

Review

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Review

Myocarditis and Pericarditis Following the SARS-CoV-2 Infection and COVID-19 Vaccination

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Abstract: Cardiac complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been well-identified since the beginning of the current coronavirus disease 2019 (COVID-19) pandemic. Such conditions can occur of various etiologies, such as respiratory failure and hypoxemia, direct cardiac tissue damage due to viral replication, indirect myocarditis as systemic inflammation, and the interaction of different medications. Recently, with the start of the COVID-19 vaccination programs, COVID-19 vaccine-associated cardiac adverse events (AEs) have emerged and are increasingly being reported. Although these AEs are usually mild and self-limited, they can sometimes cause severe, catastrophic outcomes. This review compares the pathophysiology, diagnosis, and treatment of the de novo SARS-CoV-2 infection-related and COVID-19 vaccine-related myocarditis and pericarditis.

Keywords: SARS-CoV-2; COVID-19; Vaccines; Myocarditis; Pericarditis

1. Introduction

Early studies on coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection reported cardiac involvement in nearly 30% of the patients [1]. Later studies have shown that the rate of cardiac involvement in COVID-19 patients is higher than previously thought. A multinational study on unselected COVID-19 patients demonstrated that 55% had an abnormality in echocardiographic examination [2]. Another study showed that 78% of unselected COVID-19 patients had cardiac involvement in cardiac magnetic resonance imaging (CMR) [3]. Some studies have also investigated the incidence of cardiac manifestations in COVID-19 patients. It was shown that heart failure, myocardial injury, and arrhythmia were the most common cardiac complications of COVID-19 patients [4]. Another study on COVID-19 patients reported that myocardial injury, arrhythmia, heart failure, and acute coronary syndrome are, respectively most common cardiac complications, and myocardial injury and heart failure are the most frequent cardiovascular complications in non-survivors and are significantly higher in non-survivors than survivors [5].

Cardiac injury can be a result of various etiologies, such as respiratory failure and hypoxemia, direct cardiac tissue damage due to viral replication, indirect myocarditis as of systemic inflammation, and the interaction of medications, of which a well-known example could be the interaction of hydroxychloroquine and azithromycin, both abundantly used at the beginning of the pandemic. Recently, with the start of the anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination program, vaccine-associated cardiac events have emerged and are increasingly being reported. Here, we discuss de novo SARS-CoV-2 infection-related and vaccine-related cardiac injuries.

2. Myocarditis

2.1. COVID-related myocarditis

Covid-19 manifestations can vary, ranging from asymptomatic to life-threatening conditions. A case series study of 187 patients demonstrated that myocardial injury, indicated by elevated troponin T levels, is significantly associated with disease severity and fatal outcome in COVID-19 patients [6]. Although the risk of myocarditis in patients infected with COVID-19 was 11 times higher than in the general population [7], the prevalence of myocarditis following COVID-19 is rare, and several studies have reported different rates varying from 0.005% to 5% [8,9]. However, it was speculated that the number of cases of myocarditis related to the COVID-19 infection is underestimated due to the lack of enough imaging studies on COVID-19 patients [10] and because almost of myocarditis-associated COVID-19 cases are mild and presented with typical COVID-19 presentation without specific manifestations related to the myocarditis [11].

Recently, SARS-CoV-2 infection has been a leading cause of myocarditis, resulting in growing numbers of acute cardiac injury cases worldwide. The pathophysiologic mechanism of myocarditis in the context of COVID-19 can result from either direct viral invasion of cardiomyocytes or indirect heart tissue damage as a result of cytokine storm, microvascular disease, hypoxia-induced excessive intracellular calcium leading to cardiac myocyte apoptosis, or angiotensin-converting enzyme 2 (ACE2)-mediated loss of protective cardiovascular effects on target organs [12,13], all leading to increased vascular permeability and the resultant myocardial edema (Figures 1 and 2).

