Cardiol Ther (2022) 11:185–201
https://doi.org/10.1007/s40119-022-00256-8

REVIEW

Imaging Findings in Pediatric COVID-19: A Review of Current Literature

Tyler A. Fick · Clifford L. Cua · Simon Lee

Received: December 15, 2021 / Published online: March 2, 2022

ABSTRACT

The recent COVID-19 pandemic has afflicted over 200 million individuals to date, with many different organ systems involved. The pediatric involvement has been variable, but of note is the risk of cardiac disease in pediatric COVID-19 patients. We review here the cardiac involvement in pediatric patients with COVID-19. Several studies highlight a possible cardiotropic nature of SARS-CoV-2, and describe the disease severity in myocarditis, both symptomatic and occult, as well as MIS-C. We describe the expected clinical course of these patients and note the lack of long-term follow-up data and the concerning prevalence of continued abnormal findings on follow-up imaging. With this paucity of long-term cardiac data, we recommend consideration of advanced imaging for pediatric patients with cardiac symptoms and/or elevation of cardiac serum biomarkers.

Keywords: Coronavirus; COVID-19; Myocarditis; MIS-C

Key Summary Points

Several studies have described direct SARS-CoV-2 myocardial infection, raising the possibility of direct cardiotropic nature of COVID-19 in some patients.

Abnormal CMR findings have been reported in up to 33% of pediatric MIS-C patients.

Up to 14% of pediatric patients continue to have abnormal CMR at follow-up.

The clinical implications of these residual abnormal features is yet unknown, highlighting the importance of continued long-term follow-up.

BACKGROUND

The novel coronavirus strain spreading throughout the world is a single-stranded positive-sense RNA virus termed SARS-CoV-2, which

T. A. Fick · C. L. Cua · S. Lee (✉)
The Heart Center, Nationwide Children's Hospital, Columbus, OH, USA
e-mail: simon.lee@nationwidechildrens.org

is the virus responsible for COVID-19. The namesake of the coronavirus is the spike protein capsid surrounding the virus [1]. Spike protein binds to the ACE2-receptor along respiratory epithelial cells, among others, facilitating entry into the cell [2]. The COVID-19 outbreak began with a cluster of patients with pneumonia where a viral source was linked back to a wholesale seafood market in Wuhan, China [3]. As the first wave of the pandemic rippled across the United States, much of its morbidity and mortality was focused on the hospitalized adult patient. The pediatric patient was thought to be spared from severe effects of COVID-19, with what appeared to be fewer total cases and less severity of pediatric disease in comparison to adult populations [4–10]. Unfortunately, this observation proved premature as the emergence of new disease entities such as multisystem inflammatory syndrome in children [11] showed that children were not spared from the ill effects of SARS-CoV-2. The emergence of other variants continues to expand the broad reach of COVID-19's effects on the population [12, 13].

SARS-COV-2 and the Myocardium

The cardiovascular system is one of the organ systems that appears to be particularly affected by SARS-CoV-2. The direct mechanism of cardiac involvement is unclear, but there have been several proposed mechanisms. Some involve a cytokine storm phenomenon that leads to subsequent cardiac involvement similar to Kawasaki disease [14, 15]. Another theory posits that spike protein, via the ACE2-receptor binding domain found in alveolar lung tissue and myocardial tissue [16], binds to cardiomyocytes in a similar fashion as has been seen for SARS-CoV-1 [17]. Oudit and colleagues demonstrated myocardial susceptibility when they demonstrated 35% of heart biopsy specimens collected from the 2009 SARS-CoV-1 outbreak carried the SARS-CoV-1 genome [17]. Recent studies have produced similar results, with 62% of cardiac biopsy specimens documenting SARS-CoV-2 viral load and nearly half of these having what was classified as high viral copy numbers [18]. In the study by Lindner et al., myocardial involvement was found without markers of fulminant myocarditis [18]. This feature may speak to the cardiotropic effects of SARS-CoV-2 separate from a fulminant myocarditis-type effect that has been previously described [19]. Baily et al. describe cardiomyocyte infection in an engineered heart tissue model, resulting in intracellular cytokine production, sarcomere disassembly, contractile deficits, and cell death [20]. Further work will be needed to delineate the exact mechanism, and whether different mechanisms are correlated to different disease phenotypes within COVID-19. The verdict is still out on whether ACE-2 is a feature of proposed cardiotropic effect of SARS-CoV-2, with some studies supporting direct involvement of ACE-2 [21, 22] and some via a secondary downstream change [16]. Additionally, future studies will need to focus on factors such as patient-specific genomics and how these may affect susceptibility to different disease states within COVID-19.

Non-Invasive Imaging Findings with COVID-19

The main cardiac imaging modalities utilized are transthoracic echocardiography (TTE) and cardiac MRI (CMR). TTE offers the advantages of being widely available, portable, requiring a shorter scan time, and providing a good evaluation of myocardial and valvar function. Several studies have noted variable findings by TTE in COVID-19 patients. Stobe et al. demonstrated that a cohort of COVID-19 patients demonstrated abnormal left ventricular echocardiographic strain in the basal segments [23]. Seventy-one percent of their cohort demonstrated abnormal strain parameters, despite normal left ventricular ejection fraction. However, while TTE is often the first-line cardiac imaging modality for a variety of disease processes, its main limitation is its inability to assess for changes in the myocardial tissue.

The evidence of the cardiotropic nature of SARS-CoV-2 requires accurate assessment of myocardial involvement in COVID-19 patients and this is where CMR plays a key role.

