COVID-19 Vaccination–Associated Myocarditis in Adolescents

Supriya S. Jain, MD,[a] Jeremy M. Steele, MD,[b] Brian Fonseca, MD,[c] Sihong Huang, MD, MMsc,[d] Sanket Shah, MD,[e] Shiraz A. Maskatia, MD,[f] Sujatha Buddhe, MD, MS,[g] Nilanjana Misra, MBBS,[h] Preeti Ramachandran, MD,[i] Lasya Gaur, MD,[j] Parham Eshtehardi, MD,[k] Shafkat Anwar, MD,[l] Neeru Kaushik, MD,[m] Frank Han, MD,[n] Nita Ray Chaudhuri, MD,[o] Lars Grosse-Wortmann, MD[p]

abstract

OBJECTIVES: In this study, we aimed to characterize the clinical presentation, short-term prognosis, and myocardial tissue changes as noted on cardiovascular magnetic resonance (CMR) or cardiac MRI in pediatric patients with coronavirus disease 2019 vaccination-associated myocarditis (C-VAM).

METHODS: In this retrospective multicenter study across 16 US hospitals, patients <21 years of age with a diagnosis of C-VAM were included and compared with a cohort with multisystem inflammatory syndrome in children. Younger children with C-VAM were compared with older adolescents.

RESULTS: Sixty-three patients with a mean age of 15.6 years were included; 92% were male. All had received a messenger RNA vaccine and, except for one, presented after the second dose. Four patients had significant dysrhythmia; 14% had mild left ventricular dysfunction on echocardiography, which resolved on discharge; 88% met the diagnostic CMR Lake Louise criteria for myocarditis. Myocardial injury as evidenced by late gadolinium enhancement on CMR was more prevalent in comparison with multisystem inflammatory syndrome in children. None of the patients required inotropic, mechanical, or circulatory support. There were no deaths. Follow-up data obtained in 86% of patients at a mean of 35 days revealed resolution of symptoms, arrhythmias, and ventricular dysfunction.

CONCLUSIONS: Clinical characteristics and early outcomes are similar between the different pediatric age groups in C-VAM. The hospital course is mild, with quick clinical recovery and excellent short-term outcomes. Myocardial injury and edema are noted on CMR. Close follow-up and further studies are needed to understand the long-term implications and mechanism of these myocardial tissue changes.

[a]*New York Medical College and Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, New York;* [b]*School of Medicine, Yale University, New Haven, Connecticut;* [c]*Colorado Children's Hospital, Aurora, Colorado;* [d]*College of Human Medicine, Michigan State University and Helen DeVos Children's Hospital, Spectrum Health, Grand Rapids, Michigan;* [e]*Children's Mercy Hospital, Kansas City, Missouri;* [f]*School of Medicine, Stanford University and Lucile Packard Children's Hospital, Palo Alto, California;* [g]*Seattle Children's Hospital and University of Washington, Seattle, Washington;* [h]*Cohen Children's Medical Center of New York, Northwell Health, Queens, New York;* [i]*University of Kentucky, Lexington, Kentucky;* [j]*School of Medicine, John Hopkins University, Baltimore, Maryland;* [k]*Northside Heart and Vascular Institute, Northside Hospital, Atlanta, Georgia;* [l]*University of California, San Francisco, San Francisco, California;* [m]*University of California, San Francisco Benioff Children's Hospitals, Oakland, California;* [n]*College of Medicine, University of Illinois, Peoria, Illinois;* [o]*West Virginia University, Morgantown, West Virginia; and* [p]*Oregon Health and Science University, Portland, Oregon*

Drs Jain and Grosse-Wortmann conceptualized and designed the study, designed the data collection form, collected data, coordinated and supervised data collection, conducted the analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Steele and Fonseca collected data, helped in editing the initial manuscript and figures, and critically reviewed the manuscript for important intellectual content; Drs Huang, Shah, Maskatia, Buddhe, Misra, Ramachandran, Gaur, Eshtehardi, Anwar, Kaushik, Han, and Chaudhuri collected data and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: On the basis of the recent Centers for Disease Control and Prevention data and smaller case series, there is a temporal association of the second dose of messenger RNA vaccines against coronavirus disease 2019 with myocarditis.

