33]. This systemic inflammation may further increase the risk of thrombus formation within coronary vessels due to platelet activation and high levels of coagulation factors (including factors V and VIII) [26,33]. It is also possible that the cytokine storm may lead to exacerbation of established myocarditis and further myocardial damage [25].

In addition, myocardial damage may be exacerbated by myocardial hypoxia due to increased oxygen demand in the context of infection, which cannot be met due to the presence of pneumonia or acute respiratory distress syndrome [32] (Figure 1).

Epidemiology of COVID-19 myocarditis

The incidence of COVID-19-induced myocarditis is unclear. One study revealed that about 28% of patients with COVID-19 had myocardial injury, diagnosed by the presence of elevated troponin T [34]. A meta-analysis, however, found that 8% of patients with COVID-19 developed myocardial injury, with a 13-fold increase in prevalence among ICU patients [35]. Halushka et al. found 7.2% of 277 post-mortem cases showing evidence of myocarditis, with only less than 2% of cases demonstrating clinically significant myocarditis [36]. This study reveals that the true incidence of COVID-19 myocarditis may be underestimated, as some patients may be asymptomatic or have minor symptoms. Puntman et al. studied 100 patients who had recently recovered from severe COVID-19 and found that 78% showed cardiac involvement on cardiac magnetic resonance imaging (cMRI), with 60% having ongoing

inflammation [37]. The various published studies show that myocardial involvement increases mortality in patients hospitalized with COVID-19 [38].

Ruan et al. showed that among the 68 deaths of patients with COVID-19, 7% were attributable to fulminant myocarditis leading to circulatory failure, while 33% died from a combination of respiratory and cardiac failure [39]. In the latter study cited above, the diagnosis of fulminant myocarditis was made on the basis of evaluation of the clinical data available to the authors, not on immunohistology analysis. This may affect the reliability of these findings due to an increased risk of misdiagnosis.

A systematic review and case series showed that patients with cardiovascular comorbidities were at higher risk of developing COVID-19 myocarditis [40,41]. The exact mechanism by which this occurs is not entirely clear. In addition, black, Asian and ethnic minority (BAME) individuals may be more severely affected by COVID-19-induced myocarditis due to a higher prevalence of cardiovascular disease among these groups [42-48]. However, other evidence suggests that those of African descent express lower levels of ACE2, particularly those with pre-hypertension [49]. The evidence is conflicting, so the association between race and risk of developing COVID-19 myocarditis requires further research.

An important group to pay attention to, however, is those involved in competitive sports since myocarditis is associated with sudden cardiac death in athletes [50]. Daniels et al. evaluated 1597 athletes for the presence of COVID-19-induced myocarditis. Of these athletes, 37 (2.3%) were diagnosed with COVID-19 myocarditis, 28 of whom were classified as having possible myocarditis [51]. In the case that cardiac tests had been performed only on those patients with symptoms of cardiac origin, only five cases of COVID-19 myocarditis would have been recorded. Again, this highlights the possibility that the cardiac involvement of COVID-19 is underestimated due to asymptomatic patients. In another study of 26 competitive athletes undergoing cMRI, 15% were diagnosed with myocarditis, while 31% showed evidence of previous myocardial damage [52]. Athletes who have recovered from COVID-19 and are returning to sport should undergo cardiac testing, including cMRI, to screen for any active myocarditis or previous cardiac injury.

Overall, the exact incidence of COVID-19 myocarditis is still unclear; however, current literature suggests that those with severe infection run a higher risk of developing myocarditis than those who develop mild infection [45-52].

In addition, myocarditis may worsen the prognosis for patients who have developed COVID-19 infection, and patients who develop COVID-19 myocarditis may suffer from long-term cardiovascular complications, which will need to be studied over time (Table 1).

The primary COVID-19 variants were described by the World Health Organization as variants of interest (Table 2). The Alpha variant led to more hospitalization and death than the original SARS-CoV-2 virus, while the Delta variant cause more severe disease in individuals who were not vaccinated [53]. A new variant, the Omicron one arrived around November 2021 and demonstrate high infectivity and the highest hospital admission frequency, but severe illness was lower than Delta and Alpha variants. Moreover, Delta variant seems more affective to induce myocarditis than Omicron [54-56]. A study evaluates 44 patients recovering from the Delta variant versus 25 controls and found 20% of patients with evidence of myocarditis at cMRI, especially in young men (16-30 years). The prevalence of women was 64% [57]. In conclusion, myocarditis remains a complication of COVID-19 for all variants [58].