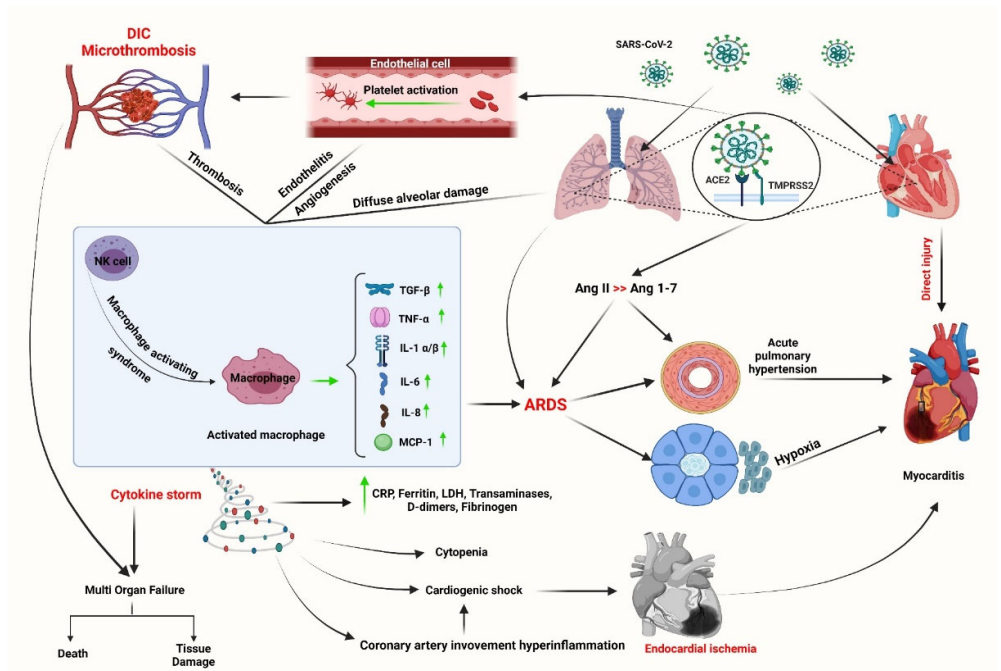


Figure 1. Summary of the possible mechanisms of SARS-CoV-2 infection-related myocarditis.

After entering the body, the virus can exert its cardiotoxic effects via several different pathways. It can directly damage the heart after entering via the ACE2 receptors expressed on heart cells, or it can go to the lungs and act on the alveoli through the ACE2 receptors, causing an overgrowth of Ang II compared to Ang 1-7, increasing the risk of ARDS. When the virus spreads through the arteries, it activates platelets, causing DIC and microthrombosis, eventually leading to multiple organ failure. The SARS-CoV-2 virus also activates macrophages and increases cytokines, such as TGF- β , TNF- α , IL-1 α/β , IL-6, IL-8, and MCP-1, by triggering diffuse alveolar damage, angiogenesis, endotheliitis, and thrombosis through NK cells, initiating cytokine storm and multi-organ failure, cytopenia, coronary artery involvement hyper-inflammation and increasing CRP, ferritin, LDH, transaminases, D-dimers, and fibrinogen levels. Coronary artery involvement could cause hyperinflation, cardiogenic shock, endocardial ischemia, and myocarditis. Elevated cytokine levels and the ACE2 receptor involvement with the SARS-CoV-2 virus cause ARDS, leading to acute pulmonary hypertension and hypoxia, eventually causing myocarditis. **Abbreviations:** ACE2, Angiotensin-converting enzyme 2; Ang II, Angiotensin II; Ang 1-7, Angiotensin 1-7; ARDS, Acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; TGF- β , Transforming growth factor β ; TNF- α , Tumor necrosis factor α ; IL-1 α/β , Interleukin 1 α/β ; IL-8, Interleukin 8; MCP-1, Monocyte chemoattractant protein 1; NK cell, Natural killer cell; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