Evaluation of the myocardium requires great equipoise between the invasiveness of testing and diagnostic accuracy, particularly in the pediatric patient. While endomyocardial biopsy is considered the reference standard for myocardial tissue characterization, innovations in CMR (including new sequences and rapid acquisition techniques) coupled with experience and expertise have brought non-invasive evaluation to the forefront. The recent AHA Scientific Statement on Pediatric Myocarditis is a prime example of the prominent role that CMR plays in evaluating the myocardium, elevating CMR findings close to the reference standard of endomyocardial biopsy [24]. These recommendations mirror the current clinical practice of shifting away from endomyocardial biopsy to less-invasive diagnostics. This recommendation is supported by the myriad of literature demonstrating accuracy of tissue characterization by CMR. Ferreira and colleagues provided an update to the previous standard CMR guidelines known as the Lake Louise Criteria (LLC), describing tissue characteristics of patients with nonischemic myocardial inflammation [24]. Briefly, myocardial inflammation alters the T1 and T2 relaxation times of the myocardium measured by CMR imaging compared to normal reference T1 and T2 values for the myocardium (Fig. 1). When inflammation leads to myocyte injury, this feature manifests as late gadolinium enhancement (LGE), one of the keystones for myocardial tissue characterization by CMR [25]. Late gadolinium enhancement is the reference standard for myocardial viability assessment and is one of the most widely utilized CMR techniques. These features combined are indicative of myocardial edema and necrosis [26].

Given this and other studies highlighting the benefit of non-invasive imaging, current guidelines state that CMR carries the same class 1 indication as endomyocardial biopsy for the diagnosis of myocarditis [24]. Several studies have utilized CMR for myocardial evaluation in the COVID-19 patient and demonstrated important findings within the myocardium after SARS-CoV-2 infection. We review some of the important evidence of cardiac involvement of patients suffering from COVID-19 and seek to highlight the different non-invasive imaging findings within different subsets of this cardiac involvement. We will also call to attention areas in the literature that require further studies, as we all continue to rapidly learn different

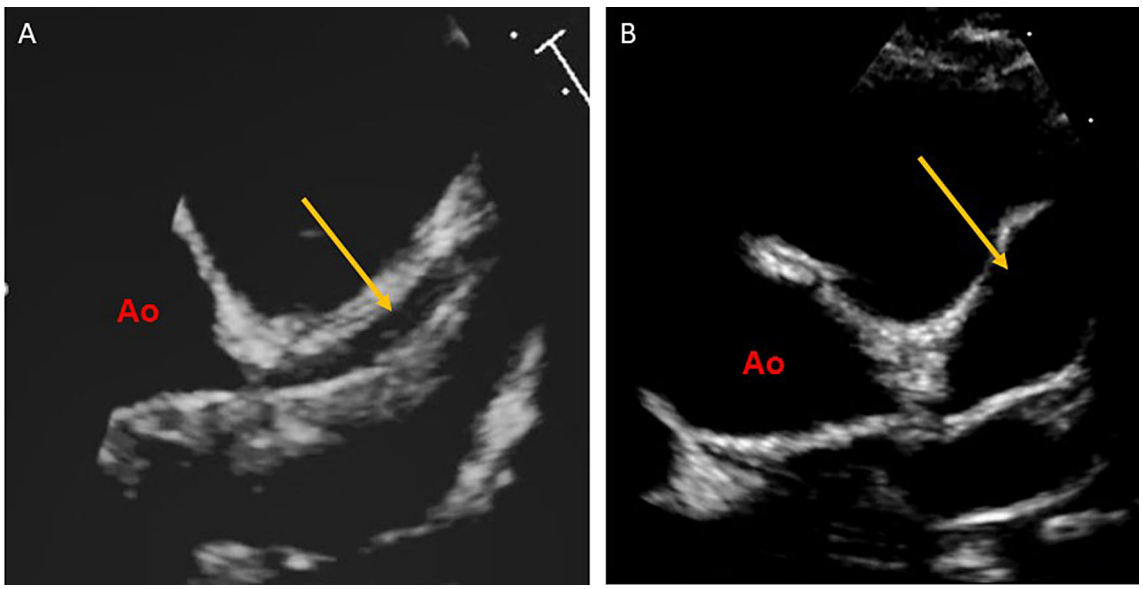

Fig. 1 2D Transthoracic echocardiographic images in the parasternal short axis demonstrating coronary abnormalities seen in MIS-C. **A** Mild coronary ectasia of LAD (*arrow*). **B** Giant aneurysm in the left anterior descending (*arrow*)

features of this new disease. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

MYOCARDITIS

Patients with COVID-19 myocarditis can present with many different cardiac findings, and many will describe chest pain and palpitations along with the common symptomatology associated with COVID-19 infection. As previously discussed, COVID-19 myocarditis is diagnosed by CMR using modified-LLC criteria, where abnormalities in T1 and T2 relaxation time are seen and caused by myocardial edema and necrosis. Patients with COVID-19 myocarditis may have echocardiographic changes such as decreased left ventricular ejection fraction, segmental hypokinesia, and pericardial effusions [27–29]. Elevated cardiac biomarkers such as troponin can be seen in up to 45% of hospitalized COVID-19 patients [30–32].

Imaging Findings in Adults with COVID-19

Several studies have highlighted that patients presenting with elevated serum cardiac biomarkers are more likely to have findings consistent with myocarditis as defined as myocardial edema or other features of positive T2 criterion, which is the most common finding in the COVID-19 myocarditis patient, in addition to at least one T1-based criterion [33, 34]. Chen and colleagues describe a 25-patient cohort of adults who had CMR performed in the acute phase (defined in their study as 3–8 days after diagnosis) of COVID-19 infection. Patients with at least one marker of cardiac involvement had significantly elevated T1 relaxation time, extracellular volume, T2 mapping, and LGE in addition to worse global longitudinal strain [34]. Importantly, these findings were significantly increased compared to healthy controls, irrespective of troponin values. The average age in this study was 23 years old, highlighting the lack of protection for the young adult patient against cardiac involvement.

Cases of cardiac involvement harbor a poor prognostic factor in the adult population [27, 28, 31, 35–37], and the prevalence of cardiac involvement has been on the rise. The odds of myocarditis diagnosis has been found to be 16 times greater for those with COVID-19 than those without COVID [38]. In a large study of hospitalized COVID-19 adults, those with cardiac injury had a 59% incidence of acute respiratory distress syndrome (ARDS) and a 51% mortality rate, compared to 15% and 5%, respectively, in those without cardiac injury [39].