Presentation of COVID-19 myocarditis

The classic presentation of myocarditis is similar to heart failure, with symptoms of dyspnea, orthopnea, and chest pain likely to be present [59]. However, the clinical presentations of patients with COVID-19 myocarditis may vary from patient to patient. Some patients have relatively mild presentations such as cough, fever and dyspnea [20,59-61]. These symptoms may be due to COVID-19 itself and not myocarditis. Therefore, some patients may have a silent presentation of COVID-19 myocarditis [20]. Others may present with chest pain that may or may not be described as pressure without the concomitant presence of cough or dyspnea or palpitations [62].

In more severe cases, patients may initially present with new-onset heart failure in the absence of a history of cardiovascular disease [63].

After the initial presentation of symptoms, if treatment is not initiated or is inadequate, the clinical situation may worsen to the point of developing signs of heart failure and hemodynamic compromise [61]. This is the classic presentation of fulminant myocarditis, a condition characterized by sudden and severe cardiac inflammation, which can lead to arrhythmias, severe heart failure, or death [64,65].

Diagnosis of COVID-19 myocarditis

C-reactive protein (CRP), lactic dehydrogenase (LDH) and white blood cell count (WBC) have been shown to be increased in patients with COVID-19 myocarditis but, are not specific for myocarditis [62-64]. The presence, on the other hand, of elevated Troponins (TnT or TnI) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) values should raise suspicion for COVID-19 myocarditis [41,65]. Therefore, baseline TnT /TnI and NT-pro-BNP levels should be measured at the time of admission of a patient with COVID-19, allowing assessment of rapid changes in values during hospitalization that are associated with increased risk of mortality [26]. However, some patients with COVID-19 myocarditis may not have an elevated troponin, meaning that a normal TnT or TnI does not exclude myocarditis [20,66]. Regarding electrocardiogram (ECG) changes can also be observed in patients who develop myocarditis. Most of the changes are nonspecific and may include ST supra/subleveling, T-wave inversion, tachycardia/bradyarrhythmia, and QT interval prolongation [41,64]. Therefore, ECG changes are not diagnostic of myocarditis, but may be useful as a tool to assess possible myocardial damage or the presence of arrhythmias, indicating the severity of the disease.

Echocardiography also is diriment in placing the suspicion of myocarditis through evaluation of ejection fraction, presence of pericardial effusion, and cardiac kinetics [65-67]. Therefore, cardiac magnetic resonance (cMRI) has a high sensitivity for the diagnosis of myocarditis and is therefore the best noninvasive test through the Lake Louis criteria [68-70]. This criterion uses a combination of T2-weighted imaging, early gadolinium enhancement, and late gadolinium enhancement to detect myocardial edema, hyperemia, and myocardial necrosis and fibrosis, respectively [64,71-73]. However, the gold standard for the diagnosis of myocarditis remains endomyocardial biopsy (EMB). Biopsy specimens can confirm the diagnosis of COVID-19-induced myocarditis through the presence of SARS-CoV-2 RNA [74]. EMB specimens were previously interpreted using the Dallas criteria that described myocarditis as myocyte necrosis or damage associated with inflammatory infiltrates [75]. The reliability of the Dallas criteria is questionable as it has been shown not to apply to 50% of virus-positive cases. Therefore, an immunohistochemical criterion was added to the Dallas criteria to make it more reliable. This criterion defines myocarditis as the presence of leukocytes $\geq 14/\text{mm}^2$ with monocytes $\leq 4/\text{mm}^2$ and CD3+ cells $\geq 7/\text{mm}^2$ alongside evidence of nonischemic necrosis on histologic examination [27]. Use of these criteria may increase the sensitivity of cMRI in the diagnosis of COVID-19 myocarditis.

