COVID-19 and Myocarditis: Review of Clinical Presentations, Pathogenesis and Management

Jana P Lovell,[1] Daniela Čiháková[2,3] and Nisha A Gilotra[1]

1. Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 2. Department of Pathology, Johns Hopkins University of Medicine, Baltimore, MD, USA; 3. W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

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There are four main myocarditis presentations identified in the context of severe acute respiratory coronavirus 2 (SARS-CoV-2): myocarditis associated with acute coronavirus disease 2019 (COVID-19) infection, post-acute COVID-19 syndrome, multisystem inflammatory syndrome, and vaccination-associated myocarditis. This article reviews the clinical features and current management strategies for each of these presentations. The overall prevalence of myocarditis is considered to be rare, although accurate estimation is affected by heterogeneity in diagnostic criteria and reporting, as well as infrequent use of gold-standard diagnostic endomyocardial biopsy. Severity of disease can range from mild symptoms to fulminant myocarditis. Therapeutic interventions are typically supportive and extrapolated from treatment for non-COVID-19 viral myocarditis. Several pathogenic mechanisms for the development of myocarditis have been proposed, and ongoing research is critical for elucidating disease pathogenesis and potentially identifying therapeutic targets. The long-term cardiovascular sequelae of SARS-CoV-2 infections and associated myocarditis require further elucidation and understanding.

Keywords

Myocarditis, COVID-19 infection, SARS-CoV-2, post-acute COVID-19 syndrome, multisystem inflammatory syndrome, COVID-19 vaccine

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Corresponding author: Nisha A Gilotra, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, 600 N Wolfe St, Carnegie Bldg Suite 568, Baltimore, MD, 21287, USA. E: naggarw2@jhmi.edu

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), has been associated with several cardiovascular disease manifestations, including acute coronary syndromes, arrhythmias, heart failure, thromboembolic complications and myocardial injury.[1] Myocardial injury, defined as elevation in serum cardiac troponin levels, can occur with myocarditis, stress cardiomyopathy and microvascular thrombosis, and is associated with increased morbidity and mortality in the context of COVID-19 infection.[2,3]

Myocarditis is an inflammatory process involving the myocardium. The US Centers for Disease Control and Prevention (CDC) working case definition of acute myocarditis in patients 12 years or older designates a probable or confirmed case of myocarditis based on clinical symptoms and diagnostic findings (*Table 1*).[4–6] Viral myocarditis is the most common type of myocarditis, most commonly due to Coxsackievirus B and adenoviruses.[7] These viral infections cause cardiomyocyte damage through immune-mediated pathways and direct viral cytotoxicity.[7] Prior to the emergence of SARS-CoV-2, the human coronaviruses SARS-CoV-1 and the Middle East respiratory syndrome coronavirus were known but very rare causes of viral myocarditis.[8,9]

This article will focus specifically on myocarditis associated with SARS-CoV-2. At present, four main myocarditis presentations have been identified in the context of SARS-CoV-2: myocarditis associated with acute COVID-19 infection, post-acute COVID-19 syndrome (or long COVID-19 syndrome), multisystem inflammatory syndrome (MIS) and vaccination-associated myocarditis. For each presentation, we will review the clinical features, proposed pathogenic mechanisms and current treatment strategies. Finally, we will discuss the existing gaps in the mechanistic understanding and management of myocarditis in the context of SARS-CoV-2 and the potential next steps to further elucidate this condition.

Acute COVID-19 infection

Prevalence

Myocarditis is an infrequently reported complication of acute COVID-19 infections. Heterogeneity in diagnostic criteria and case reporting prohibits an accurate estimation of the true prevalence of myocarditis. Given the overall lower rates of endomyocardial biopsies in patients with COVID-19, the diagnosis of myocarditis relies more heavily on evidence of myocardial injury or cardiac magnetic resonance imaging (CMR) in addition to clinical symptoms to fulfil the CDC working definition of myocarditis.

