Sports Medicine and Health Science 6 (2024) 232–239

Contents lists available at ScienceDirect

Sports Medicine and Health Science

journal homepage: www.keaipublishing.com/smhs

Review

Myocarditis – A silent killer in athletes: Comparative analysis on the evidence before and after COVID-19 pandemic

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ARTICLE INFO

Keywords:
COVID-19
Myocarditis
Cardiovascular symptomatology
Athlete susceptibility
Return-to-play
Sudden cardiac death
Viral pathogens
High-intensity exercise

ABSTRACT

Myocarditis is a rare cardiomyocyte inflammatory process, typically caused by viruses, with potentially devastating cardiac sequalae in both competitive athletes and in the general population. Investigation into myocarditis prevalence in the Coronavirus disease 2019 (COVID-19) era suggests that infection with Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is an independent risk factor for myocarditis, which is confirmed mainly through cardiovascular magnetic resonance imaging. Recent studies indicated that athletes have a decreased risk of myocarditis after recent COVID-19 infection compared to the general population. However, given the unique nature of competitive athletics with their frequent participation in high-intensity exercise, athletes possess distinct factors of susceptibility for the development of myocarditis and its subsequent severe cardiac complications (e.g., sudden cardiac death, fulminant heart failure, etc.). Under this context, this review focuses on comparing myocarditis in athletes versus non-athletes, owing special attention to the distinct clinical presentations and outcomes of myocarditis caused by different viral pathogens such as cytomegalovirus, Epstein-Barr virus, human herpesvirus-6, human immunodeficiency virus, and Parvovirus B19, both before and after the COVID-19 pandemic, as compared with SARS-CoV-2. By illustrating distinct clinical presentations and outcomes of myocarditis in athletes versus non-athletes, we also highlight the critical importance of early detection, vigilant monitoring, and effective management of viral and non-viral myocarditis in athletes and the necessity for further optimization of the return-to-play guidelines for athletes in the COVID-19 era, in order to minimize the risks for the rare but devastating cardiac fatality.

1. Introduction

Myocarditis is clinically described as an inflammatory process of the cardiac myocytes that is characterized by wide-ranging etiologies, histopathologic patterns, and clinical manifestations.[1] In developed countries, myocarditis is most commonly caused by viral infectious pathogens (e.g., coxsackievirus, adenovirus, parvovirus), but has also been attributed to a wide variety of toxins, drugs, and other non-viral infectious etiologies.[2,3] During the Coronavirus disease 2019 (COVID-19) pandemic, the increasing prevalence of myocarditis became of particular concern in the public health sphere, as early reports demonstrated that Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the viral pathogen of COVID-19, led to a plethora of cardiovascular complications, including arrhythmias, myocarditis, and pericarditis.[4] These reports in early 2020 were substantiated by multiple epidemiologic studies, demonstrating that SARS-CoV-2 infection increased the incidence of myocarditis/pericarditis at least 15-fold compared to patients that were not affected by SARS-CoV-2 (*i.e.*, pre-COVID incidence at 1 to 10 cases in 100 000 individuals, versus post-COVID incidence ranging from 150 to 4 000 cases per 100 000 individuals).[5,6] Thus, while myocarditis remains a rare condition in the general population, infection with SARS-CoV-2 poses a significantly increased risk of myocarditis cases in otherwise healthy individuals.

Due to its ability to negatively impact cardiovascular performance and its potentially devastating cardiac sequalae, myocarditis has been of particular interest in the context of Sports Medicine. High-intensity exercise has been shown to exacerbate viral-induced myocardial inflammation, leading to potential sequelae of sudden cardiac death (SCD) owing to electrical instability and ventricular arrhythmia from lymphocytic involvement of the electrical conduction system.[7] In this way, even well before the onset of the COVID-19 pandemic, myocarditis was a

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https://doi.org/10.1016/j.smhs.2024.03.003
Received 11 December 2023; Received in revised form 6 March 2024; Accepted 12 March 2024
Available online 16 March 2024