As concern sex difference, myocarditis pre-COVID-19 occur more often in young men under the age of 50 years, with a sex ratio of 2 to 4:1 men to women, while women are more likely

to develop myocarditis after menopause, which is reviewed in previous studies [76,77]. This sex difference remains unchanged as clinical myocarditis caused by COVID-19. Several studies. In fact, demonstrated an equal distribution of cytokines in COVID-19 myocarditis or in that caused by other viruses [78-80]. Figure 2 summarizes the process for diagnosis of COVID-19 myocarditis.

COVID-19 vaccine-associated myocarditis

The mRNA vaccines against COVID-19 contain modified mRNA (not live or heat-inactivated virus) that encodes the viral spike glycoprotein of SARS-CoV-2 encapsulated by lipid nanoparticles [81]. Not long after COVID-19 vaccination, myocarditis have been described as a complication of vaccination. Subsequently, several studies have been conducted and showed the incidence of myocarditis depending on the vaccine type and how many doses were administered, with the highest levels reported for the Moderna mRNA vaccine, with an overall incidence of $\approx 10/100\ 000$ and around $50/100\ 000$ in men under 40 years of age. However, myocarditis vaccine-related remains a rare adverse complication (0.38 cases/100 000 individuals for COVID-19 vaccines in the United States compared with 1000 to 4000 cases/100 000 individuals for COVID-19) [82-84].

These studies agree that the greatest risk of developing myocarditis occurs after the second vaccine dose in young men aged 12 to 39 years. Ages past 50 years had few reports of vaccine-associated myocarditis, similar to pre- and COVID-19-associated myocarditis. Moreover, most cases of myocarditis associated with vaccines have been reported to be mild and of short duration. For these reasons, most of the myocarditis vaccine cases were diagnosed without the use of cMRI or EMB [85,86]. Nowadays, a number of mechanisms have been hypothesized for myocarditis related to mRNA vaccines. First of all, mRNA vaccines could cause an innate immune response directed against the spike protein of SARS-CoV-2 [82-87].

Thurner *et al.* found that patients with biopsy-confirmed myocarditis following COVID-19 vaccination had elevated levels of antibodies directed against IL-1RA, which is part of the TLR4/IL-1R signaling family. The TLR4/IL-1R signaling pathway that produces IL-1 β is upregulated on mast cells and macrophages in males and is key in initiating myocarditis [85]. Furthermore, both the mRNA against the SARS-CoV-2 spike protein and the lipid nanoparticle vehicle could provide the adjuvant effect needed to promote myocarditis following COVID-19 vaccination [85-88].

As regards COVID-19 vaccines, the importance of getting vaccinated remains fundamental because even if myocarditis can be a possible complication, its incidence is relatively lower than the possibility of both myocarditis and all other COVID-19 related complications.

Moreover, vaccination reduced the risk of infection associated myocarditis by approximately half, suggesting that the prevention of infection associated myocarditis may be an additional longer-term benefit of vaccination.

Treatment of COVID-19 myocarditis

Treatment of myocarditis involves the management of both myocardial inflammation and the complications that may result. Intravenous immunoglobulins (IVIGs) have been studied for their efficacy in the treatment of viral myocarditis. IgG, IgA, and IgM immunoglobulins have anti-inflammatory effects; in addition, they neutralize and facilitate pathogen clearance from the myocardium [76]. It is known that immunoglobulin therapy for cytomegalovirus myocarditis demonstrated by biopsy showed favorable outcomes with a reduction in inflammatory and viral levels [89]. However, in cases of suspected myocarditis without biopsy evidence of viral infection, the use of immunoglobulin therapy has shown inconsistent results [75]. Hu et al. used a combination of glucocorticoid and immunoglobulin treatment to successfully treat COVID-19 myocarditis [76]. A meta-analysis revealed that the use of IVIG to treat acute myocarditis significantly reduced mortality by improving left ventricular ejection fraction [77]. Furthermore, the effect of IVIG was even more pronounced in patients with fulminant myocarditis where it was shown to significantly increase survival rates of this life-threatening condition [77].

Corticosteroid use, on the other hand, especially prednisolone and dexamethasone, may be effective in treating viral myocarditis in the absence of viral replication [90]. It is believed that the use of immunocompromising drugs, such as corticosteroids, may worsen acute myocarditis in the presence of viral replication [91].