Table 1: Case definition of acute myocarditis based on the Centers for Disease Control and Prevention working definition[4–6]

Myocarditis	
Probable case	Confirmed case
Presence of ≥1 new or worsening of the following clinical symptoms: • Chest pain/pressure/discomfort • Dyspnoea/shortness of breath/pain with breathing • Palpitations • Syncope **AND** ≥1 new finding of: • Elevated troponin above upper limit of normal • Abnormal electrocardiogram or rhythm monitoring findings consistent with myocarditis* • Abnormal cardiac function or wall motion abnormalities on echocardiogram • CMR findings consistent with myocarditis† **AND** no other identifiable cause of symptoms and findings	Presence of ≥1 new or worsening of the following clinical symptoms: • Chest pain/pressure/discomfort • Dyspnoea/shortness of breath/pain with breathing • Palpitations • Syncope **AND** • Histopathological confirmation of myocarditis‡ ***OR*** • Elevated troponin above upper limit of normal AND • CMR findings consistent with myocarditis† **AND** no other identifiable cause of symptoms and findings

**Requires at least one of the following: ST-segment or T-wave abnormalities; paroxysmal or sustained atrial, supraventricular or ventricular arrhythmias; atrioventricular nodal conduction delays or intraventricular conduction defects. †Using original or revised Lake Louise criteria (Ferreira et al.* J Am Coll Cardiol. *2018;72:3158–76).*[5]

‡Using Dallas criteria (Aretz et al. Am J Cardiovasc Pathol. *1987;1:3–14).*[6]
CMR = cardiac magnetic resonance imaging; COVID-19 = coronavirus disease 2019.

Myocardial injury, as demonstrated by elevated serum cardiac troponin levels, has been reported in up to 36% of patients hospitalized with acute COVID-19 infection.[2] However, even in fulminant cases of non-COVID-19-related myocarditis, normal serum troponin levels have been reported, limiting the utility of troponin elevation as a key diagnostic criterion for myocarditis.[10] Subclinical myocardial dysfunction has also been reported in up to 79% of patients with COVID-19 infection undergoing speckle tracking echocardiography based on strain imaging.[11] Myocardial injury and echocardiographic evidence of subclinical myocardial dysfunction may prompt further diagnostic evaluation for active myocarditis but may overestimate the true prevalence of COVID-19-related myocarditis and reflect alternative cardiovascular processes.

Endomyocardial biopsy (EMB), or direct histopathological examination, remains the gold standard for diagnosis of myocarditis.[12,13] Using the Dallas criteria for diagnosis, myocarditis is generally defined as myocyte necrosis or injury in the setting of inflammatory infiltrates.[6] Based on limited histopathological studies in acute COVID-19 infections, the prevalence of myocarditis is estimated to be much lower than the reported rates of myocardial injury. In a recent review of 277 autopsied hearts, histopathology with evidence of inflammation consistent with myocarditis was found in only 20 hearts (7.2%).[14] The true prevalence of myocarditis in these patients was likely to be less than 2.0%, given the inconsistencies in reporting inflammatory changes as myocarditis. Additionally, the authors identified a substantial cohort of autopsy samples with non-myocarditis-related inflammation in cardiac tissue. In another observational study evaluating 404 patients with acute COVID-19 infection, only 5 patients (1.2%) were diagnosed with myopericarditis based on clinical presentation, troponin elevation and evidence of left ventricular systolic dysfunction on echocardiography.[15] While existing autopsy studies provide an approximation of myocarditis cases in acute COVID-19 infection, they cannot be generalized to estimate the incidence of myocarditis in all acute COVID-19 infections.

Clinical manifestations

The clinical presentation typical for myocarditis associated with acute COVID-19 infection is a viral prodrome beginning with symptoms of fever, cough and shortness of breath, followed by the development of characteristic chest pain, signs or symptoms of heart failure, and/or cardiac arrhythmias. The clinical course of myocarditis can range from mild symptoms not requiring hospitalization to fulminant myocarditis resulting in severe heart failure, cardiogenic shock or clinically significant ventricular arrhythmias.[16–20]

Myocardial injury is the most commonly reported clinical finding in published case reports and series.[15] Findings on electrocardiography (ECG) may include non-specific ST and T wave changes, diffuse ST elevations or ventricular ectopy/arrhythmias. When available, CMR findings should fulfil Lake Louise diagnostic criteria: evidence of non-coronary distribution of myocardial injury with late gadolinium enhancement (LGE) or T1 abnormalities and concurrent tissue oedema with increased signal intensity in T2-weighted images or increased myocardial T2 relaxation time (*Figure 1*).[5,21] Evidence of left ventricular systolic dysfunction, typically in a pattern of global hypokinesis, and/or pericardial effusion is commonly identified on echocardiography or CMR.