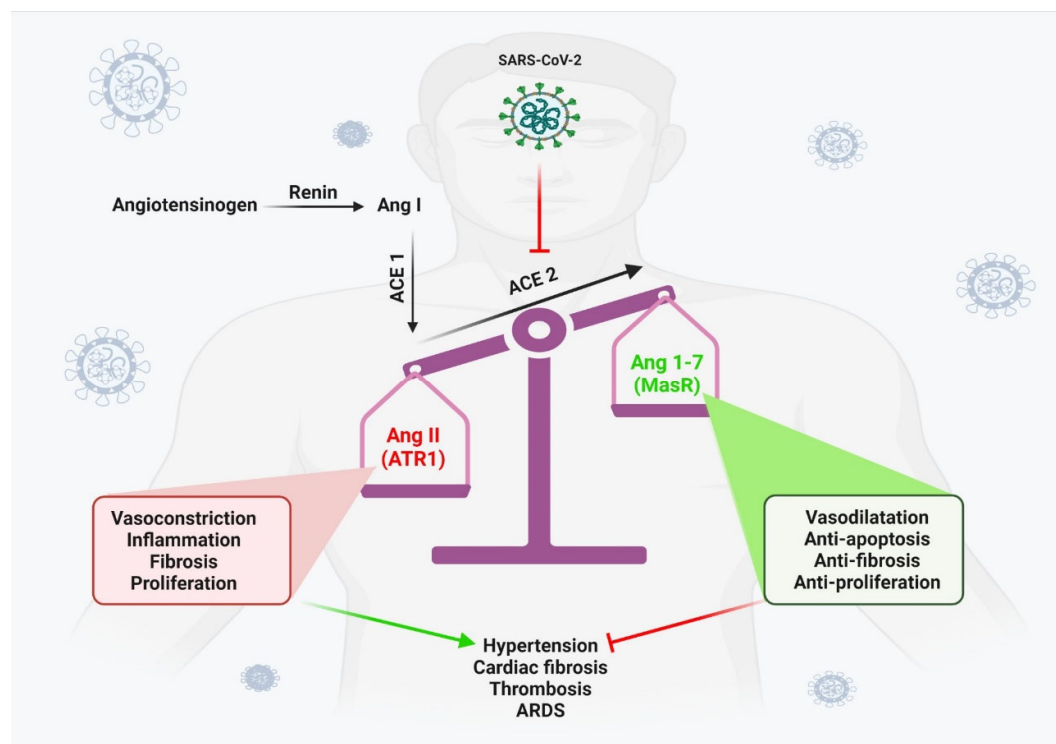


Figure 2. Effect of SARS-CoV-2 on the renin-angiotensin system (RAS). During the RAS pathways, the enzyme renin actively converts angiotensinogen to Ang I, which produces Ang II under the influence of ACE1. Then, ACE2 breaks down Ang II, a pro-inflammatory agent, to Ang 1-7. Meanwhile, SARS-CoV-2 infection disrupts the balance between Ang II and Ang 1-7 by altering the ACE2 function, resulting in increased levels of Ang II and enhancing the risk of hypertension, cardiac fibrosis, thrombosis, and ARDS. **Abbreviations:** Ang I, Angiotensin I; Ang II, Angiotensin II; ACE1, Angiotensin-converting enzyme 1; ACE2, Angiotensin-converting enzyme 2; Ang 1-7, Angiotensin 1-7; ARDS, Acute respiratory distress syndrome.

Like any other complications, myocarditis can occur alongside or following other typical COVID-19 manifestations [14,15] or may represent the infection's presenting or sole manifestations without fever, cough, or other respiratory involvements [16,17]. Moreover, it can appear as a

Kawasaki-like disease in SARS-CoV-2-infected pediatric patients, known as the multisystem inflammatory syndrome in children (MIS-C). A multisystem inflammatory syndrome is a rare and severe clinical condition linked to COVID-19 that can appear in children (MIS-C) and adults (MIS-A). MIS-C can present with cardiac manifestations and other organ involvements, leading to recurrent hospitalization [18].

Fever and enhancement of the level of inflammatory markers are an example of common features of MIS-C and myocarditis. The similarities between myocarditis and MIS-C induced by COVID-19 proposed the common underlying mechanism. However, some differences were observed between myocarditis and MIS-C. In this regard, myocarditis and MIS-C are developed in two different age groups, whereas MIS-C is present in older children, and myocarditis is related in adult patients. Besides, myocarditis is an acute presentation of COVID-19 that can emerge simultaneously or shortly after the appearance of COVID-19, but MIS-C is a present lately when the IgG test was positive for SARS-CoV-2 [19,20].

Myocarditis related to COVID-19 can present either indolently or sub-clinically such that it is only detected at autopsy or in a fulminant manner with significant life-threatening arrhythmias and hemodynamic instability [21,22]. However, most COVID-19-related myocarditis cases are mild and present with mild non-specific manifestations like chest pain, fatigue, and dyspnea, which is similar between COVID-19 patients with and without myocarditis [23]. Early studies have reported myocarditis only in hospitalized COVID-19 patients, but further studies have shown that myocarditis can be present even in post-covid athletes, whereas myocarditis and CMR abnormality was significantly lower in athletes than non-athletes [24].

Takotsubo (stress) cardiomyopathy (TTC) has been a prevalent cardiac manifestation of various infections, including COVID-19, defined as a regional wall motion abnormality presenting with transient apical ballooning in the setting of emotional or physical stressors, leading to various arrhythmias. Presentations of myocarditis vary from mild symptoms, such as palpitation, fever, chest pain, and weakness, to more severe manifestations, such as cardiogenic shock or significant arrhythmias, leading to sudden cardiac death.

It was demonstrated that tachycardia, dyspnea, shock, and fever are the most frequent clinical manifestations of myocarditis associated with COVID-19 and were estimated to be present in 76%, 74%, 53%, and 37% of patients, respectively [25]. Additionally, although comorbidities do not accompany most myocarditis-associated COVID-19 patients, hypertension (41%) and diabetes (17%) are the most commonly reported comorbidities [25].

Myocarditis is suspected in any patient presenting with compatible symptoms, including acute chest pain, new-onset or worsening at rest or exercise dyspnea, unexplained fatigue, palpitation, arrhythmias, syncope, and cardiogenic shock. It could be confirmed by an electrocardiographic, laboratory, imaging, and histopathologic finding [26,27]. Diagnostic criteria for detecting COVID-19-related myocarditis do not differ from myocarditis of other etiologies. However, a de novo severe SARS-CoV-2 infection can cause chest pain, dyspnea of exertion, or increased NT-proBNP and troponin levels due to supply-demand mismatch, even without actual cardiac damage. Thus, the distinction between these conditions is vital [28,29]. The cardiac damage of myocarditis in COVID-19 patients can be detected by ECG or troponin elevation. It is important to note that the absence of cardiac troponin elevation does not rule out myocarditis, and diagnosis of myocarditis can be confirmed by echocardiography, CMR, cardiac catheterization, and endomyocardial biopsy (EMB), respectively [25]. It is important to note that the American Heart Association (AHA) recommends using at least one imaging modality, like CMR and echocardiography, to confirm the diagnosis of myocarditis-associated COVID-19 [30]. Although CMR provides more high-quality images than echocardiography and is the paramount non-invasive diagnostic tool (31), it has some limitations and makes it unavailable for all COVID-19 patients. However, cardiac CT and ECG can be considered in the absence of CMR and as a suitable alternative to the CMR [23]. Therefore, it can conclude that although CMR imaging is the imaging modality of choice for the diagnosis of myocarditis, primarily when an EMB cannot be performed, and EMB is the decisive diagnostic tool [23], we should choose the safest diagnostic tool firstly in the work-up of covid-related myocarditis. Nevertheless, the