Imaging Findings in Collegiate Athletes with COVID-19

Due to the concern for SARS-CoV-2 having a predilection for affecting the myocardium and the risk of exercise precipitating arrhythmias [40], a subset of COVID-19 patients that has encountered specific controversy is the asymptomatic or minimally symptomatic competitive athlete recovering from COVID-19. There is great uncertainty surrounding how to screen these patients for disease, how to determine cardiac involvement, and how to counsel these athletes regarding return to sporting activity. This involvement has extended all the way to the professional level [41]. Expert recommendations, as early as fall 2020, have recommended a tiered approach with clinical symptoms, serum biomarkers, and electrocardiogram (ECG)/echocardiographic assessment to guide which patients warrant further imaging via CMR [40–42].

Daniels and colleagues report on a large cohort of collegiate athletes from the Big Ten Conference undergoing screening after SARS-CoV-2 infection. While there was some variation in screening strategy, a large number of athletes underwent primary CMR screening. They found COVID-19 myocarditis, as defined by LLC on CMR, in 2.3% of athletes amongst the Big Ten COVID-19 cardiac registry [43]. Twenty-eight of the 37 myocarditis cases were asymptomatic and the diagnosis was made on

CMR findings alone, where all other imaging modalities were normal, highlighting the prevalence of subclinical myocarditis in this disease and the importance of CMR. Follow-up CMR on these patients showed that all had resolution of markers of myocardial edema, but that 60% had continued myocardial scar. The authors describe several considerations regarding these findings, and importantly note the risk of sudden cardiac death, even in asymptomatic athletes with myocarditis, as was described to occur in nearly half of viral myocarditis cases of sudden death in young patients [44]. The occult nature of CMR findings may provide further insight into a possible cardiotropic nature of SARS-CoV-2, thus allowing cardiac involvement without overt involvement of other organs. With this in mind, the risk of sudden death during exercise must be considered when determining return-to-play recommendations for the COVID-19 athlete. Malek and colleagues similarly noted CMR abnormalities at follow-up MRI in 19% of elite athletes despite mild/asymptomatic COVID-19 infection in the vast majority of participants [45]. However, rates of cardiac involvement in other studies have not been as high as other studies [46]. As others have noted [47], the clinical significance of these CMR findings are yet to be identified for the competitive athlete, and further studies will be required to delineate restrictions and return-to-play given the importance prevalence of myocarditis in the competitive athlete after COVID-19. There is a paucity of data showing that such features as isolated myocardial edema affect long-term prognosis in other cases of myocarditis [45]. The possibility of ongoing inflammation and a potential nidus for dysrhythmia should be entertained, but this will need to be balanced with the notable likelihood of false-positive findings on CMR. Of the 97 deaths due to viral myocarditis described in a study by Harris et al., 58 were physically active at or near time of death [48], bringing to light the importance of safe return to play. Nearly half of these sudden unexpected deaths in myocarditis patients were precluded by a viral prodrome, which may assist in restricting athletes that continue to be symptomatic following infection and/or the "Long Covid" subgroup of COVID-19 patients [49]. These findings are summarized in Table 1.

MIS-C

Multisystem inflammatory syndrome in children (MIS-C) is a rare, new disease entity temporally associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [50]. Patients with MIS-C, defined as those < 21 years of age, present with fever, elevated inflammatory markers, and evidence of multisystem organ involvement (Table 2). MIS-C has shown a higher-than-expected prevalence in the Hispanic and non-Hispanic Black populations [51]. The emerging nature of this disease subset led to many challenges for the pediatric provider. Infection control and provider/sonographer safety while screening for cardiac involvement stressed the pediatric hospital system nationwide, as the high level of personal protective equipment further strained an already-stressed cohort. Providers across the country worked tirelessly to learn more about MIS-C and its features as a subset of pediatric COVID-19 [52]. While mortality in MIS-C is fortunately rare, overt cardiac involvement during hospitalization is very common. Cardiac dysfunction is reported in 34–41%, ECG abnormalities in 35%, and coronary artery abnormalities in 13–24% of patients hospitalized for MIS-C [53, 54]. Valverde and colleagues described similar cardiac morbidities in their large European cohort and found that 40% of patients presented in shock and over 50% required admission to the intensive care unit. Elevated troponin has been found in up to 93% of MIS-C patients, elevated BNP in up to 94%, and cardiac dysfunction in 34–50% [53, 55–58]. Treatment of MIS-C has centered around intravenous immunoglobulin (IVIG) with possible addition of glucocorticoids, with a lack of consensus currently on the best treatment regimen [54, 59].

Table 1 Summary of a collection of pertinent findings regarding abnormal imaging in patients with COVID-19

Study authors	No. of patients	Age (years)	COVID-19 cardiac diagnosis	Echo findings	CMR, normal/abnormal?	CMR findings
Puntmann et al.	100	49 ± 14	Recovered COVID-19 (1/3 hospitalized during Dx)	-	78% abnormal CMR	73% had increased native T1, 60% had increased native T2 32% had LGE, 22% had PCE
Chen et al.	25	(range 18—35)	Symptomatic COVID-19	-	CMR performed within 10 days of symptom onset	Increased mean native T1 mapping vs. controls Increased mean T2 mapping vs. controls Increased mean ECV vs. controls Worsened mean LV GLS vs. controls
Daniels et al.	1597	(collegiate athletes)	Myocarditis in 9 Subclinical myocarditis in 28	Abnormal in 5/37 (2 myocarditis, 3 subclinical myocarditis)	37/1597 diagnosed with myocarditis (2.3%)	31 had CMR findings of myocarditis 31/37 (84%) having increased T2, 5/37 (14%) had increased T1 LGE was seen in 36/37 (97%) 27/38 had follow-up CMR; resolution of T2 elevation in 100%, LGE resolution in 41%