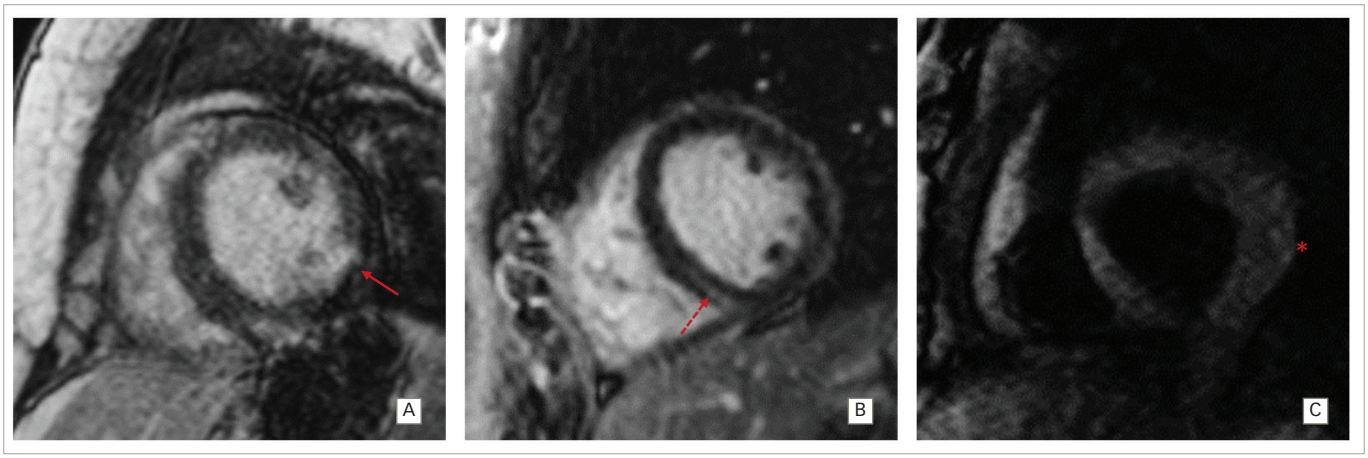
EMB has been infrequently utilized during the COVID-19 pandemic due to infection exposure concerns and lack of direct management implications. In other cases of viral myocarditis, which is a notoriously patchy inflammatory process, EMB diagnosis is challenged by limited sensitivity, even with newer techniques such as voltage mapping-guided biopsy.[22,23]

Pathogenesis

The pathogenesis of myocarditis in patients with acute COVID-19 infection is an area of ongoing research. Proposed mechanisms include direct viral invasion and indirect effects of viral infection. SARS-CoV-2 enters host cells through the binding of viral spike protein to angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface.[24] ACE2 is found on the surface of cardiomyocytes, pericytes and fibroblasts. Viral infection is also dependent on the host transmembrane serine protease 2, which primes the viral spike protein, allowing for viral entry into host cells.[24]

RNA and spike protein have been detected *in vitro* in stem-cell-derived cardiomyocytes, with entry dependent on the expression of ACE2 and inhibited by the antiviral medication remdesivir.[25] In 2 reported cases of fulminant myocarditis occurring during active COVID-19 infection, SARS-CoV-2 RNA was isolated from cardiomyocytes.[20,26] In both cases, nasopharyngeal testing for SARS-CoV-2 was negative, indicating isolated myocardial infection. In another patient with isolated cardiac involvement who developed cardiogenic shock, EMB revealed both the presence of RNA, as well as SARS-CoV-2 viral particles, in myocyte sarcoplasm.[27] The presence of SARS-CoV-2 viral particles has also been detected in cardiac interstitial cells of another patient with cardiogenic shock in the setting of acute COVID-19 infection.[28] The histopathology of these patients was notable for mixed inflammatory infiltrates with predominantly macrophages and T lymphocytes. It is thus hypothesized that direct viral

Figure 1: Cardiac magnetic resonance findings in COVID-19-associated myocarditis



A: focal transmural LGE in the inferolateral wall (solid arrow) in a patient with acute COVID-19 infection myocarditis; B: mid-myocardial LGE in the inferoseptal wall (dashed arrow) in an adult patient with MIS-A; C: punctuate areas of increase T2 signal in the lateral wall (asterisk) in a patient who had recovered from COVID-19.
COVID-19 = coronavirus disease 2019; LGE = late gadolinium enhancement; MIS-A = multisystem inflammatory syndrome in adults.

invasion of cardiac tissue and subsequent immune-mediated response may contribute to the development of fulminant myocarditis.