diagnosis of some of the reported cases of myocarditis has been based on clinical, laboratory, and electrocardiography findings due to the unavailability of echocardiography and CMR in some institutions.

Positron-emission tomography (PET) scan is another useful imaging modality in diagnosing active inflammatory states, such as myocarditis, via assessing the amount of glucose uptake. It was recognized that PET/CT is associated with some advantages compared to CMR and can provide a quantity of inflammation. Therefore, PET/CT is indicated for intensive observation of disease progression and response to treatment [31]. There was any study that assessed the sensitivity and specificity of PET scan for myocarditis following COVID-19 infection, but previous studies have shown that PET/CT scan has a 74% and 97% sensitivity and specificity, respectively [32]. Eighty-seven percent accuracy was attributed to the PET/CT versus CMR, which revealed that PET/CT is a practical choice when the CMR is unavailable or cannot be performed [32]. Moreover, PET/CT scan is helpful in myocarditis patients when the diagnosis is suspected, and the accuracy of CMR is insufficient.

A clinical study proved that 18F-2-fluoro-2-deoxy-D-glucose PET/CT scan (FDG-PET/CT) might help enhance the specificity and sensitivity of the myocarditis diagnosis and reduce the requirement of EMB, providing supplementary data for classification post-discharge risk. This illuminates that using FDG-PET/CT with or without CMR can significantly increase the accuracy of the diagnosis of myocarditis [33]. Besides, combining CMR and PET/CT scans and using contemporary PET/CT-CMR imaging is associated with complementary value and provides a more accurate diagnostic tool [34] (Figure 3).

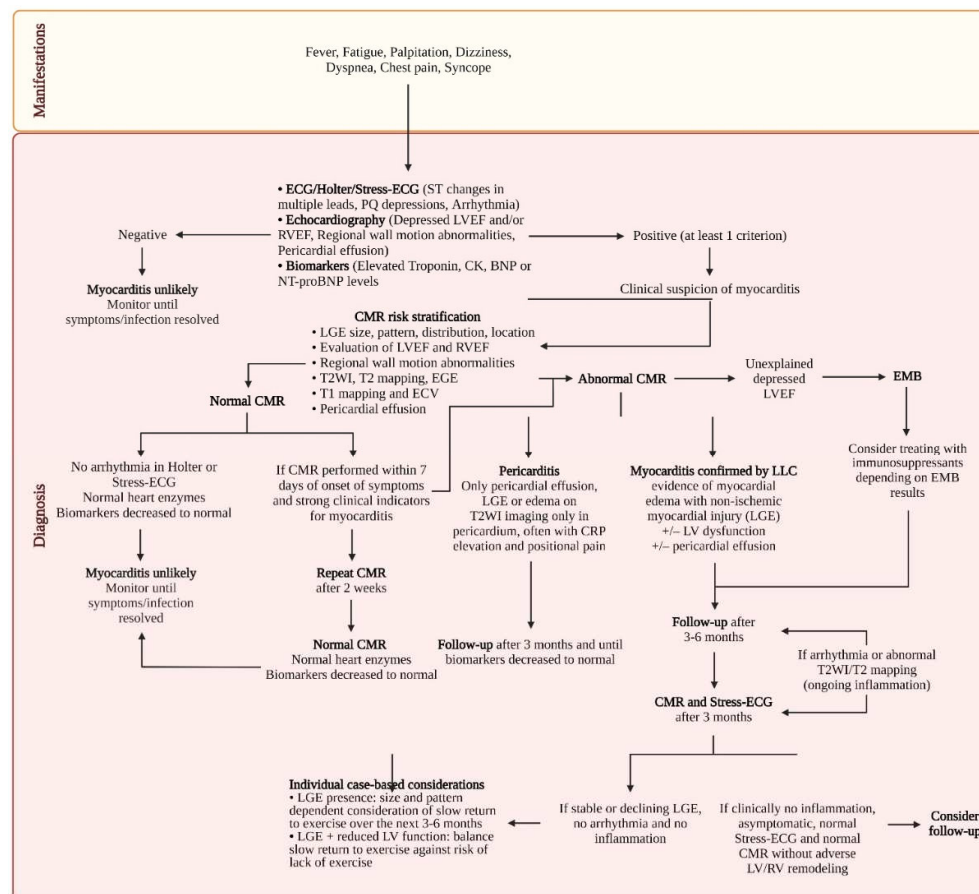


Figure 3. Myocarditis algorithm. Algorithm for manifestations and diagnosis of myocarditis due to SARS-CoV-2 infection or COVID-19 vaccination. **Abbreviations:** ECG, electrocardiogram; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; CK, Creatine kinase; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; T2WI, T2-weighted; EGE, early gadolinium