Table 1 continued

Study authors	No. of patients	Age (years)	COVID-19 cardiac diagnosis	Echo findings	CMR, normal/ abnormal?	CMR findings
Malek et al.	26 elite athletes	24 (IQ 21—27)	Asymptomatic/ mild COVID-19	-	5/26 (19%) abnormal CMR CMR performed 32 days from diagnosis	No cases of myocarditis (LLC) 4/26 (15%) had edema by T1/T2/ ECV 1/26 (4%) had LGE 1/26 (4%) had PCE
Martinez et al.	789 professional athletes	25 ± 3	Recovered symptomatic or mild/ asymptomatic COVID-19	2.5% had abnormal echocardiography (mild LV dysfunction, PCE)	27 CMR performed	3/27 (11%) had myocarditis 2/ 27 (%) had PCE
Kotecha et al.	148	64 ± 12	Recovered severe COVID-19	Decreased LVEF in 11%	CMR performed 68 days from confirmed COVID Dx	13% had increased T1 3% had increased T2 35% had LGE
Huang et al.	26	38 (IQ 32—45)	Recovered (prev hospitalized) COVID-19	-	58% had abnormal CMR	28% had increased T1 25% had increased T2 24% had increased ECV 31% had LGE
Joy et al.	149	37 (range 18—63)	Mild COVID in healthcare workers	-	CMR performed 6 months post COVID-19 DX	6/149 4%) had increased T1 9/149 (6%) had increased T2 13/149 (9%) had LGE

Table 1 continued

Study authors	No. of patients	Age (years)	COVID-19 cardiac diagnosis	Echo findings	CMR, normal/abnormal?	CMR findings
Valverde et al.	286	8.4 (IQ 3.8—12.4)	MIS-C	Decreased LVEF in 34% PCE mod + in 3.1% Reduced LV GLS in 26.5% CA abnormal in 24.1%	42/286 had CMR performed 33% abnormal	Increased T2 signal in 33% LGE in 14.3%
Feldstein et al.	1116	9.7 (IQ 4.7—13.2)	MIS-C	Decreased LVEF in 34% CA abnormal 13.4%	-	-
Belhadjer et al.	35	10 (IQ 2—16)	MIS-C	LVEF < 30% in 28% LVEF 30—50% in 72%	-	-
Bermejo et al.	20	8 (range 17 months to 14 years)	MIS-C	LVEF decreased in 50% CA abnormal in 25%	CMR performed 27 ± 14 days from SSX onset	1/20 (5%) had increased T1 1/20 (5%) had increased T2 2/20 (10%) had LGE

Note that patients are grouped by COVID-19 cardiac diagnosis, and " – " represents aspects that were not covered in the indicated study

Echocardiographic Features of MIS-C

Despite presenting with significant dysfunction, normalization of left ventricular ejection fraction (LVEF) was achieved in nearly all patients following recovery from MIS-C. Findings from Belhadjer and colleagues described a 35-patient cohort of patients, median age 10 years, diagnosed with MIS-C. All 35 patients in this cohort presented with fever and had a LVEF of < 50%, with 28% having an LVEF of < 30%. Eighty percent of these patients required inotropic support and a striking 28% required extracorporeal membrane oxygenation (ECMO). A total of four of 35 showed segmental wall hypokinesis in addition to the left ventricular dysfunction. Recovery in LVEF was seen in 71% of the patients and was achieved at a median of 2 days, which is a strikingly fast recovery rate for patients presenting with such severe features.

Table 2 Single-center study highlighting different features of MIS-C reported at admission, as well as cardiac involvement, clinical course, and treatment strategy

Age in years (median; range)	8 (0.3–19)
Male	52.3% (n = 46)
Female	47.7% (n = 42)
Race	
White	42% (n = 37)
African American	46.6% (n = 41)
Latino/Hispanic	4.6% (n = 4)
Multiracial	6.8% (n = 6)
Systems involved by symptoms at admission	
Fever	100% (n = 88)
Duration of fever in days	4.5 (SD = 3.3)
Gastrointestinal	85.2% (n = 75)
Mucocutaneus	46.6% (n = 41)
Cardiovascular	46.6% (n = 41)
Respiratory	39.8% (n = 35)
Musculoskeletal	13.6% (n = 12)
Neurologic	44.3% (n = 39)
Clinical outcomes	
Length of stay in days	8.4 (SD = 4.9)
Admission to PICU	44.3% (n = 39)
Use of vasoactives	34.1% (n = 30)
Cardiac dysfunction	40.7% (n = 35)
Coronary involvement	27.6% (n = 24)
Therapies used	
IVIG	94.3% (n = 83)
Steroids	89.8% (n = 79)
Anakinra	10.2% (n = 9)
Remdesivir	1.1% (n = 1)
Aspirin	92% (n = 81)
Anticoagulation	
Prophylactic	73.9% (n = 65)
Therapeutic	23.9% (n = 21)

Note the persistence of fever, high prevalence of gastrointestinal involvement, cardiac involvement in nearly half of patients, and the preponderance of patients receiving IVIG and steroids. *"IVIG"* intravenous immunoglobulin

Regional wall motion abnormalities have been described in 7–10% of MIS-C patients, and 35% of patients have been found to have arrhythmias during hospitalization [53]. Several studies evaluating echocardiographic strain demonstrated residual abnormalities in these patients, particularly those who presented with more severe illness, speaking further to residual occult disease [60, 61]. Sanil et al. found that those who had worse left ventricular longitudinal strain (LVGLS) on admission had higher peak troponin elevation and less improvement in LVGLS by 10 weeks of follow-up.

Right heart involvement has yet to clearly been demonstrated in MIS-C, as the majority of the pathologic findings appear isolated to the left ventricle. When involved, changes in right ventricular parameters such as abnormal echocardiographic strain has been predictive of myocardial injury [60] and has been shown to be a predictor of mortality in adult patients [62]. Further pediatric echocardiography studies regarding this topic are on-going.