Abbreviations

ACE2	Angiotensin converting enzyme 2
CMR	Cardiac magnetic resonance
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
EBV	Epstein-Barr virus
HHV-6	Human herpesvirus-6
HIV	Human immunodeficiency virus
IL-1	Interleukin 1
IL-6	Interleukin 6
LGE	Late gadolinium enhancement
NCAA	National Collegiate Athletic Association
ORCCA	Outcomes Registry for Cardiac Conditions in Athletes
PVB19	Parvovirus B19
RTP	Return-to-play
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCD	Sudden cardiac death
$\dot{V}O_{2max}$	Maximal oxygen consumption

leading cause of SCD in athletes.[8] Given the heightened risk of myocarditis with recent COVID-19 infection, there is a particular concern for adverse cardiac events in athletes that may have asymptomatic or have mild COVID-19 symptomatology. Due to these concerns, cardiac magnetic resonance (CMR) imaging and blood tests for cardiac biomarkers have been utilized to monitor the changes of myocarditis prevalence estimates in athletes during the COVID-19 era. Elucidating myocarditis prevalence and its subsequent cardiac sequelae is paramount in reducing SCD in athletes and may have implications in revising the evidence-based return-to-play guidelines.[9]

Under this context, the purpose of the present review is to provide an overview of myocarditis in athletes in the setting of the COVID-19 pandemic. Special attention is given to 1) the unique pathophysiology of myocarditis in athletes; 2) prevalence estimates and athlete susceptibility to myocarditis, and clinical manifestations of myocarditis during the pre- and post-COVID time periods; 3) comparing long-term outcomes of myocarditis in the athletes as compared with the general population; and 4) future considerations regarding return to athletic activity following a recent SARS-CoV-2 infection.

2. Pathophysiology features of viral myocarditis in athletes: comparison between pre- and post-COVID-19 cases

Viruses, such as SARS-CoV-2, are the most common pathogens known to cause myocarditis; however, bacterial, fungal, protozoal, and drug/autoimmune reactions represent less frequent causes of myocarditis in the athlete.[10] Before COVID-19, endometrial biopsy revealed that adenovirus, enterovirus, and parvovirus B19 were the most common viral infectious agents implicated in myocarditis.[11] However, with the mounting evidence suggesting SARS-CoV-2's major role in the recently increased myocarditis prevalence rates, the mechanistic elucidation of SARS-CoV-2's spike protein and its induction of myocardial damage has become vitally important.

2.1. Viral myocarditis phasic progression

Initial postulations suggested that viral myocarditis is a triphasic disease process that stems from initial viral replication, followed by autoimmune injury, and then ultimately to progressive dilatation/cardiac remodeling after resolution or reduction of the autoimmune injury.[12] More recent pathophysiologic understanding also suggests a three-stage process but categorizes progression into: viral entry stage (acute), inflammatory cell infiltration (subacute), and cardiac remodeling (long term sequalae/chronic).[13]

The acute phase of myocarditis lasts over several days, and chiefly involves viral replication. The subacute phase is characterized by immune response mechanisms occurring approximately one week to one month after initial viral infection.[14,15] In this phase, natural killer cells and macrophages followed by T-lymphocytes invade cardiac myocytes and activate inflammatory cytokines, *e.g.,* interleukin 1 and 6 (IL-1, IL-6).[15] Subsequently, the immune response-triggered antibodies against viral and cardiac proteins can lead to impairment in cardiac contractile function and can also cause mechanical-electrical dissociation due to invasion into cardiac conductive tissues.[16] While active myocarditis may cause prolonged cardiac inflammation, some athletes may develop residual myocardial damage with long term sequelae consisting of fibrosis, ventricular chamber dilatation, and persistent contractile dysfunction, even in the phase of healed myocarditis.[16] The phasic pathophysiology of myocarditis caused by the selected viral pathogens is summarized in Fig. 1.

2.2. Comparison of myocarditis before and after COVID-19

Due to its arrhythmic potential, the acute and subacute phases of myocarditis pose the greatest immediate risk to the athletes participating in high-intensity exercise. The potentially devastating cardiac sequalae can occur during both acute and subacute phases, days or months after the initial viral entry – specifically, the heightened risk of SCD due to arrhythmia. It comes as no surprise, therefore, that myocarditis has been implicated in up to 14% of cases of SCD in young athletes and remains one of the leading causes of SCD in athletes prior to COVID-19.[17–19]