enhancement; ECV, extracellular volume fraction; EMB, endomyocardial biopsy; CRP, C-reactive protein; LLC, Lake Louise criteria; LV, left ventricular; RV, right ventricular. Adapted from “Myocarditis in Athletes Is a Challenge: Diagnosis, Risk Stratification, and Uncertainties,” by Eichhorn, C., Bière, L., Schnell, F., Schmied, C., Wilhelm, M., Kwong, R. Y., & Gräni, C., 2020, JACC. Cardiovascular imaging, 13(2 pt 1), p. 494–507. Copyright [2021] by Elsevier. Adapted with permission.

Currently, the revised 2018 Lake Louise criteria (LLC) are used for myocarditis confirmation (Table 1) [35,36]. Nonetheless, CMR is not recommended in unstable patients with severe heart failure, cardiogenic shock, or high-grade AV block, and a PET scan can be performed instead, as it takes only seconds rather than hours to scan the patient. Thus, an EMB should be obtained in these patients by taking precautionary measures to avoid getting infected. However, EMB findings cannot differentiate between SARS-CoV-2-associated myocarditis, and other causes since interstitial mononuclear inflammatory infiltrate accompanied by myocyte degeneration and nonischemic necrosis are the prominent findings in the histopathological assessment, rather than evidence of direct myocardial viral invasion [37,38]. Additionally, studies denoted that CMR is central in diagnosing most myocarditis patients, and EMB is conducted in a small proportion of studies [39]. Therefore, despite the need for a positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test result for COVID-19 proof, other virological tests should also be performed to exclude other etiologies since COVID-19 per se is not a cardiotropic virus and other cardiotropic viruses, such as enteroviruses, or parvovirus B19, can cause myocarditis more commonly.

Table 1. Updated Recommendations of CMR Criteria of Myocardial Inflammation.

Updated Lake Louise Criteria (2 out of 2)	Diagnostic Targets
Main criteria	
T2-based imaging Regional* high T2 SI or Global T2 SI ratio $\geq 2.0^{\dagger}$ in T2WI CMR images or Regional or global increase in myocardial T2 relaxation time [†]	Myocardial edema
T1-based imaging Regional or global increase of native myocardial T1 relaxation time or ECV ^{‡,§}	
or Areas with high SI in a nonischemic distribution pattern in LGE images	
Supportive criteria Pericardial effusion in cine CMR images or High signal intensity of the pericardium in LGE images, T1-mapping or T2-mapping or T1 mapping or T2 mapping	Pericardial inflammation
Systolic LV wall motion abnormality in cine CMR images	
	LV dysfunction

* “Regional” refers to an area of at least 10 contiguous pixels. [†]Published or local normal values, LV coverage, and proper analysis tools must be acknowledged. [‡]T1 mapping is highly sensitive to detecting both acute and chronic forms of increased free water content within the myocardium, and thus, the Consensus Group recommends treating it as an alternative criterion to EGE. If paired with LGE to diagnose myocarditis, the areas of T1 abnormality should be beyond that of LGE imaging. **Abbreviations:** SI, Signal; T2WI, T2-weighted imaging; CMR, Cardiac magnetic resonance imaging; ECV, Extracellular volume; LGE, Late gadolinium enhancement; LV, Left ventricular. Adapted from “Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation,” by Ferreira, V. M., Schulz-Menger, J., Holmvang, G., Kramer, C. M., Carbone, I.,

Sechtem, U., Kindermann, I., Gutberlet, M., Cooper, L. T., Liu, P., & Friedrich, M. G., 2018, *Journal of the American College of Cardiology*, 72(24), p. 3158–3176. Copyright [2021] by Elsevier. Adapted with permission.

Moreover, the treatment of non-viral myocarditis relies on immunosuppressive therapy. In contrast, no definitive treatment is introduced for myocarditis in the SARS-CoV-2 infection-related cases, and treatment options are variable. Antiviral agents, high-dose corticosteroids, immunosuppressive agents, and intravenous immunoglobulin (IVIG) are recommended treatment options for myocarditis-associated COVID-19, particularly if the patient has the COVID-19 cytokine storm syndrome (COVID-CSS) [40,41]. Although several therapeutic approaches are established for managing myocarditis-associated COVID-19, most cases are resolved spontaneously, and supportive therapy is sufficient [25]. However, corticosteroids are the most frequent drug prescribed for treating myocarditis in COVID-19 patients [42]. It is essential to note that although there is a belief that systemic corticosteroids may lead to diminished viral clearance and increased risk of sepsis in the settings of COVID-19, the benefits of systemic immunosuppression in this setting often outweighs the disadvantages and is considered an effective therapy for myocarditis-related to the COVID-19 [25].