WHAT THIS STUDY ADDS: This study enhances our understanding into the spectrum, severity, and associated myocardial tissue changes in coronavirus disease 2019 vaccination-associated myocarditis as compared with multisystem inflammatory syndrome in children. It provides valuable and timely follow-up information in these children.

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Recently, an association of the messenger RNA (mRNA)–based coronavirus disease 2019 (COVID-19) vaccine with myocarditis has been reported.[1–3] In June 2021, the Centers for Disease Control and Prevention (CDC) observed a rate of postvaccine myocarditis that was higher in adolescents and young adults than the expected baseline.[3] Thus far, only small case series in the pediatric population, with rudimentary information about the myocardium, have been reported.[1] In the current study, we aimed to understand the spectrum and severity of this recently recognized condition in the young, to evaluate the associated myocardial tissue changes, and to compare it with the degree of cardiac involvement seen in multisystem inflammatory syndrome in children (MIS-C).

METHODS

After the initial reports of a possible association between COVID-19 vaccines and myocarditis, a call went out to physicians who specialize in cardiovascular imaging around the nation to report such cases from their institutions to this retrospective study. Most investigators are clinical pediatric cardiologists and cardiovascular magnetic resonance (CMR) experts. The cases were reported to the CDC's Vaccine Adverse Event Reporting System at the respective centers. The local research ethics boards of several of the participating centers issued an institutional review board exemption, and written informed consent was obtained from patients and/or their guardians at the others. Patients ≤21 years of age with a diagnosis of acute myocarditis based on clinical presentation, abnormal biomarkers, and/or cardiovascular imaging findings within 2 weeks of COVID-19 vaccination were included. Demographic information (including race and/or ethnicity to learn how different populations may be impacted), clinical presentation, cardiovascular imaging findings, viral testing (including comprehensive viral serological testing), hospital course, and follow-up information were collected. Patients with a plausible alternative etiology for their myocarditis, including a concurrent acute viral infection, were excluded.

From the CMR studies, ventricular volumes, and ejection fraction (EF) were obtained. The 2009 Lake Louise criteria[4] or, when parametric mapping was available, the 2018 revised Lake Louise CMR criteria were used to test for a diagnosis of acute myocarditis[5,6] (Supplemental Information). Evidence of myocardial edema was determined on the basis of abnormally high signal intensity on T2-weighted imaging or prolonged T2 relaxation time on T2 mapping. Hyperemia was determined by myocardial early gadolinium enhancement (EGE). Native T1 times, extracellular volume (ECV) fraction, and myocardial late gadolinium enhancement (LGE) imaging were collected as markers of cardiomyocyte injury and necrosis. Consistent with Society for Cardiovascular Magnetic Resonance guidelines, native T1 results were only used if institutional normal ranges were available and converted into categorical values.[7] CMR image analysis and interpretation was done by the performing center to best reflect real-world practice. The study was not intended to identify and/or track pericarditis and was focused on the clinical and imaging characteristics of coronavirus disease 2019 vaccination–associated myocarditis (C-VAM).

To gain perspective about the observed myocardial tissue changes, patients with a diagnosis of MIS-C who had undergone CMR with a myocarditis protocol during their acute or subacute phase of illness were included for comparison from few select centers. Because obtaining CMR data in the acute phase of illness in MIS-C had been logistically challenging earlier owing to the risk of exposure of others to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), these data were limited.[8]

Data are presented as means and SDs if normally distributed, as medians and ranges otherwise, or as counts and percentages as applicable. Older versus younger adolescents with C-VAM and patients with MIS-C versus those with C-VAM were compared by using unpaired, two-tailed Student's *t* tests. *P* values $<.05$ were regarded as statistically significant.