Regarding less severe cases of myocarditis, the pathogenesis probably involves more indirect effects related to viral infection, including dysregulated activation of innate immune pathways and cytokine release, thrombotic microangiopathy and endothelial dysfunction.[29] Typical viral myocarditis is characterized by lymphocytic-predominant infiltrates with associated myocyte necrosis. In contrast, histopathology of autopsied hearts with COVID-19-associated myocarditis have revealed an increased number of Cluster of Differentiation 68-positive macrophages and monocytes.[30,31] Interstitial macrophage infiltration without associated myocardial injury has also been detected in autopsied hearts of COVID-19 patients without myocarditis.[31] The predominance of macrophage/monocytes in the hearts of patients with acute COVID-19 infections may indicate a distinct mechanism for myocardial injury compared with typical viral myocarditis.

Management

The management of myocarditis associated with acute COVID-19 infection is heterogeneous, depending on clinical severity. COVID-19-specific therapies, including antiviral medications (e.g. remdesivir) and steroids, are typically used based on severity of respiratory illness.[29] For severe cases of myocarditis, use of intravenous immunoglobulin (IVIG) and intravenous methylprednisolone has been reported.

In non-COVID-19 myocarditis, data for treatment with corticosteroids and immunosuppressive therapy are mixed, with the largest benefit shown in certain myocarditis subtypes, such as giant cell, eosinophilic and non-viral myocarditis.[32,33] Despite the lack of proven mortality benefit in viral lymphocytic myocarditis, corticosteroids are often used for the acute presentation of fulminant or haemodynamically compromised myocarditis and may improve left ventricular systolic function.[34] Improved outcomes with corticosteroid treatment have been associated with the presence of cardiac autoantibodies in patients with lymphocytic myocarditis.[35] In acute COVID-19 myocarditis, reviews of published cases indicate that steroid treatment may be associated with favourable outcomes.[36,37] Given the multiple mechanisms of myocardial injury and inflammation in COVID-19, including potential virus-induced autoimmunity, corticosteroids may be more beneficial in COVID-19-related myocarditis than in viral lymphocytic myocarditis.

Tocilizumab, an inhibitor of interleukin-6 (IL-6) receptor, was granted an emergency use authorization by the US Food and Drug Administration for the treatment of hospitalized patients with severe COVID-19 infection already receiving systemic corticosteroids. The efficacy of tocilizumab and other IL-6 inhibitors for the treatment of COVID-19-associated myocarditis is not yet known. Fulminant myocarditis resulting in severe heart failure and cardiogenic shock may necessitate the use of vasopressors, inotropes or mechanical circulatory support, including veno-arterial extracorporeal membrane oxygenation (VA-ECMO). For patients with evidence of left ventricular dysfunction, initiation of heart failure guideline-direct medical therapy with renin-angiotensin-aldosterone system antagonism and beta blockade is reasonable, pending clinical stability.

In terms of counselling patients who recover from acute COVID-19 myocarditis, recommendations are extrapolated from expert consensus on the management of acute myocarditis. Patients should be advised to avoid competitive sports for 3–6 months following initial acute myocarditis diagnosis.[38] It is also reasonable to repeat transthoracic echocardiography at 3 months in clinically stable patients and to obtain baseline CMR if available.

Post-acute COVID-19 syndrome

Post-acute COVID-19 syndrome is typically defined as symptoms persisting beyond 4 weeks from the initial onset of COVID-19 symptoms. These symptoms can include persistent fatigue, dyspnoea, cough and loss of smell.[39] Cardiovascular manifestations may include chest pain, palpitations and increased resting heart rate.[39]

The incidence of clinically significant myocarditis in post-acute COVID-19 syndrome is unknown. There have been several small cohort studies utilizing CMR as a screening tool for persistent cardiac involvement and subclinical myocarditis in asymptomatic or mildly symptomatic patients who have recovered from acute COVID-19 infection. One study involving 26 recovered competitive athletes identified 4 (15%) athletes with CMR abnormalities that the authors described as consistent with myocarditis.[40] All athletes had mild COVID-19 infection not requiring

hospitalization or COVID-19-specific therapies. Of the 4 athletes with CMR, findings consistent with myocarditis, 2 were asymptomatic at the time of CMR, while the other 2 had mild symptoms. Troponin elevation, left ventricular dysfunction and ECG changes were absent in all athletes defined as having evidence of myocarditis on CMR.