The presence of coronary artery involvement in the form of coronary ectasia or aneurysm formation is another prominent imaging finding of MIS-C. A large cross-sectional study of MIS-C patients in the USA found a coronary artery abnormality prevalence of 16.5% [63]. Although less frequent, giant coronary aneurysms have been reported with MIS-C and based on literature from the Kawasaki disease population, are the most likely to have long-term sequelae [64]. Figure 1 describes aneurysmal changes in two different MIS-C patients.

CMR Findings in MIS-C

CMR assessment of MIS-C has followed shortly behind the clinical and echocardiographic assessment of the disease, as we continue to learn more about the subacute and longer-term course of these patients. Early reports from the United Kingdom described varying findings in CMR parameters when assessing mean T1 and T2 mapping. A large multicenter MIS-C registry from Europe included 42 pediatric patients with CMR and showed myocardial edema via T2 mapping to be present in 33% and LGE in 14% of patient during the acute hospitalization [53]. A study by Bermejo and colleagues performed at a mean of 27 days after onset of symptoms showed no increased mean T1 and T2 mapping, but 2 of 4 did show LGE [65]. Complicating interpretation was that all but one of these 20 patients described by Bermejo and colleagues had normal biventricular systolic function as assessed by CMR, despite half of the patients having reduced LVEF by transthoracic echocardiography. Upon further review, two of the 20 were found to have segmental T2 mapping abnormalities. These areas were associated with elevated C-reactive protein (CRP) at initial presentation. A smaller study of four patients in the acute period of MIS-C found that 75% of patients had elevated mean T1 and/or T2 mapping, without evidence of LGE in the acute phase [66]. Similar to the previously noted TTE studies, abnormal strain imaging by CMR has also been reported in MIS-C [67]. The summary of most findings, highlighted by these and others, seem to show acute findings consistent with myocarditis on CMR that resolves with clinical improvement (Fig. 2). These findings are summarized in Table 1. Future study into the long-term recovery of the myocardium and subsequent sequelae is needed.

POST-ACUTE SEQUELAE OF COVID-19

As our knowledge has grown regarding COVID-19, we have found different disease phenotypes emerging out of those that have suffered from the virus. Post-Acute Sequelae of COVID-19, or "long COVID," has been defined as signs and symptoms of COVID-19 that continue for more than 4 weeks and are not explained by an alternate diagnosis [68, 69]. Symptoms can include similar presenting-symptoms such as cough, shortness of breath, and joint pains but can also include fatigue and altered memory and/or cognitive function described as "brain fog" [68, 70]. The mechanistic explanations for continued symptomatology have included post-inflammatory lymphatic drainage alterations, post-infectious fibrotic changes to different organ systems, cytokine profile maladaptation or direct viral cellular injury as described by Crook and colleagues [71]. Long COVID is not restricted to only those that have had severe illness at initial COVID-19 diagnosis, as it has been seen in a number of mild infections as well. Some reports have shown symptoms to persist in up to over 85% of patients when assessed 2 months following initial onset [72–74], however most reports cite that roughly one in four patients may experience degrees of long COVID [68, 75]. The most common symptoms experienced in long COVID are fatigue, dyspnea, joint pain, and chest pain. This high prevalence, albeit seen in only a smaller cohort, highlights the importance of continued care in COVID-19 patients. Recommendations for evaluation of long COVID patients remains sparse, with individual providers often determining follow-up plans. Different degrees of COVID severity, different time frames of follow-up and via different modes of imaging, cardiac restrictions, and/or therapies continue to be unanswered questions.

Imaging Findings in Long COVID

Previously noted EG and echocardiographic abnormalities from acute infection may persist for some time, however to date, no studies have identified overt heart failure persisting in COVID-19. Some studies have shown both ischemic and non-ischemic changes on CMR for patients recovered from severe COVID-19 infection [32], highlighting the importance in considering cardiac ischemia in the recovered COVID-19 patient with new chest pain or other