RESULTS

Clinical Characteristics

Sixty-nine patients with a diagnosis of acute myocarditis after COVID-19 vaccination who had presented between March 2021 and June 2021 were submitted from 16 institutions. Six patients were excluded with a possible concurrent acute infection that could have caused the myocarditis. Sixty-three patients with a mean age of 15.6 ± 1.8 years (range 12–20 years) were included. Thirty-one patients (49%) were in the 12- to 15-year-old age group. Fifty-eighty patients (92%) were male. Forty-three patients (68%) were White, 9 (14%) were Hispanic, 3 (5%) were of Asian American descent, 2 (3%) reported as "other," and 6 (10%) were unreported. All patients had been previously healthy before receiving the vaccine, without any viral prodrome. None of the patients had a history of or reactions to previous vaccines. Fifty-five (87%) had no significant past medical history. Pertinent past medical history in 7 patients included a remote history of viral myocarditis in 2 patients and

juvenile idiopathic arthritis, eosinophilic esophagitis, hyperlipidemia, irritable bowel syndrome, and Wolff-Parkinson-White syndrome in one each. One patient had a history of mild COVID-19 infection 6 months before his first dose of the vaccine, with no residual symptoms. There was a family history of viral myocarditis and Brugada syndrome in one patient each. Fifty-nine patients (94%) had received the Pfizer-BioNTech vaccine, and 4 (6%) had received the Moderna vaccine. All except for one patient presented after the second dose. The patient who presented after the initial dose had no known previous COVID-19 infection.

The mean onset of symptoms from the day of vaccination was 2.1 ± 1.3 days (range 0–7 days). Forty-five patients (71%) presented with symptoms within 2 days of receiving the vaccine. Predominant symptoms are summarized in Table 1. All patients displayed elevated serum troponin levels, and all but one had abnormal C-reactive protein levels. Approximately half of the patients had an elevated erythrocyte sedimentation rate (44%) and/or B-natriuretic peptide level (53%). Acute COVID-19 infection was ruled out on the basis of negative results on real-time reverse transcription polymerase chain reaction tests to detect SARS-CoV-2 in 56 patients (89%); the others were not tested. Past exposure to COVID-19 infection was ruled out on the basis of negative nucleocapsid antibody test results in 53 (84%) patients. Of these, 18 patients were positive for spike protein, suggesting an active immune response to the vaccine.

The length of stay in the hospital was 3.0 ± 1.4 days (range 1–7). Twenty-seven (43%) patients were supervised in the ICU during their hospitalization, mainly for arrhythmia monitoring, with a mean stay of 2.5 days. None of the patients required inotropic support, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). There were no deaths. Treatments included nonsteroidal antiinflammatory drugs in 54 patients (86%), intravenous immunoglobulin in 17 (27%), corticosteroids in 15 (24%), and colchicine in 4 (6%). Six patients (10%) had received aspirin, clopidogrel, nitroglycerine, heparin,

TABLE 1 Clinical Characteristics in Children and Young Adults with Myocarditis After COVID-19 Vaccination