In another cohort of 50 soldiers with persistent cardiopulmonary symptoms following acute COVID-19, 4 soldiers (8%) were found to have evidence of myocarditis on CMR.[41] The majority of soldiers referred for CMR had initial COVID-19 infection that was mild to moderate in severity and did not require hospitalization; however, 94% of them reported cardiovascular symptoms, including dyspnoea on exertion or chest pain, in the convalescent phase. Similarly to the previous study, all soldiers with myocarditis on CMR also had preserved biventricular systolic function.

In a larger cohort of 148 patients who underwent delayed CMR after severe acute COVID-19 infection requiring hospitalization and complicated by troponin elevation, LGE was present in 70 patients (49%).[42] Forty patients (27%) had a myocarditis-like injury, defined as non-ischaemic myocardial injury with LGE and myocardial oedema on T2 mapping. Of these 40 patients, 12 (30%) had CMR findings consistent with active myocarditis, as defined by a pattern of non-ischaemic distribution of LGE with coexisting elevation in T1 and T2 signal intensity or T2 alone. Biventricular systolic function was similarly preserved in all patients with myocarditis-like injury.

These and other cohort studies indicate a relatively common prevalence of subacute cardiac inflammation on CMR following recovery from acute COVID-19 infection, including even mild cases.[43] In the absence of troponin elevation, left ventricular systolic dysfunction, ECG changes and significant symptoms, however, the clinical significance of subclinical myocarditis or myocarditis-like injury on CMR is unclear.

CMR abnormalities in the convalescent phase are likely to indicate a low level of residual inflammation following initial infection rather than a novel inflammatory process, although there is limited EMB data in patients with post-acute COVID-19. In a cohort of 100 recovered patients undergoing CMR, 3 patients with severe CMR abnormalities, depressed LV systolic function and/or significantly elevated troponin underwent EMB, with histopathology revealing active lymphocytic inflammation.[44] In patients with subclinical myocarditis and less severe CMR abnormalities, the predominant histopathological features are unknown.

Given the high sensitivity of CMR for detecting cardiac inflammation, CMR can be utilized as a screening tool to rule out cardiac involvement in patients who report persistent cardiovascular symptoms in the post-acute phase of COVID-19 infection. Additional prospective long-term studies following patients with post-acute COVID-19 infection are needed to help determine the clinical significance of CMR abnormalities and to guide appropriate diagnostic evaluation and management of post-acute COVID-19 myocarditis.

Multisystem inflammatory syndrome

Prevalence and clinical manifestations

MIS was first reported in children as a clinical syndrome characterized by hyperinflammatory shock and multiorgan dysfunction presenting days to weeks after initial COVID-19 infection or exposure. The CDC case definition for MIS in children (MIS-C) less than 21 years of age requires the presence of fever, laboratory evidence of inflammation (e.g. elevated erythrocyte sedimentation rate or C-reactive protein) and clinical evidence of a severe illness requiring hospitalization and involvement of at least two organs, with concurrent positive SARS-CoV-2 laboratory testing or exposure to a COVID-19 case within 4 weeks prior to the onset of symptoms.[45] Myocarditis has been reported in up to 17% of children with MIS, with the highest incidence (30%) in patients aged 18–20 years.[46]

MIS in adults (MIS-A) aged 21 years or older is not as well described as MIS-C. The CDC defines MIS-A in the context of COVID-19 as a recent or current COVID-19 infection requiring hospitalization with fever and laboratory evidence of active inflammation and the fulfilment of at least three clinical criteria, including one primary clinical criterion.[47] Primary clinical criteria include 1) severe cardiac illness, such as myocarditis or new-onset heart failure, and 2) rash and non-purulent conjunctivitis. Secondary clinical criteria include 1) new-onset neurological signs and symptoms, 2) shock or hypotension, 3) abdominal pain, vomiting or diarrhoea and 4) thrombocytopenia.

While the true incidence of MIS-A is unknown, it is considered to be a rare clinical syndrome. Given the similar timing of symptom development, MIS-A may be misclassified as post-acute COVID-19 syndrome. However, in contrast to post-acute COVID-19 syndrome, the clinical presentation of MIS-A is characterized by new-onset hyperinflammatory illness and severe extrapulmonary multiorgan dysfunction within 2–5 weeks of initial COVID-19 infection or exposure, typically after a period of recovery.