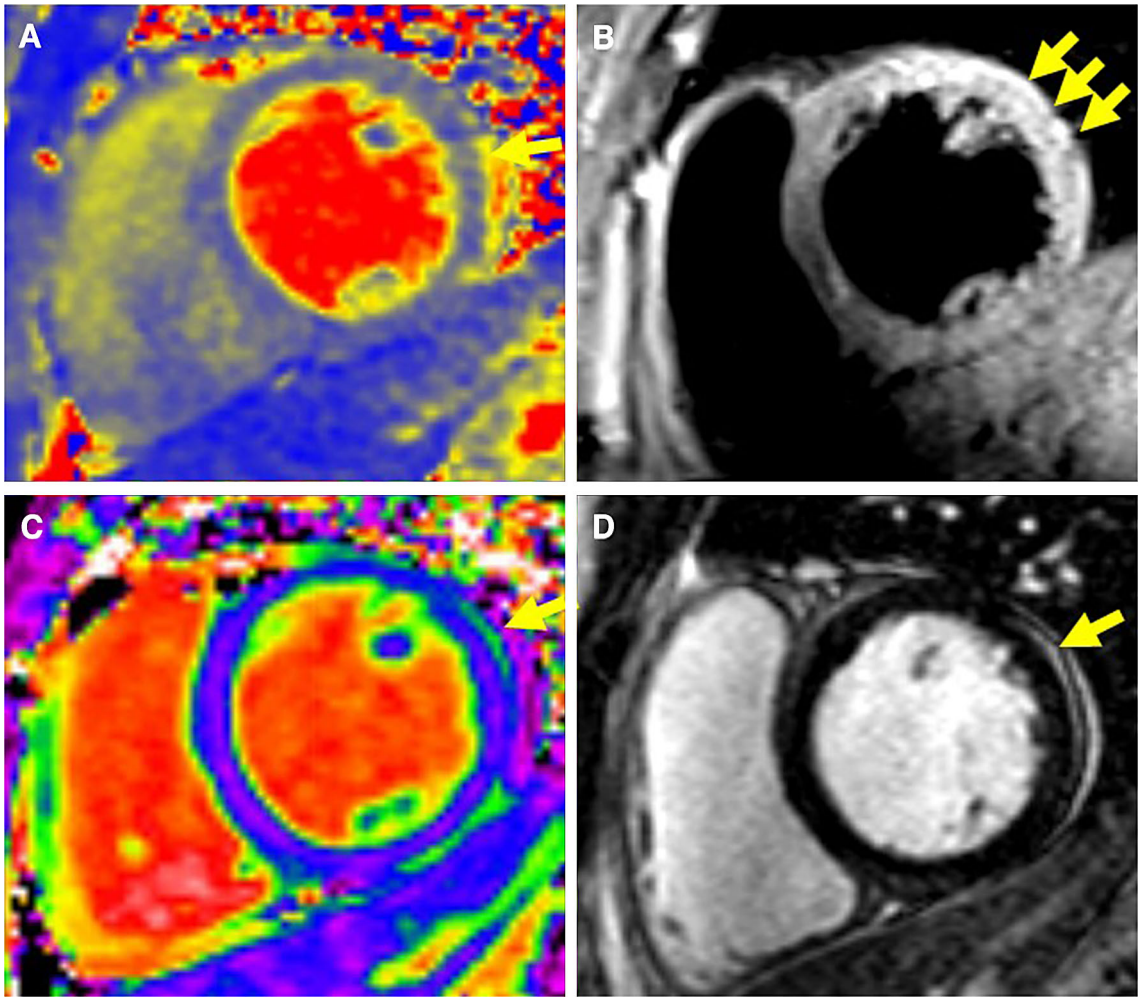

Fig. 2 Cardiac MRI of an MIS-C patient with evidence of myocarditis. **A** T2 map demonstrating subepicardial enhancement (*arrow*) consistent with myocardial edema. **B** T2-weighted triple inversion recovery imaging showing enhancement along the lateral wall (*arrow*). **C** Extracellular volume mapping and **D** late gadolinium enhancement post-contrast imaging both showing rim of subepicardial enhancement (*arrow*) consistent with myocardial injury

cardiac symptomatology. Puntmann and colleagues showed that 78% of patients recovered from COVID illness had positive CMR findings at an average of 71 days following symptom onset (Table 1). Similar findings have been shown by Kotecha and colleagues [32]. A large majority of these patients had elevated troponin, possibly indicating a disease subset more likely to show cardiac involvement at follow-up assessment. Importantly, only one-third of the patients in this study had illness requiring hospitalization, showing that disease severity and cardiac involvement are not exclusive. In a study by Huang et al., of 26 patients with moderate-to-severe COVID infection who reported cardiac symptoms during recovery, 58% had abnormal CMR findings at an average follow-up time of 47 days after cardiac symptom onset [76]. None of these patients had prior known myocarditis during their COVID illness. There was no difference found between CMR-positive and CMR-negative groups and different cardiac symptoms, suggesting that symptomatology did not play a factor in predicting CMR findings. Also, no difference was seen in LV function and volumetric assessments, further

challenging mechanistic interpretation. The high prevalence of CMR positive findings in this cohort of moderate-to-severe COVID, at an average of 47 days, suggests some type of underlying cardiac involvement and may carry a higher risk in those with residual cardiac symptoms during recovery. Several studies have similarly shown that cardiac symptoms are less likely following recovery of mild COVID, but still occur in 10–20% of cases [74] and cardiac symptoms and/or biomarkers seem to portend higher likelihood of CMR findings [77]. Further studies, as discussed previously, are likely to center around mechanisms surrounding cardiotropic effects of ACE2 receptor binding domain of spike protein versus the inflammatory storm induced in some patients suffering COVID-19 infection [17, 37].

Challenging this inclination are studies such as those performed by Joy and colleagues [29]. They found that when comparing mild seropositive infections 6 months following onset to seronegative controls, CMR abnormalities were no more likely in the mild COVID infections compared to healthy controls. It is important to note that this cohort included mild or asymptomatic COVID infections found in healthcare workers, which may limit applicability. Studies such as these lead to the suspicion that mild COVID infection has reduced cardiac pathology 6 + months following infection, but this cannot yet be applied to more severe infection or at a shorter follow-up window.

VACCINATION

The rapid development of vaccines against SARS-CoV-2, done with rapid scientific advancement and equally impressive effectiveness, was a true marker of great scientific achievement for the ages. In terms of vaccine safety, multiple large-scale studies have proved that the RNA-based vaccines currently available are widely safe and side effects primarily consistent of local symptoms and low-grade, short-term systemic symptoms [78] [79]. Case series of patients experiencing vaccine-associated myocarditis have found that this feature is exceedingly rare, and as yet has not shown lasting morbidity nor mortality [80, 81]. While vaccine protocols continue to develop, SARS-CoV-2 has undergone different mutations that have led to some instances of breakthrough infection. Specifically, changes in the spike protein in new variants have led to variations in vaccine protection [78]. A primary feature of vaccination, however, has been its ability to protect against severe disease. A recent study published in January 2022 by the Overcoming COVID investigators have shown that full vaccination provides 91% vaccine effectiveness against MIS-C. Of 102 MIS-C patients over 24 hospital, only five were fully vaccinated. Importantly, no patients that were fully vaccinated required mechanical ventilation, vasoactive support or ECMO support [82]. This protection has similarly been seen for severe COVID-19 in the adolescent vaccinated population [83].