On the other hand, other studies show that the use of corticosteroid therapy does not reduce mortality in patients with viral myocarditis [92]. Tocilizumab, which is an anti IL-6-receptor monoclonal antibody, was tested with the combination of the anti-viral, favipiravir, for the treatment of COVID-19 patients who had developed a cytokine storm [93]. The study found that the combination of Tocilizumab and favipiravir significantly reduced the inflammation caused by the cytokine storm [27,93,94]. Because COVID-19 myocarditis can be exacerbated

by the cytokine storm, the use of this combination therapy may provide positive results [26]. Treatment of myocarditis in stable patients should be based on standard pathways unrelated to COVID-19. Use of intravenous corticosteroids and IVIG may be considered in those with suspected or confirmed COVID-19 myocarditis with hemodynamic compromise or a hyper-inflammatory state with acute heart failure and/or cardiogenic shock in the absence of sepsis, as this approach was associated with a favorable prognosis in a small series. In the presence of myocarditis with systolic dysfunction, heart failure therapy should be initiated (especially beta-blocker along with a renin-angiotensin- aldosterone system inhibitor) prior to discharge and close follow-up should be offered [92-95]. For patients in whom myocarditis initiates as cardiogenic shock, the inotropic agents, such as dobutamine, and mechanical support should be used to maintain cardiac output [65,69]. The presence of tachyarrhythmias can be, instead, treated with intravenous amiodarone or by external electrical cardioversion [94]. Finally, bradyarrhythmia that may occur can be treated with intravenous atropine or, if necessary, pacing [94].

As concern athletes recovering from COVID-19 myocarditis, for asymptomatic ones with COVID-19 infection, 3 days of abstinence from training is recommended to ensure that symptoms do not develop. As opposite, for which with cardiopulmonary symptoms, intense exercise training should be limited until symptoms resolve, and a graded return-to-exercise program equates to more qualitative gradual increases in effort and often recovery from myocarditis assessed through a cMRI and a triad testing [95].

Conclusions

COVID-19 myocarditis is a significant complication of SARS-CoV-2 infection that can worsen the prognosis for patients. Although some cases may be insignificant or asymptomatic, physicians are likely to encounter more severe cases that require prompt treatment. Therefore, it is imperative to recognize how to diagnose and treat this condition. If possible, it is a good idea to perform serial troponins, echocardiography, and ECG to monitor any development of myocarditis or other myocardial injury. Because the symptoms of myocarditis may be nonspecific and may overlap with the respiratory symptoms of COVID-19, it may be difficult to diagnose this condition at first. Several gaps need further investigation. First of all, myocarditis occurs primarily in young men under the age of 50 years regardless of cause, data

on myocarditis including autopsy studies should be reported according to sex, age, and race. Currently, there is no standard method of reporting cases and incidence. Secondly, the risk of hospital admission or death from myocarditis is greater after COVID-19 infection than COVID-19 vaccination. However, the risk of myocarditis after vaccination is higher in younger men, particularly after a second dose of the mRNA vaccine. Nowadays, the exact mechanism myocarditis following COVID-19 vaccination requires further investigations. In conclusion, special attention should be paid to any signs of heart failure or arrhythmias, as these could be signs of fulminant myocarditis. Although no definitive treatment for COVID-19 myocarditis has been published, the combination of IVIG and corticosteroids promises to reduce mortality, particularly in the case of fulminant myocarditis.

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Table 1. Epidemiology of COVID-19 myocarditis

Study	Country	Data of myocarditis (%)
Halushka et al. [36]	USA	7.2% (2% clinically significant)
Puntmann et al. [37]	Germany	78% cardiac involvement 60% ongoing inflammation
Ruan et al. [39]	China	7%
Laganà et al. [40]	Italy	1%
Daniels et al. [51]	USA	2.3%
Rajpal et al. [52]	USA	15%

Table 2. SARS-CoV-2 variants.