In a recent systematic review of 221 patients with MIS-A, 30% presented with myocarditis and 54% with cardiac dysfunction.[48] The median age of all MIS-A patients was 21 years (interquartile range 19–35 years), but, as this study included patients aged 18–20 years, about 50% of patients included are considered MIS-C patients. Compared with MIS-C patients younger than 18 years, myocarditis was overall more prevalent in patients 18 years or older with MIS (15% versus 30%).

Pathogenesis

There are several proposed pathogenic mechanisms of MIS, including molecular mimicry due to similar immunological epitopes between the virus and host, bystander activation of immune cells resulting from exposure of self-antigens and persistent low-level viral infection driving continued immune responses.[49] The timing of MIS correlates with the peak SARS-CoV-2 antibody production weeks after the initial infection.[50] However, virus-specific antibody profiles differ between children and adults. Children, both with and without MIS, have reduced neutralizing activity compared with adults, suggesting a potential predisposition for children to develop persistent low-level viral infection that leads to increased risk of MIS.[50]

An alternative hypothesis for the pathogenesis of MIS-C is that the development of autoantibodies leads to autoreactive immune responses and subsequent widespread tissue damage.[51,52] In patients with MIS-C, T-cell receptor (TCR) skewing has also been reported, possibly as a result of the SARS-CoV-2 spike protein acting as a superantigen.[53] TCR skewing is correlated with increased cytokine level and disease severity. Further study of autoantibodies and TCR skewing may define potential therapeutic targets in MIS.

Management

Therapies for MIS-C and MIS-A are primarily supportive, depending on clinical severity. Aspirin is frequently prescribed for children with MIS. Use of IVIG and intravenous steroids has been reported to be effective in improving recovery of left ventricular systolic function.[54] Combined use of IVIG and IL-6 receptor inhibitors has also been reported as effective

treatment for patients with MIS-C.[52] In severe cases of myocarditis resulting in cardiogenic shock, vasopressor support and VA-ECMO may be required. Tocilizumab and other immune modulators have been infrequently reported, but their clinical utility in myocarditis associated with MIS is unclear.

Vaccination-related myocarditis

Prevalence

Vaccine-related myocarditis has been recognized as a rare adverse event of prior vaccinations, most notably the smallpox vaccine. Myocarditis associated with COVID-19 vaccines has been rarely reported in the Vaccine Adverse Events Reporting System (VAERS), as well as peer-reviewed case reports and small case series. The overwhelming majority of vaccine-related myocarditis cases have been reported following the administration of second doses of messenger RNA (mRNA) vaccines, BNT162b2 mRNA (Pfizer, New York, NY, SA; BioNTech, Mainz, Germany) and mRNA-1273 (Moderna, Cambridge, MA, USA).[55–60] Through passive reporting to VAERS, the CDC estimates 3.5 cases per million second doses of mRNA vaccine administered in the USA as of 30 June 2021.[61] The highest rate of myocarditis occurs in men aged 18–29 years, with 24.3 cases per million second doses.[61,62] Two studies evaluating private healthcare databases in the USA estimated between 0.8 and 6.3 cases of myocarditis per million doses of mRNA vaccine, with higher rates similarly seen in young men after the administration of the second dose.[63,64]

A slightly higher incidence of cases of mRNA vaccine-related myocarditis has been reported in countries with active surveillance, compared with passive reporting in the USA. For example, the Israeli Ministry of Health reported 136 cases in over 5 million residents who received two doses of BNT162b2 vaccine between December 2020 and June 2021.[65] In a large Israeli health provider database, the estimated risk of myocarditis was 21–27 cases per million persons receiving at least one dose of BNT162b vaccine.[66,67] As reported in the USA, the highest incidence of myocarditis was in young men, estimated at about 100 cases per million persons.

In a study of almost 39 million vaccinated persons in England, the estimated risk of myocarditis associated with the adenovirus vaccine ChAdOx1 (AstraZeneca, Cambridge, UK) was 2 cases per million first doses.[68]

Clinical manifestations

The typical clinical presentation of vaccine-related myocarditis occurs with the development of chest pain 2–4 days after the administration of the second dose of vaccine. Vaccine-related myocarditis has also been reported even less commonly following first-dose vaccination, typically in patients who have had remote COVID-19 infection.[58] Chest pain, classic for myocarditis, is the most common presenting symptom, reported in up to 86% of patients.[58] Diagnostic characteristics include ECG changes such as ST or T wave changes, elevated troponin levels, and LGE and myocardial oedema on CMR characteristic of myocarditis. Reduction in left ventricular systolic function and heart failure symptoms are uncommon.[58] When available, all patients with vaccine-related myocarditis have had negative COVID-19 polymerase chain reaction testing. The clinical course is typically benign, with full recovery of symptoms within days and without long-term effects on left ventricular systolic function.

