Myocarditis in children 2024, new themes and continued questions

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Purpose of review
While pediatric myocarditis incidence has increased since the coronavirus disease 2019 (COVID-19) pandemic, there remain questions regarding diagnosis, risk stratification, and optimal therapy. This review highlights recent publications and continued unanswered questions related to myocarditis in children.

Recent findings
Emergence from the COVID-19 era has allowed more accurate description of the incidence and prognosis of myocarditis adjacent to COVID-19 infection and vaccine administration as well that of multi-system inflammatory disease in children (MIS-C). As cardiac magnetic resonance technology has shown increased availability and evidence in pediatric myocarditis, it is important to understand conclusions from adult imaging studies and define the use of this imaging biomarker in children. Precision medicine has begun to allow real-time molecular evaluations to help diagnose and risk-stratify cardiovascular diseases, with emerging evidence of these modalities in myocarditis.

Summary
Recent information regarding COVID-19 associated myocarditis, cardiac magnetic resonance, and molecular biomarkers may help clinicians caring for children with myocarditis and identify needs for future investigations.

Keywords
cardiac magnetic resonance, coronavirus disease 2019, molecular biomarkers, myocarditis, pediatrics

INTRODUCTION

Each year, 1 to 2 children per 100 000 are hospitalized for myocarditis [1,2]. Despite substantial research into the molecular and myocardial pathophysiology of this condition, there remain many questions regarding the care of children with this diagnosis, including optimal treatment strategies and indicators of long-term prognosis. Since 2020, myocarditis incidence has increased in relation to the coronavirus disease 2019 (COVID-19) pandemic, raising continued questions about the diagnosis, treatment, and prognosis of the disease. The most recent developments in pediatric myocarditis include knowledge gained from COVID-19 viral- and vaccine-adjacent myocarditis, which may have disparate pathophysiology and outcomes compared to other inflammatory etiologies; the increasing availability of cardiac magnetic resonance (CMR) imaging and its impact on diagnosis and prognosis; and novel data on molecular biomarkers of myocarditis, including genetic variants and microRNAs. This review describes recent publications in these areas and their knowledge impact on the etiology, diagnosis, and prognosis of pediatric myocarditis.

CURRENT LANDSCAPE OF PEDIATRIC MYOCARDITIS

Myocarditis, defined as inflammation of the myocardium, is most commonly the result of a viral immune response, but it can result from any inflammatory process, including exposure to medications/immunizations and rheumatologic conditions. Prior to 2020 and the onset of the COVID-19 pandemic, the most commonly implicated pathogens in myocarditis included the adenoviruses, enteroviruses, and parvoviruses, which have been greatly surpassed in the current era by myocarditis

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KEY POINTS

- The incidence of pediatric myocarditis increased significantly between 2020 and 2023, temporally related to the coronavirus disease 2019 (COVID-19) pandemic.
- Most children with myocarditis associated with COVID-19 infection or vaccine do not have lasting myocardial dysfunction or heart failure, but many persist with late gadolinium enhancement on cardiac MRI.
- Diagnosis of pediatric myocarditis via cardiac MRI continues to evolve, with multiple sequence abnormalities associated with myocardial edema, injury, and fibrosis, consistent with those described within the adult Lake Louise Criteria.
- Genomic biomarkers, including gene variants and microRNA expression, have shown increasing prognostic value in pediatric myocarditis.
- There remain many unanswered questions in pediatric myocarditis, including risk stratification of children with persistent late gadolinium enhancement as well as efficacy of anti-inflammatory therapies.

associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or vaccination [3,4▪▪]. Children suspected to have myocarditis may present with symptoms including tachycardia, chest pain, fever, and dyspnea; biomarker abnormalities including troponin and C-reactive protein; electrocardiographic abnormalities such as ST segment elevations, atrioventricular conduction delay, and/or arrhythmias; and, potentially, evidence of myocardial dysfunction or symptomatic heart failure) [5]. As endomyocardial biopsy (EMB) is less frequently used to diagnose myocarditis, these clinical findings are used to diagnose 'suspected/possible' myocarditis, and CMR is often used (rather than EMB) for diagnosis confirmation [5].