In the COVID-19 era since December 2019, the number of reported SCDs post COVID-19 infection and/or vaccination have significantly increased compared to pre-pandemic times across all demographics.[20–22] Uniquely, SARS-CoV-2 is able to attach and enter host cells through a spike glycoprotein and its host receptor ACE-2 (Angiotensin converting enzyme 2), where it can then invade host cells through a membrane fusion or clathrin-mediated pathway.[23] It was also speculated that an interplay between catecholamines produced during exercise and SARS-CoV-2 spike protein *per se* may be contributing to the elevated incidence of SCDs, but this mechanism is not fully understood.[24]

3. Prevalence and susceptibility of myocarditis in athletes before and after COVID-19

Since many myocarditis cases are undiagnosed and asymptomatic, the exact prevalence of myocarditis in the general population (and in athletes) remains unclear. However, the latest Global Burden of Disease before the COVID-19 pandemic reports a myocarditis incidence of 6.1 per 100 000 in men and 4.4 per 100 000 in women between the ages of 35 and 39 years, with similar figures found in the range of ages between 20 and 44 years.[25] While myocarditis prevalence in athletes remains difficult to estimate, age-related prevalence data for athletes of active age versus master athletes has important implications, as myocarditis plays a significantly less role in SCD (and other cardiac sequalae) in master athletes.[26]

Although myocarditis prevalence estimates are similar pre-pandemic and post-pandemic for the patients not diagnosed with COVID-19, the incidence of myocarditis increased to 150 per 100 000 individuals in patients diagnosed with SARS-CoV-2 infection.[27,28] These data suggest an approximately 15-fold increase in the incidence of myocarditis secondary to SARS-CoV-2 infection compared to other causes. In addition, according to the data available from the Vaccine Adverse Events Reporting System (VAERS), COVID19-induced myocarditis risk estimates may be even more concerning, with some studies suggesting a 40-fold increase in incidence in COVID positive patients compared to non-COVID patients in the pandemic era.[29,30]

These updated prevalence estimates pose a heightened risk to athletes, as participating in high-intensity exercise can exacerbate an already