Furthermore, recombinant interleukin-1 receptor antagonists, such as anakinra, have also been used to treat COVID-related myocarditis. It was also demonstrated that IVIG could substantially reduce myocarditis mortality and enhance the left ventricle's cardiac output [43]. Likewise, the mixed-use of IVIG/corticosteroid successfully treated COVID-19-related myocarditis [44]. Supportive measures, including inotropes, vasopressors, mechanical ventilation, and mechanical hemodynamic support (i.e., intra-arterial balloon pump, temporary left ventricular support devices, and ECMO), should also be considered for severe cases of cardiogenic shock. Nevertheless, supportive and guideline-directed therapies for heart failure are still the mainstay of myocarditis treatment [45,46].

The prognosis of SARS-CoV-2 infection-associated myocarditis is unpredictable since a minority of these patients develop heart failure due to dilated cardiomyopathy (DCM) and systolic dysfunction. Nevertheless, it was estimated that the overall mortality rate was about 14% [25]. Besides, it is essential to note that the mortality rate is higher in COVID-19 patients with myocarditis than in COVID-19 patients without myocarditis [47]. There is the possibility of developing more severe complications, such as cardioembolic stroke following myocarditis, implicating the need to carefully manage any suspected case of COVID-19-associated myocarditis according to current guidelines for heart failure and dysrhythmia.

3. COVID-19 vaccine-associated myocarditis

Several COVID-19 vaccines have been generated worldwide and implanted advantages to the health of communities. However, vaccines are associated with complications and are considered a potential risk factor for several adverse events. Most adverse events following COVID-19 vaccination are minor in severity, including local reactions such as injection site pain and induration, systemic manifestations such as myalgia, fever and chills, and coryza-like symptoms. Although it is rare, cardiac complications of COVID-19 vaccines are not excepted, and it was observed that COVID-19 vaccination could lead to acute myocarditis. Large population studies on individuals who received vaccines documented a rate of 2.13 to 5.34 per 100,000 persons and a 1.8 risk ratio of myocarditis in vaccinated compared to unvaccinated persons.

Moreover, the rate of myocarditis following COVID-19 vaccination in persons younger than 30 years and young males was 12.2 and 10.7 per 100,000, which shows young men are more susceptible than other groups of sex and age [48]. US Vaccine Adverse Event Reporting System (VAERS) stated that from December 2020 to August 2021, 1626 patients experienced myocarditis induced by the COVID-19 vaccine, most of which occurred after the second dose of the vaccine. The median age was 21, with a male predominance in sex and the median interval between vaccination and symptoms initiation was 2 days [49]. However, studies have shown that COVID-19 vaccine-induced myocarditis is mild in 95% and 98.6% of adults and children, respectively and the clinical symptoms were resolved rapidly [50,51].

This unfavorable consequence was previously demonstrated for other vaccines, such as the smallpox vaccine [52,53]. This complication has been reported more commonly in younger males aged between 12 to 30 years who received COVID-19 mRNA vaccines [54,55]. The exact pathophysiology of myocarditis following COVID-19 vaccination is still unknown. However, hypersensitivity reaction, genetic predisposition, sex-specific factors, and molecular mimicry are some potential mechanisms responsible for myocarditis after COVID-19 vaccination [56]. Therefore, evidence supports hyperimmunity as the underlying mechanism, similar to other drugs- and vaccine-associated myocarditis cases. Additionally, it was shown that specific alleles of human leukocyte antigen (HLA) are correlated with unfavorable reactions to some of the medications and vaccines [57,58]. Since a small proportion of individuals who received the COVID-19 vaccine demonstrated myocarditis, it can be assumed that such specific alleles of HLA play a vital role in developing myocarditis following COVID-19 vaccine administration [59].

Up to now, few COVID-19 vaccine-associated cases of cardiac complications, including myocarditis, have been reported. However, most reported cases have occurred following the second dose of the vaccines. Moreover, these vaccine-induced AEs have been reported following mRNA (Moderna or Pfizer/BioNTech) and adenoviral vector (Johnson & Johnson) vaccines [55,60–62]. Although the risk of developing myocarditis following COVID-19 vaccination is much lower than infection to SARS-CoV-2, the risk of vaccine-induced myocarditis increases following sequential administration of further vaccine doses [7,63]. Nonetheless, the Centers for Disease Control and Prevention (CDC) guidelines still indicate safety assurance for receiving these COVID-19 vaccines based on benefit-risk assessment in adolescents and young adults. Regarding the immunological basis of such complications, it should be noted that manifestations of vaccine-induced myocarditis can occur as soon as 2 to 3 days after COVID-19 vaccination [64]. It was suggested that a longer interval between doses of vaccines could reduce the risk of myocarditis.