Despite intravenous immune globulin (IVIg) and steroids not being shown to improve survival in myocarditis, these medications are frequently given to patients with myocarditis, more commonly among those meeting CMR diagnostic criteria and/or having systolic dysfunction [6–9]. Targeted therapies are also considered for viral etiologies as well as myocarditis related to rheumatologic disorders such as systemic lupus erythematosus (SLE) [10–12]. Risk factors for acute fulminant myocarditis (defined as those with acute hemodynamic deterioration) include depressed left ventricular ejection fraction, ventricular arrhythmia, end-organ dysfunction, and marked elevation of brain-type natriuretic peptides at presentation [6,13–15]. The 2015 Task Force 3 guidelines set recommendations for return to sports participation, with favorable evaluations at 3–6 months postevent including normalized cardiac function, injury/inflammatory markers, Holter monitor, and exercise stress testing [16]. Among patients hospitalized for myocarditis, 3–11% require mechanical circulatory support (MCS) or die during initial hospitalization, with as many as 40% of myocarditis patients dying or requiring heart transplantation within 10 years of diagnosis, related to a phenotype of chronic myocarditis and/or dilated cardiomyopathy [2,6,17,18]. However, adverse event rates for children treated for myocarditis in the current era are likely lower given more frequent troponin evaluation in children, identifying many with mild, self-resolving disease.

CORONAVIRUS DISEASE 2019 AND MYOCARDITIS

Coronavirus disease 2019 myocarditis and coronavirus disease 2019 vaccine-adjacent myocarditis

In early 2020, reports of myocarditis during SARS-CoV-2 infection emerged, with the first U.S. pediatric report in April 2020 describing a 12-year-old COVID-19 positive female who presented with evidence of elevated troponin, severely depressed systolic function with heart failure, and complete heart block [19]. This patient had a complete recovery within 10 days of hospitalization after administration of inotropes, mechanical ventilation, and IVIg. As increasing associations emerged between COVID-19 and myocarditis, US population-based data from 2020 and 2021 were analyzed finding an increase in myocarditis rates from 1 to 10 cases per 100 000 to 150 to 4000 cases per 100 000, children with COVID-19 having a nearly 40-fold increased risk of developing myocarditis than those without COVID-19, and the highest overall rates of COVID-19 myocarditis being found in children (<16 years) and older adults (>50 years) [4▪▪,20–22]. Adult data show a 19% incidence of cardiogenic shock and 6% incidence of MCS use in COVID-19 associated myocarditis [23▪]. Large-scale outcome data in children, however, remain unpublished, with clinical experience suggesting a high likelihood of resolution, even among the case reports of those requiring MCS [24–26].

Later in 2020 and into 2021, vaccine adverse event data reported myocarditis after COVID-19 vaccination, with rates ranging from 2 to 15 cases per 100 000 doses, particularly in adolescent males and after the second vaccination dose (Fig. 1a) [27▪,28]. As compared to historical expected incidence, myocarditis incidence among adolescent males after receipt of the second dose increased as high as 14-fold [29].