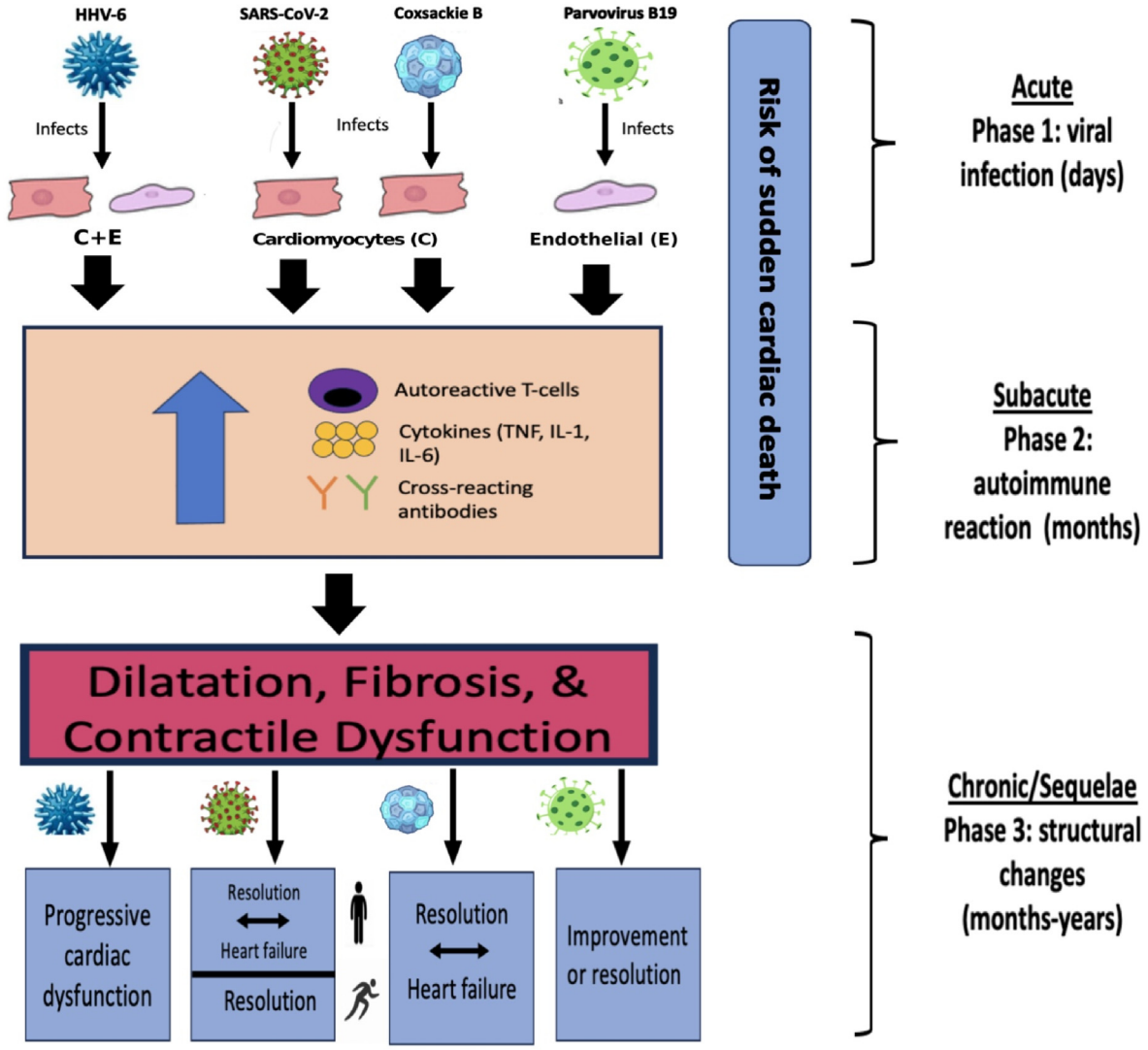

Fig. 1. Schematic summary of viral myocarditis phasic pathophysiology and clinical outcomes in selected viral pathogens.
Abbreviations: HHV-6, human herpes virus-6; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; IL-1, interleukin 1; IL-6, interleukin 6.

elevated risk of serious cardiac sequalae secondary to myocarditis.[31] Numerous studies have utilized CMR imaging to determine myocarditis prevalence in athletes, a modality which looks for myocardial edema by elevated T2 signal and myocardial injury by presence of nonischemic late gadolinium enhancement (LGE).[32] An initial study by Rajpal et al. at The Ohio State University, found that 15% of athletes with recently recovered COVID-19, from a variety of both contact and non-contact sports, had CMR findings consistent with myocarditis.[33] However, a plethora of other CMR-based studies estimate a significantly lower, but still robust, myocarditis prevalence in athletes with recent SARS-CoV-2 infection, ranging from 0.4% to 3%.[34–39]

The interplay between myocarditis and athlete susceptibility is a complex and multifactorial relationship, involving various contributing factors that are summarized in Table 1. Several studies have indicated that athletes engaged in frequent high-intensity exercise may be more susceptible to myocarditis as a potential consequence of COVID-19.[40] Further, an earlier study in 1989 reported that coxsackie B virus myocardial titers were acutely augmented by exercise and even significantly increased overall mortality in mice.[41] Recent human studies have demonstrated that athlete susceptibility to myocarditis can vary based on intensity and duration of exercise (> 6 hours[h]) of intense exercise weekly), gender, genetic factors, and sport type.[35,40] Furthermore, it is posited that elite athletes likely have increased exposure to more pathogens, as they may experience potentially impaired immune systems due to frequent travel, sleep deprivation, climate shifts, and exhaustive exertion.[42] It is suggested that elevated levels of cortisol following endurance exercise events (*e.g.*, marathon running) may be contributory to immune suppression, but the underlying mechanism remains equivocal.[42,43]

Table 1
List of the key risk factors affecting myocarditis susceptibility in athletes.

Risk Factors	Causes	References #
Impaired Immunologic Competence	Sleep deprivation, climate shifts, exhaustive exertion	Ref. 17: Halle, M. et al. *Eur J Prev Cardiol.* 2020
Age	Increased risk of cardiomyopathy comorbidity	Ref. 25: Roth, G. et al. *J Am Coll Cardiol* 2020
Endurance Sports	Exhaustive exertion/increased cortisol levels/ immunosuppression	Ref. 42: Nieman, D. *Sports Med* 2007

Myocarditis and SCD may occur in athletes from a wide variety of athletic disciplines (*e.g.*, contact sports, high-intensity endurance events,

etc). A 20-year mixed retrospective and prospective study using multiple National Collegiate Athletic Association (NCAA) databases found that basketball has the highest incidence of SCD among all NCAA Division I sports, but that football, track and field, soccer, cross country, baseball, and swimming all had at least 5 or more confirmed SCDs during 2002–2022.[44] Based on a study of 15 female college volleyball players and a study of 19 national triathletes, researchers demonstrated that intense cardiovascular training significantly decreased the total number of natural killer cells and inhibited thymic production of T cells.[45,46] These studies suggest an adverse impact of high-intensity exercise on the immune system, likely increasing risk for viral infection and subsequent myocarditis.