It is vital to note that diagnostic evaluation, preferably CMR, is indicated in any SARS-CoV-2-infected or -vaccinated individual presenting with evidence of myocardial injury with viral or autoimmune etiologies. Physicians and healthcare workers should generally consider myocarditis in vaccinated individuals presenting with severe acute chest pain and abnormal electrocardiogram results. In this condition, cardiac enzymes, electrocardiography (ECG), and echocardiography are mandated, and if indicated, a CMR can also be performed (Figure 3). Notably, a systematic review of the COVID-19 vaccine-induced myocarditis showed that all patients underwent CMR, and CMR finding related to the myocarditis was evident in 89% of patients [65]. One must be careful not to immediately attribute all cardiac events to the vaccine, and other etiologies must be excluded [64]. It is necessary to rule out a de novo SARS-CoV-2 infection, leading to cardiac sequelae. According to the CDC recommendation, a diagnosis of COVID-19 vaccine-induced myocarditis is made by the following criteria: 1) the presence or deterioration of clinical manifestations, 2) confirming the diagnosis by histological examination, CMR, or either by elevation of troponin level exceed to the upper limit, 3) and the absence of any other cause for clinical and para-clinical findings [66].

In conditions where a viral prodrome has been observed, or if a coincident positive SARS-CoV-2 RT-PCR test result is available, the cardiac event is more likely to be attributed to the infection rather than the vaccine. However, the after-vaccine effects can mimic the viral infection's prodromal symptoms, making it difficult to differentiate between these entities. It should also be noted that a negative serology test (anti-SARS-CoV-2 antibodies) cannot conclusively rule out the possibility of a de novo infection. Again, it should be emphasized that vaccine-related myocarditis is a diagnosis made by exclusion of other possible causes [66], and defining a causal association between myocarditis and vaccination is usually tricky, necessitating thorough evaluation of the patient, e.g., to rule out ischemic injury, autoimmune, and other potential infectious causes of myocarditis. Nonetheless, a useful paraclinical indicator of the potential role of vaccines in triggering myocarditis is an increase in the numbers of a specific subset of natural killer (NK) cells and some autoantibodies [64].

On the other hand, the MRI can sometimes differentiate between vaccine-induced myocarditis and virus-associated MIS-C-related cardiac involvement. For example, late gadolinium enhancement

with patchy subepicardial and mid-wall enhancement in the anterior, lateral, and inferior walls, as demonstrated in the revised 2018 Lake Louise criteria, are indicative of the former, while diffuse myocardial edema without evidence of late gadolinium enhancement described by Blondiaux et al. can be suggestive for the latter [67,68].

There is no perspective or clinical trial study on treating the myocarditis-associated COVID-19 vaccine. Regardless of its etiology, NSAIDs, steroids, intravenous immunoglobulin, and colchicine are treatment options for myocarditis. It was shown that NSAIDs, colchicine, and steroids are the most frequent medications used to manage COVID-19 vaccine-induced myocarditis [65]. Regarding COVID-19 vaccine-induced myocarditis in pediatrics, NSAIDs were recommended as a first-line treatment option. Besides, IVIG and corticosteroids are recommended only in severe cases and should be avoided in cases that experienced clinical amelioration 48 hours after initiation of clinical manifestation or prescription of NSAIDs [69]. Additionally, some studies have reported that aspirin, beta-blocker, and ACE inhibitors are also used to treat these patients, and β -blockers and ACE inhibitors should be prescribed in cases with left ventricular systolic dysfunction [64].

3. Pericarditis

COVID-related pericarditis

Extrapulmonary manifestations of COVID-19 frequently develop concomitantly with its pulmonary involvement. However, some complications may occur in the absence of pulmonary findings. Pericarditis as the sole manifestation of SARS-CoV-2 infection has been reported rarely. It occurs either as the presenting feature of COVID-19 or as an infection-related heart complication, early or delayed onset. In addition, recurrent acute pericarditis has also been observed following the SARS-CoV-2 infection. Pericardial involvement rarely occurs following intubation and positive pressure ventilation (PPV) in intensive care unit (ICU)-admitted COVID-19 patients. Pericarditis may coincide with myocarditis (i.e., myopericarditis), but several cases of isolated pericarditis have also been reported [70,71]. In the context of COVID-19, acute pericarditis has been presented as a self-limiting phenomenon, which may lead to pericardial effusion and cardiac tamponade [72]. While the most common symptom of pericarditis is dyspnea and chest pain radiating to the neck and left shoulder, progressive orthopnea and the presence of Beck's triad (hypotension, jugular venous distension, and muffled heart sounds) are suggestive of cardiac tamponade [73,74]. The most likely pathophysiologic mechanism of COVID-related pericarditis is felt to be the body's systemic inflammatory response to the virus.