Characteristic	Overall (N = 63)	12–15 y (n = 31)	16–20 y (n = 32)	P
Age, y	15.6 ± 1.8 (12–20)	14.4 ± 1.1	16.9 ± 1.0	—
Height, cm	172 ± 11	169 ± 11	176 ± 10	.01
Wt, kg	73.3 ± 19.4	67.5 ± 16.6	79 ± 20.5	.02
BSA, m^2	1.86 ± 0.30	1.77 ± 0.30	1.95 ± 0.30	.008
Male sex, *n* (%)	58 (92)	27 (87)	31 (97)	.16
Second dose, *n* (%)	62 (98)	30	32	.32
Days from recent vaccination to symptoms onset	2.1 ± 1.3 (0–7)	1.9 ± 0.9 (1–3)	2.3 ± 1.7 (0–7)	.15
Symptoms, *n* (%)				
Onset <2 d since vaccination	45 (71)	22 (71)	23 (72)	.94
Fever (≥100.4°F)	28 (44)	13 (42)	15 (47)	.70
Shortness of breath	22 (35)	9 (29)	13 (41)	.34
Chest pain	63 (100)	31 (100)	32 (100)	.98
Nausea or emesis	15 (24)	7 (23)	8 (25)	.82
Headache	16 (25)	7 (23)	9 (28)	.62
Fatigue, myalgias, or arthralgias	24 (38)	8 (26)	16 (50)	.05
Laboratory values				
Troponin, ng/mL	8.8 ± 9.1	7.7 ± 8.4	9.9 ± 9.9	.34
C-reactive protein, mg/L	37 ± 35	28 ± 23	46 ± 43	.05
BNP, pg/mL	94 ± 147	109 ± 168	68 ± 107	.50
Treatment and hospital course				
IVIg, *n* (%)	17 (27)	5 (16)	12 (38)	.05
Steroids, *n* (%)	15 (24)	5 (16)	10 (31)	.14
NSAIDs, *n* (%)	54 (86)	28 (90)	26 (81)	.31
Colchicine, *n* (%)	4 (6)	1 (3)	3 (9)	.32
ICU admissions, *n* (%)	27 (43)	10 (32)	17 (53)	.09
Length of ICU stay, d	2.5 ± 1.5 (1–7)	2.1 ± 1.1 (1–4)	2.7 ± 1.6 (1–7)	.23
Length of hospital stay, d	3.0 ± 1.4 (1–7)	2.8 ± 1 (1–5)	3.3 ± 1.7 (1–7)	.18
Inotropic, mechanical, or circulatory support; ECMO; or mortality	0	—	—	—

Data are reported as mean ± SD (range), unless specified. Percentages may not total 100 because of rounding. The denominator for calculation of percentages is the total sample size. BNP, B-natriuretic peptide; BSA, body surface area; IVIg, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug; —, not applicable.

or β-blockers because of concerns for ST-segment elevation myocardial infarction on presentation.

Cardiovascular Findings

Forty-four patients (70%) had abnormal electrocardiogram (ECG) findings. Predominantly diffuse ST-segment elevations and/or T-wave inversion was noted (Fig 1). One patient (2%) presented with complete heart block but did not require pacing and regained normal conduction after admission. Three (5%) patients were noted to have nonsustained ventricular tachycardia, of whom one was treated with amiodarone (Fig 2) and another with an oral β-blocker.

Nine patients (14%) had mildly decreased left ventricular function (EF 45%–54%) by echocardiography (Table 2). Coincidental findings on echocardiography included a bicuspid aortic valve and an anomalous origin of the right coronary artery from the left sinus of Valsalva in one patient each. Fifty-six patients (89%) underwent CMR. The CMR study was performed within a week of the COVID-19 vaccination in 51 patients (91%). Fifty (89%) patients had evidence of myocardial edema based on T2-weighted imaging or T2 mapping (Fig 3). T1-weighted imaging to evaluate EGE denoting hyperemia was performed in 13 patients (21%), and findings were universally negative. Forty-nine patients (88%) had evidence of LGE (Figs 4 and 5), which occurred nearly uniformly in the inferolateral and lateral walls of the left ventricle in the subepicardial region, a typical location encountered in myocarditis and a pattern consistent with nonischemic myocardial injury and necrosis.[9] LGE were predominantly reported in the American Heart Association myocardial segments 4, 5, 6, 10, 11, and 12, along with segments 1, 13, 14,15,16 in some patients.[10] The mean ECV was 32.6% ± 9.0%. Thirteen patients (23%) had mildly reduced left ventricular function, whereas 3 (7%) had mildly reduced right ventricular function. Mildly increased left ventricular volume was reported in 1 patient, whereas 3 had borderline or mild right ventricular dilation.[11,12] Forty-nine patients (88%) fulfilled the CMR Lake Louise imaging criteria for myocarditis.