Further, a case report has suggested that athletes who participate in contact sports (*i.e.*, football, basketball, soccer) may be at an increased risk of myocarditis-induced SCD. This case report of two rugby players with myocarditis suggests that chest contact sports may increase the risk of rhythmic complications (*commotio cordis*) in cases of confirmed myocardial scarring.[47] Therefore, athletes participating in sports that require both extended exertional output and body contact (*i.e.*, basketball, rugby, soccer, football, etc.) may be at the greatest risk for SCD in the setting of myocarditis, though this relationship is incompletely understood with lack of robust evidence. Further understanding of the susceptibility factors in athletes may help reduce myocarditis incidence, and the targeted measures may potentially improve cardiovascular outcomes in athletes with SARS-CoV-2 infection.

4. Concerns and evidence related to physical performance and myocarditis after COVID-19 mRNA vaccination in young athletes

According to a recent review by Altman et al., COVID-19 vaccine-associated myocardial injury can be caused by inflammatory immune cell infiltrate, as well as microvascular thrombosis. Myocarditis occurs primarily with mRNA platform with an incidence of 1.9 and 3.5 per 100 000 individuals after the first 2 doses of BNT162b2 and mRNA-1273 vaccines respectively, which are higher than the myocarditis rate for influenza vaccines.[48] They also mentioned that mortality and major morbidity are less and recovery is faster with mRNA vaccine-associated myocarditis compared to COVID-19 infection, because the vaccine-associated myocarditis has a higher incidence in young adults and adolescents, with typically no adverse involvement of other organs.[48]

With circulating evidence suggesting that COVID-19 vaccination could increase the incidence of myocarditis and impair cardiovascular performance, some athletes have been hesitant to receive mRNA vaccination. A prospective cohort study by Miljoen et al. found that athletes did experience a statistically significant 2.7% decrease in maximal oxygen consumption ($\dot{V}O_{2\ max}$) 7 days after receiving BNT162b2 mRNA booster vaccinations but generally had unchanged sports participation.[49,50] Another study involving 127 Olympic and Paralympic athletes demonstrated that 70% of athletes experienced systemic side effects, but only 6% of athletes felt unable to train in the days after receiving the vaccination.[51] These studies demonstrate that athletes generally tolerate the COVID-19 mRNA vaccination with only minimal functional impairment.

To date, it was claimed by Julius et al. that no confirmed cases of COVID-19 mRNA vaccination associated cardiac complications have been reported in athletes.[50] Furthermore, according to the National Immunization Database, mRNA vaccination posed no elevated risk of myocarditis development compared to natural SARS-CoV-2 infection in individuals less than 40 years of age.[52] Whereas mRNA COVID-19 vaccination is currently considered safe for athletes to receive, more athlete vaccination data are needed to truly determine vaccine-induced short-term and long-term cardiac complication risk and to optimize vaccine regimen selection for maximal athletic performance.

5. Clinical presentations of viral myocarditis in athletes

5.1. Clinical presentations of myocarditis before COVID-19

Many viruses have been known to cause myocarditis, with potentially devastating cardiovascular sequalae, well before the onset of the COVID-19 pandemic. The most common pre-COVID viruses found in endomyocardial biopsy samples include adenoviruses, enteroviruses (*i.e.*, coxsackievirus), parvovirus B19 (PVB19), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and influenza virus.[53–57]

Clinical manifestations of acute virally induced myocarditis remain difficult to study, as asymptomatic cases preclude a more thorough investigation. However, symptomatic myocarditis presents with a wide range of symptomatology, from mild symptoms of chest pain to life threatening cardiogenic shock and ventricular arrhythmia.[58] Athletes also experience similar variability in myocarditis presentations, but some evidence suggests that they may be more likely to detect minor physiological disturbances (*e.g.*, increased heart rate at rest and during exercise) and more commonly express non-specific symptoms of fatigue and muscle soreness.[40] Despite athletes' heightened awareness to their bodily functions, nearly half of young athletes who experienced myocarditis related SCD were asymptomatic before death.[7]