The presence of two of the following criteria is suggestive of pericarditis: 1) Typical pericardial chest pain (abrupt, pleuritic, substernal or left precordial, with radiation to the neck, arms, or jaw, and relieving with leaning forward); 2) Pericardial friction rub; 3) Typical ECG findings, and 4) New or worsening pericardial effusion on echocardiography. Pericarditis-associated typical ECG findings include sinus tachycardia, diffuse ST-segment elevation without reciprocal depression, and diffuse T-wave inversions with isoelectric ST segments. Trans-thoracic echocardiography (TTE) and CMR are used to diagnose pericardial effusion and thickening of the pericardium. Pericardiocentesis is the gold standard for demonstrating the underlying cause [75]. Nevertheless, like pericarditis with other viral etiologies for which molecular PCR testing on the pericardial fluid can be diagnostic, COVID-19-related pericarditis can also be diagnosed via such assays as a suitable SARS-CoV-2 detection method via PCR on the pericardial fluid is yet to be developed [76]. Nonetheless, complete biochemical, microbiological, and cytological analysis of the pericardial fluid is warranted to exclude other potential causes of pericardial effusion, including infectious (herpesviruses, enteroviruses, adenoviruses, mycoplasma, human immunodeficiency virus, and syphilis), and rheumatologic causes.

Choosing therapeutic approach in COVID-19-related pericarditis is according to the hemodynamic state and size of effusion [77]. Management of pericarditis with hemodynamic stability is based on supportive care, high-dose NSAIDs (aspirin), and colchicine [74]. Patients with hemodynamic instability due to massive pericardial effusion or tamponade should undergo pericardiocentesis,

often with the placement of a pericardial drain, and in patients experiencing recurrent pericardial effusions, the surgical pericardial window may be required [77]. For pericardial involvement in the settings of SARS-CoV-2 infection, apart from its beneficial role in preventing relapses, colchicine seems to be specifically beneficial due to its anti-inflammatory and anti-cytokine [78,79]. Although NSAIDs may be beneficial in reducing the risk of severe COVID-19, they also can be harmful in COVID-19, as they may increase the risk of stroke but not myocardial infarction [80]. Despite their favored anti-inflammatory effects in the settings of SARS-CoV-2 infection, corticosteroids have been demonstrated to promote pericarditis relapse possibly. Other notable therapeutic options that have been tried for COVID-related pericarditis are monoclonal antibodies, such as anakinra and emapalumab [81,82]. The prognosis of COVID-related pericarditis seems favorable, whereas myopericarditis and cardiac tamponade would worsen the outcome.

4. COVID-19 vaccine-associated myocarditis

Pericarditis may occur following COVID-19 vaccination, both as new-onset pericarditis or a recurrent flare in patients with prior episodes. This phenomenon is rarely associated with other vaccines, except following meningococcal and live vaccines, such as the smallpox vaccine [83–85]. On the other hand, recurrent pericarditis had previously been reported after influenza vaccination. This complication occurs most frequently in the setting of underlying auto-inflammatory diseases but can also manifest as a new (previously undiagnosed) autoimmune disorder, such as adult-onset Still's disease [86,87]. Like virus-induced pericarditis, it usually occurs as myopericarditis but can also occur as an isolated disease [74,88,89].

Moreover, pericarditis has been reported as an adverse event following SARS-CoV-2 vaccination in patients undergoing dialysis. Pericarditis following Pfizer-BioNTech, Moderna, Johnson & Johnson, and AstraZeneca COVID-19 Vaccines has been reported. Like myocarditis, pericarditis associated with COVID-19 vaccination has been most commonly reported following the second vaccine dose, and it has been more commonly reported in adolescents and younger individuals. The mechanism of vaccine-induced pericarditis, like most other vaccine-related complications, seems to be a hyper-immune response. The manifestations, diagnostic approach, and treatment of vaccine-associated pericarditis are the same as the pericarditis resulting from the infection. This, again, emphasizes that other potential causes of pericarditis should be excluded before attributing this condition to the vaccines. So far, outcomes of myopericarditis following COVID-19 vaccination appear to be favorable. Nonetheless, there is a probability of life-threatening arrhythmias, effusive pericarditis, and tamponade associated with a worse prognosis.

4. Conclusions

Clinicians should be aware that cardiac involvement, particularly myocarditis and pericarditis, may manifest in patients, usually occurring 2-4 days after COVID-19 vaccination. This review has emphasized that such rare vaccine-induced adverse events would not change the highly favorable risk-benefit ratio of COVID-19 vaccination, even in patients with underlying heart disease or cardiomyopathy. However, despite limited data, CDC recommends that patients with a history of previous severe adverse events following a COVID-19 vaccine, such as myocarditis/pericarditis after mRNA vaccines or thrombosis with thrombocytopenia syndrome (TTS) after adenoviral vector vaccines, may defer receiving a subsequent dose. Finally, additional surveillance of such adverse events after COVID-19 vaccination will help identify specific patients at increased risk of developing such catastrophic events and, if so, whether additional precautions are necessary.

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Conflict of Interest Disclosure: Terence T. Sio reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no relevant financial interests to be declared.

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