CONCLUSIONS

We review the current clinical and imaging findings surrounding cardiac involvement in the pediatric patient with COVID-19. At present, the mechanism of cardiac involvement in this rare subset of patients remains unclear. However, many studies highlight that there does appear to be cardiotropic effects of SARS-CoV-2 in some patients. Cardiac involvement in the hospitalized COVID-19 patient portends worse clinical outcome. The time of highest "cardiac involvement" risk, the degree of involvement, long-term sequelae and management recommendations all remain unclear. As has been seen for different aspects of this virus, the novelty and severity have created more questions than they have answered. The recent Omicron variant surge in the US and throughout the world is in the early stages, and as of this writing the literature regarding imaging changes with this new variant is lacking. It is possible that the perceived less-severe illness in B.1.1.529 (Omicron) variant may portray less risk of cardiac involvement and/or MIS-C, however this has yet to be studied.

With the paucity of long-term cardiac data, we recommend consideration of advanced imaging for pediatric patients with cardiac symptoms and/or elevation of cardiac serum biomarkers. Further testing such as strain deformation, as of this writing, has not shifted into consistent clinical use. Future research may identify ways to make this transition. Longer-term follow-up will equally be recommended for patients with positive findings in the aforementioned studies. The goal should remain to provide comprehensive and safe care for patients actively ill and those recovering from this infection.

ACKNOWLEDGEMENTS

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All names authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Tyler A Fick (primary authorship, concept and design, drafting the manuscript, revisions), Clifford L Cua (concept and design, assisting with drafting the manuscript and revisions) and Simon Lee (concept and design, assisting with drafting the manuscript and revisions).

Disclosures. Tyler A Fick, Clifford L Cua, and Simon Lee have nothing to disclose.

REFERENCES

1. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbiol Immunol Infect. 2021;54(2):159–63.

2. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271–80 e8.

3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.

4. Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of Covid-19 in children in early January 2020 in Wuhan. China N Engl J Med. 2020;382(14):1370–1.

5. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA. 2020;323(14):1335.

6. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020;382(17):1663–5.

7. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in Children in Madrid. Spain: JAMA Pediatr.; 2020.

8. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus

on congenital heart disease. Int J Cardiol. 2020;309: 70–7.

9. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323(13):1239–42.

10. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020;146(4).

11. Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatr Cardiol. 2020;41(7):1391–401.

12. Ong SWX, Chiew CJ, Ang LW, Mak TM, Cui L, Toh M, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta). Clin Infect Dis. 2021.

13. Mahase E. Delta variant: What is happening with transmission, hospital admissions, and restrictions? Bmj. 2021;373:n1513.

14. Rowley AH, Baker SC, Shulman ST, Rand KH, Tretiakova MS, Perlman EJ, et al. Ultrastructural, immunofluorescence, and RNA evidence support the hypothesis of a "new" virus associated with Kawasaki disease. J Infect Dis. 2011;203(7):1021–30.

15. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.

16. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020;116(6): 1097–100.

17. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39(7): 618–25.

18. Lindner D, Fitzek A, Brauninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. 2020;5(11):1281–5.

19. Escher F, Pietsch H, Aleshcheva G, Bock T, Baumeier C, Elsaesser A, et al. Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies. ESC Heart Fail. 2020;7(5): 2440–7.

20. Bailey AL, Dmytrenko O, Greenberg L, Bredemeyer AL, Ma P, Liu J, et al. SARS-CoV-2 infects human engineered heart tissues and models COVID-19 myocarditis. JACC Basic Transl Sci. 2021;6(4): 331–45.

21. Thum T. SARS-CoV-2 receptor ACE2 expression in the human heart: cause of a post-pandemic wave of heart failure? Eur Heart J. 2020;41(19):1807–9.

22. Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J. 2020;41(19):1804–6.

23. Stöbe S, Richter S, Seige M, Stehr S, Laufs U, Hagendorff A. Echocardiographic characteristics of patients with SARS-CoV-2 infection. Clin Res Cardiol. 2020;109(12):1549–66.

24. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 2018;72(24):3158–76.

25. Etesami M, Gilkeson RC, Rajiah P. Utility of late gadolinium enhancement in pediatric cardiac MRI. Pediatr Radiol. 2016;46(8):1096–113.

26. Fernandez-Jimenez R, Sanchez-Gonzalez J, Aguero J, Del Trigo M, Galan-Arriola C, Fuster V, et al. Fast T2 gradient-spin-echo (T2-GraSE) mapping for myocardial edema quantification: first in vivo validation in a porcine model of ischemia/reperfusion. J Cardiovasc Magn Reson. 2015;17:92.

27. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811–8.

28. Knight DS, Kotecha T, Razvi Y, Chacko L, Brown JT, Jeetley PS, et al. COVID-19: myocardial injury in survivors. Circulation. 2020;142(11):1120–2.

29. Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, et al. Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers. JACC Cardiovasc Imaging. 2021.

30. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Prog Cardiovasc Dis. 2020;63(3):390–1.

31. Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, et al. Association of troponin levels with mortality in Italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. JAMA Cardiol. 2020;5(11):1274–80.

32. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J. 2021;42(19):1866–78.

33. Doeblin P, Kelle S. Going after COVID-19 myocarditis. Eur Heart J Cardiovasc Imaging. 2021;22(8):852–4.

34. Chen BH, Shi NN, Wu CW, An DA, Shi YX, Wesemann LD, et al. Early cardiac involvement in patients with acute COVID-19 infection identified by multiparametric cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2021;22(8):844–51.

35. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J. 2021;42(2):206.

36. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):819–24.

37. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. 2020;5(7):831–40.

38. Boehmer T, Kompaniyets L, Lavery A. Association between COVID-19 and myocarditis using hospital-based administrative data—United States, March 2020—January 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1228–32.

39. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan. China JAMA Cardiol. 2020;5(7):802–10.

40. Phelan D, Kim JH, Elliott MD, Wasfy MM, Cremer P, Johri AM, et al. Screening of potential cardiac involvement in competitive athletes recovering from COVID-19: an expert consensus statement. JACC Cardiovasc Imaging. 2020;13(12):2635–52.

41. Martinez MW, Tucker AM, Bloom OJ, Green G, DiFiori JP, Solomon G, et al. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening. JAMA Cardiol. 2021;6(7):745–52.