Before the COVID-19 pandemic, a 2018 multicenter study ($n = 443$) showed that the most common myocarditis presentations were largely non-specific, but included chest pain (86.7%), viral prodromal symptoms (80.5%), fever (64.5%), sore throat (36.8%), and dyspnea (19.2%).[59] While chest pain may indicate further development into myocarditis, the remainder of these symptomatology likely reflect the underlying viral infectious pathogens rather than the cardiac sequalae itself. Some individuals may experience new onset or worsening symptoms of heart failure (*i.e.*, extreme dyspnea, peripheral edema, palpitations, etc.) in the absence of coronary artery disease and other known causes of heart failure; however, this is more likely in older individuals and would thus represent just a small portion of athlete presentations.[58,60]

There were slight differences between viruses in the symptom forcing patients to seek medical attention. For example, the patients with PVB19 infection are most likely to present with recurrent episodes of "infarct-like" chest pain, while patients with HHV-6 and comorbid PVB19+HHV-6 infection are most likely to present with dyspnea and edema (heart failure symptoms).[61] Patients with coxsackievirus-induced myocarditis usually presented with a standard viral prodrome, and those with human immunodeficiency virus (HIV)-related myocarditis often had palpitations/arrhythmias.[62] However, the small sample size of available studies precludes thorough investigation into more distinct viral myocarditis symptomatologic differences and how those differences may manifest differently in athletes.

5.2. Clinical presentations of myocarditis after COVID-19 pandemic onset

Clinical presentations of viral myocarditis have remained similar over time, with little variation between SARS-CoV-2 and other common viral etiologies. Since the onset of the COVID-19 pandemic, the common symptomatology has remained the same, with chest pain and other non-specific presentations occurring most commonly. COVID-19 induced myocarditis also presents with a wide spectrum of symptom severity, with some athletes remaining asymptomatic, some expressing mild symptoms of fatigue, cough, or dyspnea, and others presenting chiefly with pleuritic chest pain and extreme dyspnea.[63,64] Case reports in athletes, or otherwise healthy adults under 40 years of age, demonstrate that COVID-19 myocarditis may present with symptoms of rapid-onset fulminant heart failure.[65] The robust variability of clinical presentations and symptom severity engender significant difficulty in ascertaining a myocarditis diagnosis in the athlete.[66]

6. Important role of advanced cardiac imaging in detection of viral and non-viral myocarditis

To determine the true extent of myocarditis-related cardiovascular implications for COVID-19 in athletes, it remains critical to compare the clinical outcomes of SARS-CoV-2 myocarditis and etiologies from other viral genomes (*i.e.*, coxsackievirus, PVB19, HHV-6, CMV, EBV, influenza virus, etc.). As aforementioned, CMR imaging remains the reference standard non-invasive test for diagnosis of myocarditis, both for viral and non-viral etiologies.[67] One feature of CMR allows for detection of LGE in distinct and diagnostic patterns, offering unique multiparametric tissue characterization.[68] Clinical correlation of CMR findings allows for improved understanding of clinical outcomes in the setting of distinct, complex viral pathophysiology. Clinically correlating CMR findings and patient presentations also offers tractable prognostic capabilities.[69]

The Italian Multicenter Study on Acute Myocarditis (ITAMY) in 2017 demonstrated the prognostic role of CMR and LGE in determining clinical outcomes in acute viral myocarditis, and the importance of clinical presentation correlation. While this study did not investigate different viral genomes, it demonstrated that virally induced LGE burden was positively correlated with cardiac sequalae.[70] Specifically, a combination of an edematous clinical presentation with an elevated LGE burden on CMR were the most accurate prognostic factors for development of severe cardiovascular disease (*i.e.,* heart failure, SCD, etc.).[70] Patients with an increased or constant LGE burden 6 months after initial CMR imaging had a dramatically decreased survival probability as compared to patients with decreased LGE levels.[70]