Pathogenesis

There are several proposed mechanisms for the development of vaccine-related myocarditis.[69] The mRNA vaccines contain nucleoside-modified mRNA encoding the SARS-CoV2 spike protein and stimulate the production of spike protein immunoglobulin G antibodies that prevent binding of the spike protein to the ACE2 receptor. RNA molecules can stimulate the innate immune system, but nucleoside modifications of mRNA in vaccines reduce immunogenicity and subsequent cytokine cascade.[70] The lipid nanoprotein that encapsulates mRNA COVID-19 vaccines also enhances the immune response to vaccination through the stimulation of T follicular helper cell and humoral responses.[71]

Investigation into the pathophysiology of vaccine-related myocarditis is limited by an overall paucity of EMB in these patients. In rare cases of reported histopathology, the inflammatory infiltrate contains mixed cellularity, as opposed to the lymphocytic-predominant infiltrate typical for viral myocarditis.[65,72]

Proposed mechanisms for vaccine-related myocarditis include dysregulated systemic inflammatory response to the mRNA resulting in excessive cytokine activation, particularly in patients with possible genetic predisposition.[73] Molecular mimicry is also possible due to cross-reactivity between spike protein antibodies and structurally similar human proteins, such as α-myosin.[74]

Increased incidence of myocarditis in men is well established in non-COVID-19-related myocarditis.[75,76] The mechanism for increased rates of myocarditis in younger male patients has been hypothesized to be related to the differential effects of sex hormones on inflammation.[69]

Management

There are no standardized treatments or randomized data guiding current management, and most cases are mild and self-resolving. Supportive treatment and agents with anti-inflammatory properties typical for standard treatment practices for pericarditis and myocarditis have been used. Therapies include non-steroidal anti-inflammatory agents, colchicine and steroids, and – in rare severe cases – IVIG.[56,57,60] Cardioprotective medications such as renin-angiotensin-aldosterone system inhibition and beta blockade are reasonable for patients who present with reduced left ventricular systolic function. Temporary exercise restriction may also be advised.

Given the overall rare presentation and benign course of vaccine-related myocarditis, there is a clear benefit for continued vaccination according to current CDC recommendations.[61,62] For patients who develop myocarditis after the first dose of mRNA vaccine, the CDC had previously recommended delaying the second dose until full resolution of symptoms and clinical manifestations. There are no current guidelines regarding receiving the booster dose following myocarditis associated with second-dose vaccine administration.

The predominant clinical manifestations, pathogenesis and management strategies for myocarditis associated with COVID-19 infections and vaccines are summarized in *Table 2*.[14,15,19,31,40-43,48,63-68] Additional data from published literature regarding the prevalence, patient demographics and clinical features of COVID-19-related myocarditis is provided in *Supplementary Table 1*.

Areas for future research

The diagnosis of myocarditis in the COVID-19 era remains challenging due to the infrequent use of gold-standard histopathology. Reliance on evidence of myocardial injury with elevated serum troponin levels or LGE on CMR alone may contribute to the misclassification of other cardiovascular processes, such as microvascular dysfunction or thrombosis, as cases of

Table 2: Myocarditis associated with COVID-19 infections and vaccines[14,15,19,31,40–43,48,63–68]