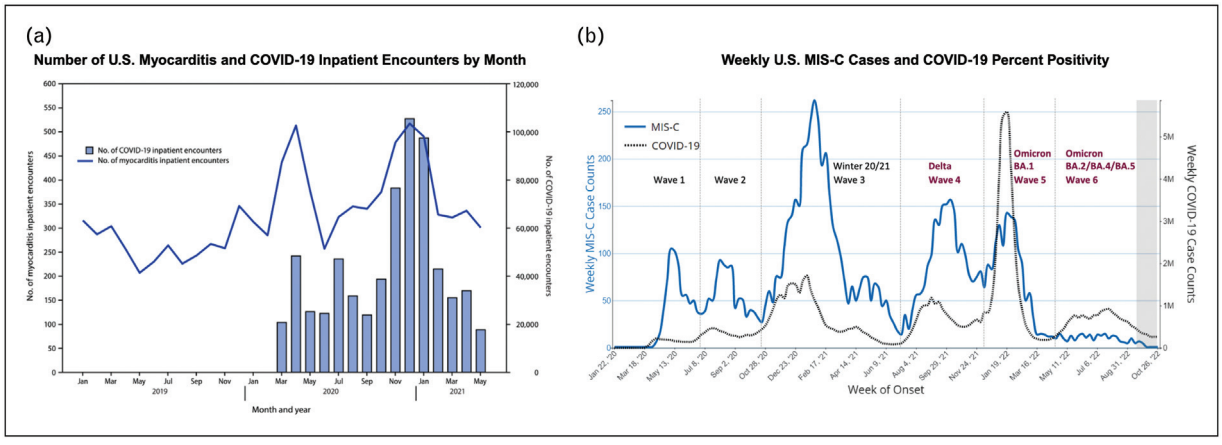

FIGURE 1. COVID-19 infection, myocarditis, and multi-system inflammatory disease in children (MIS-C). (a) Adult and pediatric COVID-19 hospitalizations peaked in early 2020 and 2021 with concurrent increases in myocarditis hospitalizations (source: Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report [20]); (B) MIS-C cases peaked throughout multiple COVID-19 variant waves, with rare MIS-C cases in late 2022 (source: Centers for Disease Control and Prevention, Updates on Multisystem Inflammatory Syndrome in Children [77]).

Large studies of vaccine-adjacent myocarditis reveal rare/mild evidence of cardiac dysfunction, with 14–20% of patients having mild left ventricular dysfunction, 0–1% having moderate to severe left ventricular dysfunction, and rare incidence of cardiogenic shock or MCS [23▪,30▪▪,31▪]. Multiple proposed mechanisms of myocarditis associated with COVID-19 infection or vaccination have been proposed, without a complete understanding of pathogenesis. These include high viral replication in the lungs with significant release of cytokines and autoantibodies affecting myocardial cells, as well as multiple receptor types on cardiomyocytes and endothelial cells permissive of SARS-CoV-2, including angiotensin-converting-enzyme 2 (ACE2) and transmembrane serine protease-2 (TMPRSS2) receptors [32]. The male predominance (approximately 60%) of COVID-19 overall and of infection- and vaccine-adjacent myocarditis is thought related both to circulating androgens in males affording a greater immune and inflammatory response and to higher expression of ACE2 receptors in males [33]. Treatment strategies for myocarditis associated with COVID-19 infection and vaccination have remained similar to that of non-COVID inflammatory/viral myocarditis, with guideline-directed heart failure management, consideration of immunosuppressive medications, CMR evaluation, and temporary restriction from athletic activity [34▪,35▪▪]. Despite near-universal resolution of cardiac dysfunction, vaccine-adjacent myocarditis has high rates of persistent myocardial injury defined by late gadolinium enhancement (LGE) among those evaluated with CMR [36,37]. Ongoing long-term evaluations of COVID-19 infection and vaccine-adjacent myocarditis may help determine long-term cardiovascular risk for these patients.

Myocarditis in multisystem inflammatory disease in children

Subsequent to the discovery of COVID-19 myocarditis was the mid-2020 recognition of multi-system inflammatory disease in children (MIS-C) as a hyperinflammatory syndrome with multiorgan dysfunction, occurring in ~1% of children (mean age 9-years-old) 3–6 weeks after COVID-19 infection or exposure and disproportionately affecting African American and Hispanic children [38,39]. Those diagnosed with MIS-C frequently had concomitant cardiovascular abnormalities, including shock (44%), pericardial effusion (22%), and coronary abnormalities (20%) [40,41]. Regarding incidence of myocarditis in MIS-C, rates depend upon myocarditis definition, ranging from 18% (by CMR criteria) to 60% (by elevation of troponin and/or natriuretic peptides) to 27–66% (by left ventricular dysfunction) [40,42,43]. An evaluation of 518 patients hospitalized with MIS-C across the US found that 47% required vasopressors, 3% required ECMO, and 2% died [44]. Despite significant short-term cardiovascular risk, there has been rare persistence of significant cardiac sequelae after MIS-C resolution [45▪,46▪,47]. The highest rates of MIS-C cases were observed during peaks of high COVID-19 incidence (January 2021 through January 2022); since that time however, MIS-C has remained infrequent (Fig. 1b) [48]. As longer term follow-up continues to be reported in children diagnosed with COVID-associated myocarditis, there will be much

to learn about its potential lasting cardiovascular effects.