42. Kim JH, Levine BD, Phelan D, Emery MS, Martinez MW, Chung EH, et al. Coronavirus disease 2019 and the athletic heart: emerging perspectives on pathology, risks, and return to play. JAMA Cardiol. 2021;6(2):219–27.

43. Daniels CJ, Rajpal S, Greenshields JT, Rosenthal GL, Chung EH, Terrin M, et al. Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes With Recent SARS-CoV-2 Infection: Results From the Big Ten COVID-19 Cardiac Registry. JAMA Cardiol. 2021.

44. Harris KM, Mackey-Bojack S, Bennett M, Nwaudo D, Duncanson E, Maron BJ. Sudden unexpected death due to myocarditis in young people. Including Athletes Am J Cardiol. 2021;143:131–4.

45. Malek LA, Marczak M, Milosz-Wieczorek B, Konopka M, Braksator W, Drygas W, et al. Cardiac involvement in consecutive elite athletes recovered from Covid-19: a magnetic resonance study. J Magn Reson Imaging. 2021;53(6):1723–9.

46. Moulson N, Petek BJ, Drezner JA, Harmon KG, Kliethermes SA, Patel MR, et al. SARS-CoV-2 cardiac involvement in young competitive athletes. Circulation. 2021;144(4):256–66.

47. Udelson. Return to Play for Athletes After COVID-19 Infection—the fog begins to clear. JAMA Cardiol. 2021.

48. Harris KM, Mackey-Bojack S, Bennett M, Nwaudo D, Duncanson E, Maron BJ. Sudden unexpected death due to myocarditis in young people, including athletes. Am J Cardiol. 2021;143:131–4.

49. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021;398(10302):747–58.

50. Prevention CfDCa. Multisystem Inflammatory Syndrome (MIS) 2021 [Available from: https://www.cdc.gov/mis-c/.

51. Stierman B, Abrams JY, Godfred-Cato SE, Oster ME, Meng L, Yip L, et al. Racial and ethnic disparities in multisystem inflammatory syndrome in children in the United States, March 2020 to February 2021. Pediatr Infect Dis J. 2021;40(11):e400–6.

52. Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE statement on protection of patients and echocardiography service providers during the 2019 novel coronavirus outbreak: endorsed by the American College of Cardiology. J Am Soc Echocardiogr. 2020;33(6):648–53.

53. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute

cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation. 2021;143(1):21–32.

54. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, et al. Multisystem inflammatory syndrome in children—initial therapy and outcomes. N Engl J Med. 2021;385(1):23–34.

55. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347–58.

56. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383(4):334–46.

57. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180(2):307–22.

58. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259–69.

59. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385(1):11–22.

60. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol. 2020;76(17):1947–61.

61. Sanil Y, Misra A, Safa R, Blake JM, Eddine AC, Balakrishnan P, et al. Echocardiographic Indicators Associated with Adverse Clinical Course and Cardiac Sequelae in Multisystem Inflammatory Syndrome in Children with Coronavirus Disease 2019. J Am Soc Echocardiogr. 2021.

62. Li Y, Li H, Zhu S, Xie Y, Wang B, He L, et al. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. JACC Cardiovasc Imaging. 2020;13(11):2287–99.

63. Belay ED, Abrams J, Oster ME, Giovanni J, Pierce T, Meng L, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr. 2021;175(8):837–45.

64. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, et al. Association of Severity of Coronary Artery Aneurysms in Patients With Kawasaki Disease and Risk of Later Coronary Events. JAMA Pediatrics. 2018;172(5).

65. Bermejo IA, Bautista-Rodriguez C, Fraisse A, Voges I, Gatehouse P, Kang H, et al. Short-term sequelae of multisystem inflammatory syndrome in children assessed by CMR. JACC Cardiovasc Imaging. 2021;14(8):1666–7.

66. Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, et al. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. Radiology. 2020;297(3):E283–8.

67. Theocharis P, Wong J, Pushparajah K, Mathur SK, Simpson JM, Pascall E, et al. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. Eur Heart J Cardiovasc Imaging. 2021;22(8):896–903.

68. Alwan NA, Johnson L. Defining long COVID: going back to the start. Med (N Y). 2021;2(5):501–4.

69. Sivan M, Taylor S. NICE guideline on long covid. Bmj. 2020;371:m4938.

70. Søraas A, Kalleberg KT, Dahl JA, Søraas CL, Myklebust T, Axelsen E, et al. Persisting symptoms three to eight months after non-hospitalized COVID-19, a prospective cohort study. PLoS One. 2021;16(8):e0256142.

71. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. BMJ. 2021;374:n1648.

72. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603–5.

73. Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. JAMA. 2021;325(19):2015–6.

74. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 2021;27(2):258–63.

75. Nehme M, Braillard O, Alcoba G, Aebischer Perone S, Courvoisier D, Chappuis F, et al. COVID-19 symptoms: longitudinal evolution and persistence in outpatient settings. Ann Intern Med. 2021;174(5):723–5.

76. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. JACC Cardiovasc Imaging. 2020;13(11):2330–9.

77. Ng MY, Ferreira VM, Leung ST, Yin Lee JC, Ho-Tung Fong A, To Liu RW, et al. Patients recovered from COVID-19 show ongoing subclinical myocarditis as revealed by cardiac magnetic resonance imaging. JACC Cardiovasc Imaging. 2020;13(11):2476–8.

78. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.

79. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078–90.

80. Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol. 2021;6(10):1196–201.

81. Patel YR, Louis DW, Atalay M, Agarwal S, Shah NR. Cardiovascular magnetic resonance findings in young adult patients with acute myocarditis following mRNA COVID-19 vaccination: a case series. J Cardiovasc Magn Reson. 2021;23(1):101.

82. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA vaccination against multisystem inflammatory syndrome in children among persons aged 12–18 years—United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52–8.

83. Olson SM, Newhams MM, Halasa NB, Price AM, Boom JA, Sahni LC, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. New England Journal of Medicine. 2022.