CMR, in combination with endomyocardial biopsy, has allowed for further elucidation of myocardial damage and clinical outcomes of myocarditis caused by distinct viral genomes. While clinical outcomes from more common viral myocarditis (*e.g.*, coxsackie B virus) have been obtained from several studies and case reports, further studies were performed to examine the damage and clinical course from less common viral pathogens (*i.e.*, PVB19, HHV-6, HIV, etc.).[71–73] In 2006, Mahrholdt et al. found that distinct viral genomes infected myocardial tissue in different, characteristic patterns, highly correlated to their respective clinical outcomes.[61] Specifically, PVB19 shows LGE in the left ventricular lateral wall, HHV-6 shows LGE chiefly in the anteroseptal wall, and dual infection of PVB19 and HHV-6 demonstrates anteroseptal wall involvement plus the entire mid-wall septum.[61] CMR also demonstrated that dually infected patients had statistically elevated end diastolic volumes compared to PVB or HHV-6 alone infected patients, predicting an increased risk of adverse cardiovascular events.[61,74]

At four-month follow-up, it was found that all patients with dual PVB + HHV-6 infection had persistent LGE, and nearly 73% of these patients experienced fulminant heart failure symptomatology.[61] Of the viruses studied, PVB19 had the most benign clinical course, with all patients experiencing either complete resolution or significant improvement.[61] Patients infected with HHV-6 had a worse clinical outcome than PVB19, with only approximately 50% of patients experiencing symptom improvement/resolution despite improved LGE. Given that HHV-6 establishes a latent state in the myocardium, and can actively infect cardiac tissue, it is postulated that viral reactivation causes the persistence of unexplained heart failure symptoms, and subsequently explains the discrepancy between clinical outcome and CMR findings.[75,76] Thus, unique viral infectious properties lead to clinically significant outcome differences. Viral myocarditis (including SARS-CoV-2) clinical outcomes and CMR findings are summarized in Table 2.

7. Clinical outcomes of COVID-19 viral myocarditis in athletes and general population

In the general population, COVID-19 myocarditis portends a poor clinical outcome compared to COVID-19 patients without myocarditis. Using the National Inpatient Sample (NIS) database, Davis et al. determined that COVID-19 patients with myocarditis had significantly higher in-hospital mortality as compared to those without myocarditis (30.5% vs. 13.1%, adjusted *OR*: 3.0 [95% *CI*,2.1–4.2], $p < 0.001$), and myocarditis patients had an elevated risk of SCD and acute kidney injury requiring hemodialysis.[77]

From a cardiovascular standpoint, athletes with COVID-19 are less likely to develop cardiac sequalae than the general population. A prospective, observational, cohort study by the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) investigated intermediate duration cardiovascular outcomes of young athletes with confirmed SARS-CoV-2 infection. ORCCA, which included 4 675 athletes with confirmed recent SARS-CoV-2 infection, showed that 0.6% of the studied athletes experienced continued myocardial or myopericardial abnormalities one year after COVID-19 diagnosis.[78] Further, none of the only two athletes (0.05%) who experienced adverse cardiac events had evidence of SARS-CoV-2-induced cardiac injury.

Given the utility of CMR in prognostication, a meta-analysis in 2021 examined CMR findings in both athletes and non-athletes. The aggregate prevalence of CMR abnormalities and myocarditis was significantly higher in non-athletes than in athletes (62.5% versus 17.1% and 23.9% versus 2.5%, respectively).[79,80] Based on prior systematic reviews, it remains likely that these differences are due to the higher prevalence of comorbidities in non-athletes compared to athletes.[81] Thus, when comparing athletes to non-athletes with SARS-CoV-2 induced myocarditis, athletes have significantly less adverse cardiovascular events with better prognosis.

8. Summary and future perspective

To summarize, myocarditis is an inflammatory process of the cardiac myocytes that can lead to potentially devastating cardiac sequalae in

Table 2
Summary of clinical and cardiac magnetic resonance findings on viral myocarditis.