CARDIAC MAGNETIC RESONANCE IMAGING

Myocarditis diagnosis

The initial 2009 and updated 2018 Lake Louise Criteria (LLC) provide a CMR-based diagnostic standard for identifying myocardial edema and non-ischemic myocardial injury in myocarditis. The updated Lake Louise Criteria require both T1 abnormalities [including LGE, native T1 mapping, and extracellular volume (ECV) mapping] and T2 abnormalities (T2-weighted imaging or T2 mapping) in order to diagnose myocarditis (Fig. 2) [49]. The 2022 Society of Cardiac Magnetic Resonance (SCMR) pediatric CMR consensus statement describes the increased use and goals of CMR in pediatric myocarditis [50,51▪▪]. Although the original LLC may have a poor yield for diagnosis of pediatric myocarditis, use of parametric mapping as recommended by the modified LLC may improve the diagnostic capability of CMR in pediatrics and is increasingly being evaluated by pediatric centers [52]. Beyond application of myocarditis diagnostic criteria, information provided by CMR can help identify the location, quantity, and extent of LGE, which has been linked to mortality in multiple adult myocarditis studies [53,54]. While LGE likely helps clinicians to understand disease severity and recovery potential after pediatric myocarditis, LGE presence has not been conclusively associated with mortality or other adverse outcomes in pediatric studies [55].

Myocarditis follow-up imaging

In addition to CMR imaging aiding in initial myocarditis diagnosis, follow-up CMR evaluations can provide myocardial characterization not visualized by serial echocardiograms. In the outpatient setting, repeat CMR months to years after initial myocarditis diagnosis can identify those patients with chronic myocarditis as having persistence of LGE (indicating transition from acute inflammatory to chronic fibrotic lesions), decreased left ventricular ejection fraction, and left ventricular dilation upon follow-up [55,56]. Despite the association between LGE and sudden cardiac death in adults, there is little guidance on resumption of sports with persistent LGE. In these settings, patients with reassuring cardiac function, injury/inflammatory markers, Holter, and stress test evaluations often enter a shared decision-making model with the understanding that sports participation may be safe, despite residual risk of cardiac events.

Cardiac magnetic resonance in coronavirus disease 2019 associated myocarditis

Given the significant incidence of COVID-19 infection and vaccine-adjacent myocarditis, there have been multiple evaluations of CMR differences between these and non-COVID myocarditis etiologies. In an adult study of over 500 patients with myocarditis-associated LGE in the presence and absence of COVID-19, the COVID-19 patients had a lower quantity of LGE and less frequent evidence of left ventricular dilation and dysfunction than those with non-COVID myocarditis; this is in contrast to high rates (as high as 76–88%) of LGE in vaccine-adjacent myocarditis [36,37,57]. The long-term sequelae related to CMR-defined myocardial injury in pediatric myocarditis will require continued surveillance and evaluation.

Emerging imaging modalities

Deformational (strain) imaging has been evaluated in multiple pediatric applications, including myocarditis. Recent adult studies have shown correlation between myocarditis diagnosis and echocardiographic global and segmental myocardial strain abnormalities, which gives promise to the possibility of echocardiographic diagnosis and follow-up of myocarditis [58▪,59]. Strain evaluation by CMR has also shown diagnostic value in myocarditis and may help improve future diagnostic criteria for pediatric myocarditis [60▪▪,61]. Additionally, positron emission tomography (PET) of increased myocardial metabolic activity has been used to evaluate myocarditis, with suggestion that this technology may provide improved prognostic ability in follow-up evaluations as well as significant utility in myocarditis mediated by systemic inflammatory or rheumatologic disorders [62,63]. These modalities have had limited evaluation in pediatric myocarditis, with investigations needed to determine multimodality cardiac imaging techniques to improve diagnosis and risk-stratification of pediatric myocarditis.