	Acute COVID-19 infection	Post-acute COVID-19	MIS-A	Vaccine-related
Prevalence	1.2–7.2% infected patients[14,15]	8.0–26.9% recovered patients[40–43]	~30.0% of MIS cases[48]	BNT162b2: 0.0001–0.003% vaccinated patients[65–68] mRNA-1273: 0.0006–0.001% vaccinated patients[68] ChAdOx1: 0.0002% vaccinated patients[68]
Timing of onset	Initial COVID-19 diagnosis	4 weeks after initial onset of COVID-19	2–5 weeks after initial COVID-19 infection or exposure	Typically within 4 days of second dose of mRNA vaccine
Age	Average age: 40–60s[15,19,31]	Average age: ~40[43]	Average age of all patients with MIS-A: 21 (range: 19–35)[48]	Average age: mid-20s[63–67]
Risk factors	• No definitive sex predominance • Hypertension • Diabetes mellitus	No definitive sex predominance	Male sex predominance in MIS-A, but unknown whether male sex is risk factor for myocarditis	• Male sex • mRNA vaccines
Clinical manifestations				
Symptoms	Chest pain, dyspnoea, fever, cough	Dyspnoea, commonly asymptomatic	Fevers, gastrointestinal symptoms, rash, conjunctivitis, neurological symptoms	Chest pain
Troponin elevation	Common	Uncommon	Common	Common
ECG abnormalities	Common	Uncommon	Common	Common
LV dysfunction	Common	Uncommon	Common	Uncommon
CMR findings consistent with myocarditis	Common	Common	Common	Common
Histopathology	Macrophage and T cells	Unknown	Unknown	Mixed cellularity
Severity	Variable, ranging from mild symptoms to fulminant myocarditis	Likely benign	Variable, ranging from mild symptoms to severe presentation with shock and multiorgan failure	Mild symptoms with full recovery within days
Therapies	• COVID-19-specific therapies • High-dose steroids • IVIG • Inotropes or MCS for fulminant myocarditis • IL-6 inhibitors? • GDMT for reduced LVEF	*	• Aspirin • Steroids • IVIG • Vasopressors, inotropes or MCS for fulminant myocarditis • IL-6 inhibitors? • GDMT for reduced LVEF	• NSAIDs • Colchicine • Steroids • IVIG • GDMT for reduced LVEF
Proposed pathogenesis	*Fulminant myocarditis* Direct invasion of SARS-CoV-2 into cardiac tissue *Mild myocarditis* Indirect effects of viral infection involving: • Dysregulated activation of innate immune pathways • Macrophage infiltration • Thrombotic microangiopathy • Endothelial dysfunction	Persistent low-level inflammation following acute infection	• Molecular mimicry • Bystander activation of immune cells • Persistent low-level viral infection leading to continued inflammation • Development of autoantibodies • T-cell receptor skewing	• Dysregulated immune response to mRNA • Molecular mimicry • Male predisposition related to differential effects of sex hormones on immune system

**As these patients were overall asymptomatic and the clinical significance of CMR findings is unknown, these patients do not receive treatment.*
CMR = cardiac magnetic resonance imaging; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; GDMT = guideline-directed medical therapy; IL-6 = interleukin-6; IVIG = intravenous immunoglobulin; LV = left ventricular; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MIS = multisystem inflammatory syndrome; MIS-A = multisystem inflammatory syndrome in adults; mRNA = messenger RNA; NSAID = nonsteroidal anti-inflammatory drug; SARS-CoV-2 = severe acute respiratory coronavirus 2.

true myocarditis. In the absence of standardized diagnosis and reporting of COVID-19-related myocarditis cases, true prevalence is unclear, and research regarding clinical outcomes, pathogenic mechanisms and potential therapeutic targets remains limited.

The long-term clinical outcomes of acute viral myocarditis can range from full recovery without residual effects on cardiac function to the development of chronic dilated cardiomyopathy. The chronic sequelae of acute COVID-19 infection are yet to be fully elucidated. Longitudinal prospective studies involving patients with myocarditis associated with acute and post-acute COVID-19 infections and vaccine-related myocarditis are necessary to further define the spectrum of diseases and to help direct appropriate diagnostic evaluation and management. Ongoing clinical investigations regarding pathogenic mechanisms will also be critical to the understanding of predisposing patient factors contributing to differences in severity of clinical presentations, as well as targets for disease-specific therapies.

Conclusions

Myocarditis associated with COVID-19 infections and mRNA COVID-19 vaccines encompasses a heterogeneous spectrum of clinical manifestations and outcomes. Overall, the incidence of clinically significant myocarditis is very low. While the inflammatory changes on CMR are relatively common in post-acute COVID-19 syndrome, they do not appear to have high clinical significance. Myocarditis associated with acute COVID-19 infection and MIS carries the highest risk for clinical deterioration, whereas vaccine-related myocarditis typically follows a benign course. Therapies for COVID-19-related myocarditis are generally supportive and are extrapolated from the standard of practice for non-COVID-19-related myocarditis. Given the potential for fulminant myocarditis related to active or recent SARS-CoV-2 infection, as well as the unknown long-term clinical sequelae of more benign myocarditis cases, prevention of SARS-CoV-2 transmission remains critical. ❑

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