Virus	Main Target Cells	Clinical Outcomes	Presenting Symptoms	CMR Findings
PVB19	Endothelial	Significant improvement/resolution	Episodic, "infarct-like" chest pain	LGE: Lateral left ventricular wall
HHV-6	Endothelial cells + cardiac tissue	Improvement in some, but not all cases; viral persistence → progressive cardiac dysfunction	Dyspnea	LGE: Anteroseptal wall
PVB + HHV-6	Endothelial cells + cardiac tissue	Fulminant heart failure in most	Dyspnea + edema	LGE: Anteroseptal wall + entire mid-wall septum
Coxsackie B virus	Cardiomyocytes	Resolution to fulminant heart failure	Viral prodrome, non-specific	Non-specific LGE pattern
HIV	Dendritic cells, macrophages, osteoclasts	Increased susceptibility to arrhythmias	Palpitations, chest pain	Not studied
SARS-CoV-2 (general population) SARS-CoV-2 (athletes)	Cardiomyocytes	Resolution to fulminant heart failure Complete resolution	Viral prodrome, non-specific/chest pain Muscle soreness	Non-specific LGE pattern

Abbreviations: HHV-6, human herpes virus-6; HIV, human immunodeficiency virus; LGE, late gadolinium enhancement; PVB19, Parvovirus B19; PVB + HHV-6, dual parvovirus B19 and human herpes virus-6 infection; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

affected individuals. While athletes remain susceptible to COVID-19-induced viral myocarditis due to multifactorial reasons such as travel exposure, sleep deprivation, and exhaustive exercise-induced immune suppression, they experience fewer cardiac abnormalities and sequalae than the general population, because athletes are usually younger and have less co-morbidity. Further, population studies have demonstrated that symptomatology, clinical outcomes, and precise cardiac involvement vary widely between different viral genomes. In this review, special consideration was given to SARS-CoV-2, a virus that targets the cardiomyocytes and vasculatures specifically and can present with more cardiovascular symptomatology for athletes.

While myocarditis remains difficult to detect in athletes, with nearly half of the cases arising from asymptomatic patients, utilization of CMR and cardiac biomarkers (not discussed in this review) can help prognosticate clinical outcomes. This review also addressed the low prevalence of myocarditis in athletes and the exceedingly rare possibility of SCD or permanent cardiovascular sequalae secondary to natural SARS-CoV-2 infection and mRNA COVID-19 vaccination in athletes.

Although myocarditis is rare in the athlete, there is ongoing discussion about return-to-play (RTP) considerations and guidelines for athletes with recent COVID-19 infection to prevent adverse cardiac sequalae. A recent study including more than 600 athletes with recent COVID-19 infection found that the majority of athletes (82%) were cleared to RTP without further investigation, with only 8% requiring temporary training restriction.[82] Current recommendations for athletes and highly active persons with suspected or confirmed COVID-19 suggest a graded return to exercise at least 7 days after viral symptom resolution.[83] However, for any case of proven myocarditis, the current American Heart Association (AHA)/American College of Cardiology (ACC) recommendation is a strict ban on high-intensity exercise for a period of at least 3–6 months along with further evaluation with resting echocardiogram, 24-h Holter monitoring, and exercise electrocardiogram (ECG).[84] The AHA/ACC also recommends that athletes only resume training, if 1) ventricular systolic function is in normal range, 2) serum markers of myocardial injury, inflammation, and heart failure have normalized, and 3) no clinically relevant arrhythmias are appreciated on Holter/exercise ECG. While there is no definitive recommendation requiring resolution of LGE for RTP, athletes with probable or definite myocarditis should not participate in competitive sports while active inflammation is present.[84]

Given the heterogeneity of myocarditis presentation and recovery timelines, many are advocating for abandonment of a one-size fits all guideline with a more individualized approach to determining RTP recommendations.[85,86] These advocates suggest greater emphasis of CMR for RTP guidelines, and they propose that the absence of scar, ventricular arrhythmias, and left ventricular dysfunction could be sufficient to enable RTP prior to 3 months.[86] Further investigation into the true prevalence of COVID-19 myocarditis in athletes, and the respective sequelae of viral and non-viral (*e.g.* mRNA vaccines) causes, may engender more precise and individualized RTP guidelines. Continued optimization of RTP guidelines remains critically important in helping to prevent adverse cardiovascular events in athletes.

Submission statement

All authors have read and agree with manuscript content. While this manuscript is being reviewed for this journal, the manuscript will not be submitted elsewhere for review and publication.

Conflict of interest

Lei Xi is an editorial board member of Sports Medicine and Health Science and was not involved in the editorial review or the decision to publish this article.The authors declare no conflict of interests in writing this review.

Authors' contribution

Jonathan Van Name: Writing – review & editing, Writing – original draft, Conceptualization. **Kainuo Wu:** Writing – review & editing. **Lei Xi:** Writing – review & editing, Supervision, Conceptualization.

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