BIOMARKERS OF MYOCARDITIS

Troponin

Based on CDC guidance, troponin elevation is an integral part of the diagnosis of myocarditis and may also be used to chart clinical improvement [64]. However, it has remained unclear in children whether troponin values correlate with CMR evidence of myocardial injury or adverse outcomes [65,66▪]. Recent data, including children and adults with COVID-19 infection and vaccine-associated myocarditis have shown that higher troponin levels

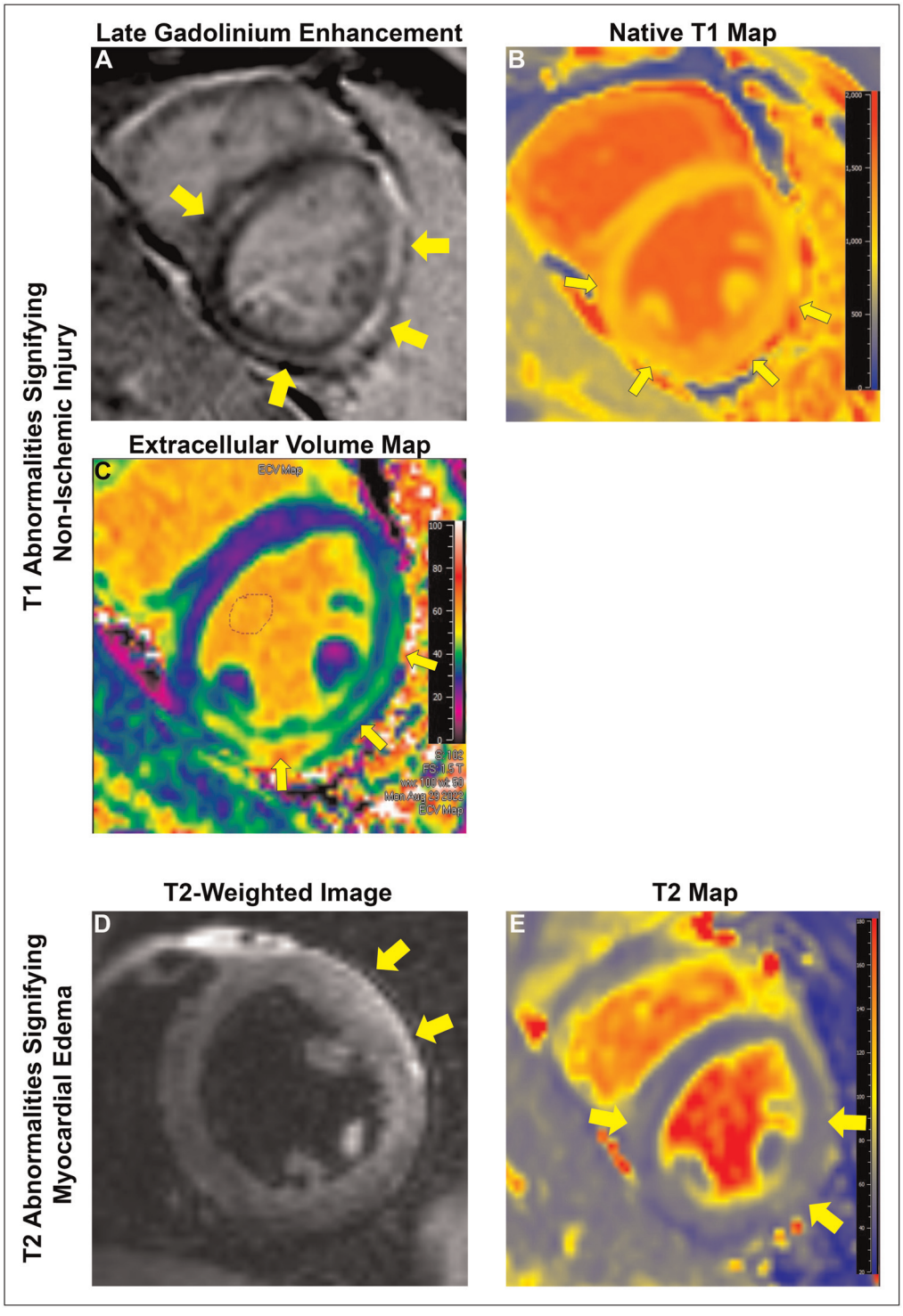

FIGURE 2. Cardiac magnetic resonance (CMR) images in the short axis from patients with myocarditis revealing abnormalities in T1 (nonischemic injury) and T2 (myocardial edema), as required by the updated Lake Louise Criteria for diagnosis of myocarditis. (a) Late gadolinium enhancement (LGE) in the subepicardium of the free wall and inferoseptal segment (arrows); (b) native T1 map, and (c) ECV map in the same patient with high T1 and ECV in a similar pattern to the LGE (arrows); (d) T2-weighted image in a different patient demonstrating myocardial edema in the anterolateral segment (arrows); (e) T2 mapping (same patient from Fig. 1a–c) with high T2 times consistent with edema in the free wall and inferoseptal segment (arrows).