Strain	Month and year emerged
Alpha (B.1.1.7)	September 2020
Beta (B.1.351)	May 2020
Gamma (P.1)	November 2020
Epsilon (B.1.429)	July 2020
Lota (B.1.526.1)	November 2020
Delta (B.1.617.2)	October 2020
Omicron (B.1.1.529)	November 2021
Omicron (XBB.1.5)	November 2022

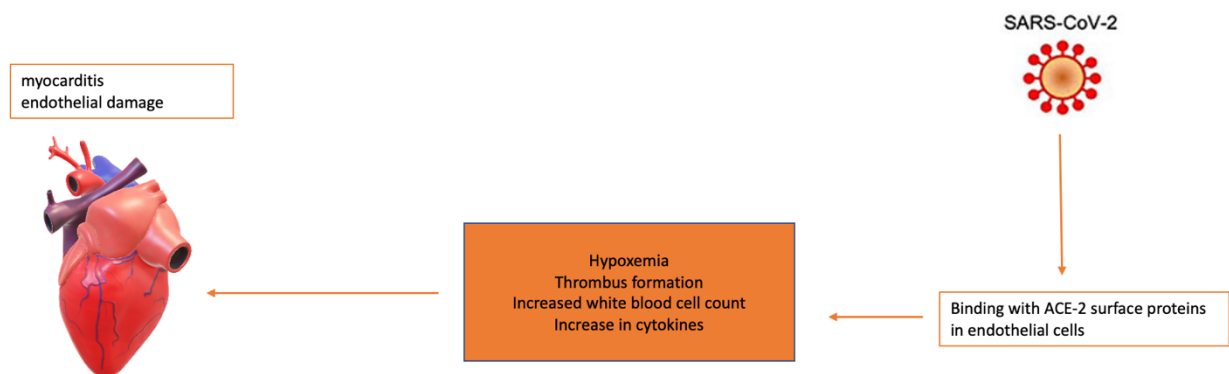


Figure 1. Pathophysiology of COVID-19 infection. The virus spike protein (S) binds to the ACE-2 surface proteins present in endothelial cells and also in myocytes. Once binding has occurred, the virus penetrates the host cell where it activates viral replication resulting in an immune response: increased white blood cell (WBC) and cytokines. The inflammatory mechanism that is generated, together with the presence of the virus inside the cells is responsible for endothelial damage and myocyte damage resulting in myocarditis and/or thrombosis.

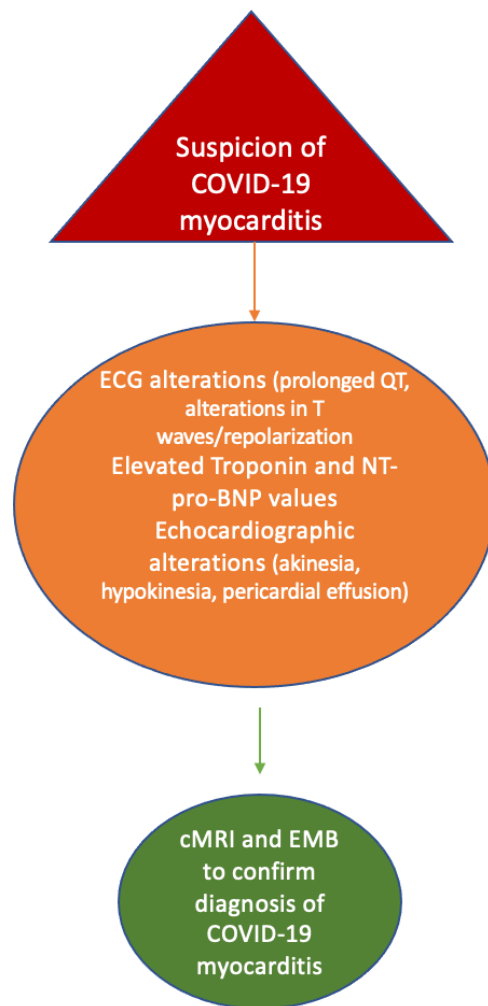


Figure 2. Diagnosis of COVID-19 myocarditis. If COVID-19 myocarditis is suspected, it is necessary to evaluate the ECG graphic alterations, the troponins and NT-pro-BNP values and the presence of echocardiographic alterations. If all mentioned above are altered, we perform a second level investigation, the cMRI. Finally, in diagnostic confirmation of myocarditis by cMRI, an EMB should be performed.