on admission correlate with persistence of myocardial injury on CMR [67▪]. Given increased awareness of myocarditis in the COVID-19 era, troponin evaluation is frequently obtained in children with chest pain or other cardiac symptoms, which has resulted in hospitalization of many children with mild troponin elevation that previously may not have been diagnosed with myocarditis. This is likely exacerbated by the shift in many US hospitals from low- to high-sensitivity troponin assays, which have been validated in adult coronary syndromes but not in pediatric applications. There is much to be learned about the prognostic value of troponin elevation (both at any and at very high concentrations) towards clinically significant myocarditis.

Emerging molecular biomarkers

The future of biomarker evaluations will likely include testing for both specific gene variants as well as markers of gene expression patterns associated with cardiomyopathy pathogenicity. As rapid 'cardiomyopathy panel' genetic evaluations have become increasingly available, the identification of known cardiomyopathy variants may help determine the diagnosis and prognosis of myocarditis in the clinical setting. In an evaluation by Seidel *et al.* [68] of dilated cardiomyopathy-associated variants in children with biopsy-proven myocarditis, those with heart failure syndromes were more likely to have such variants (including known titin, lamin, and troponin pathogenic variants) compared to those without heart failure. Another study by Ammirati *et al.* [69▪] described the association between presence of desmosomal gene variants (including desmoplakin and plakophilin mutations implicated in arrhythmogenic cardiomyopathy) in myocarditis patients and a higher likelihood of death or ventricular tachycardia/fibrillation compared to those without such variants. Whether the identification of underlying genetic abnormality signals the presence of an underlying cardiomyopathy or a susceptibility to inflammatory myocarditis with adverse outcomes remains to be fully understood.

Additionally, transcriptional signals, such as microRNAs (noncoding RNA molecules that can regulate gene expression) may help evaluate severity of disease in myocarditis, as has been identified in the association of specific miRNAs with either recovery or deterioration in pediatric and adult dilated cardiomyopathy [70]. A 2021 *New England Journal of Medicine* article described a specific microRNA (hsa-miR-Chr8 : 96) that independently identified myocarditis in four separate patient cohorts [71]. The continued study of microRNAs in preclinical human studies and animal studies has identified microRNAs associated with both disease progression and myocardial recovery in myocarditis [72,73]. There are multiple microRNAs implicated in pediatric and adult dilated cardiomyopathy and heart transplant rejection, which can be further evaluated in myocarditis [70,74,75]. In addition to microRNA diagnostic evaluation, there are ongoing trials of microRNA therapy to mitigate inflammation in myocarditis [76]. As the molecular era of medicine continues to evolve, genomic biomarkers and therapies may aid in the care of children with myocarditis.

CONCLUSION

Since 2020, clinicians have encountered higher numbers of patients presenting with myocarditis. Recent studies have evaluated the increased prevalence and implications of COVID-19 associated myocarditis, the use of CMR to diagnose and risk-stratify pediatric myocarditis patients, as well as the prognostic value of molecular biomarkers. Despite advanced diagnostic modalities, there remains a lack of evidence for risk stratification and treatment of pediatric patients with myocarditis, especially those with preserved cardiac function where treatment and prognosis remain unclear. Ultimately, the field requires large, multicenter, collaborative pediatric studies evaluating differences in long-term outcomes in COVID-19 vs. non-COVID-19 myocarditis, prognostic implications of CMR abnormalities in myocarditis, evaluations of molecular biomarkers in predicting disease severity, effects of anti-inflammatory therapies (such as IVIG, corticosteroids, and biologic agents), and updated guidance regarding the safe return to sports participation.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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