There was no significant difference in the clinical characteristics or the cardiovascular findings between the 12- to 15-year-old age group and the older adolescents in the C-VAM cohort (Tables 1 and 2). On comparison of the patients with C-

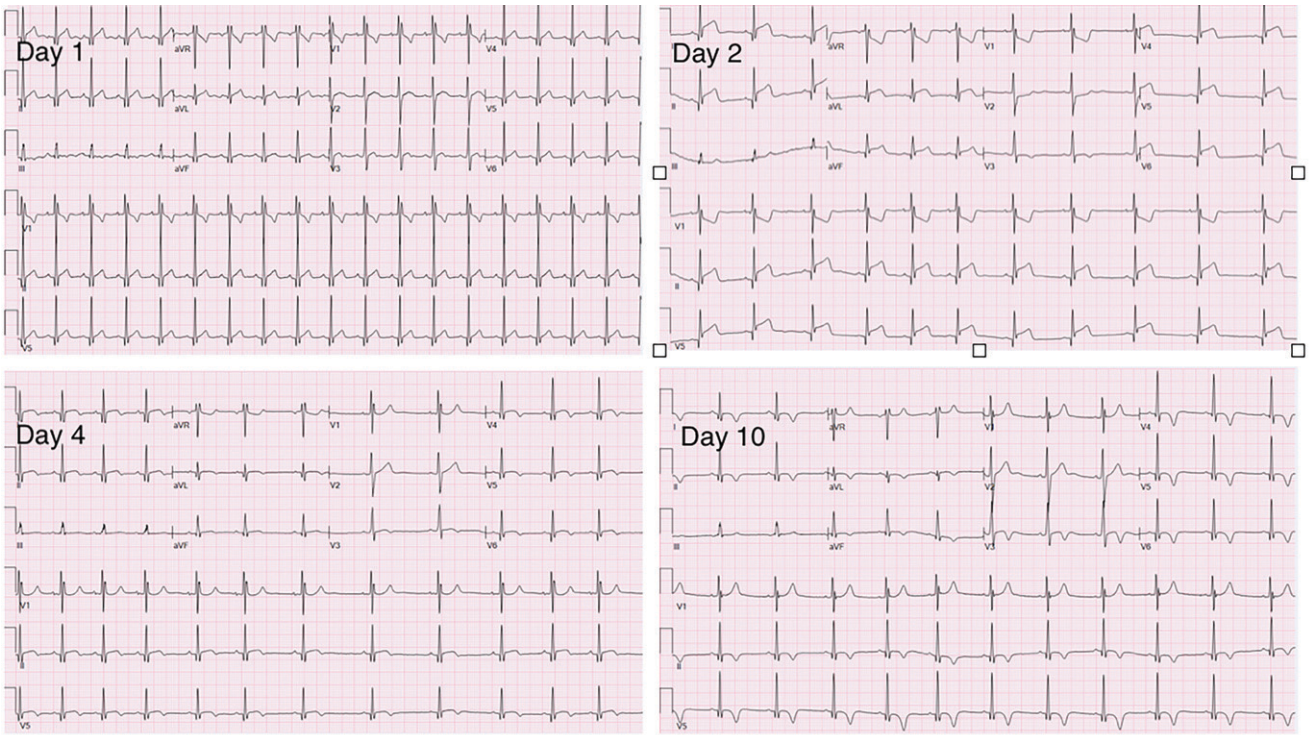

FIGURE 1
ECG in a 17-year-old patient with myocarditis after COVID-19 vaccination showing diffuse ST-segment elevation (days 1 and 2) and T-wave inversion (days 4 and 10).

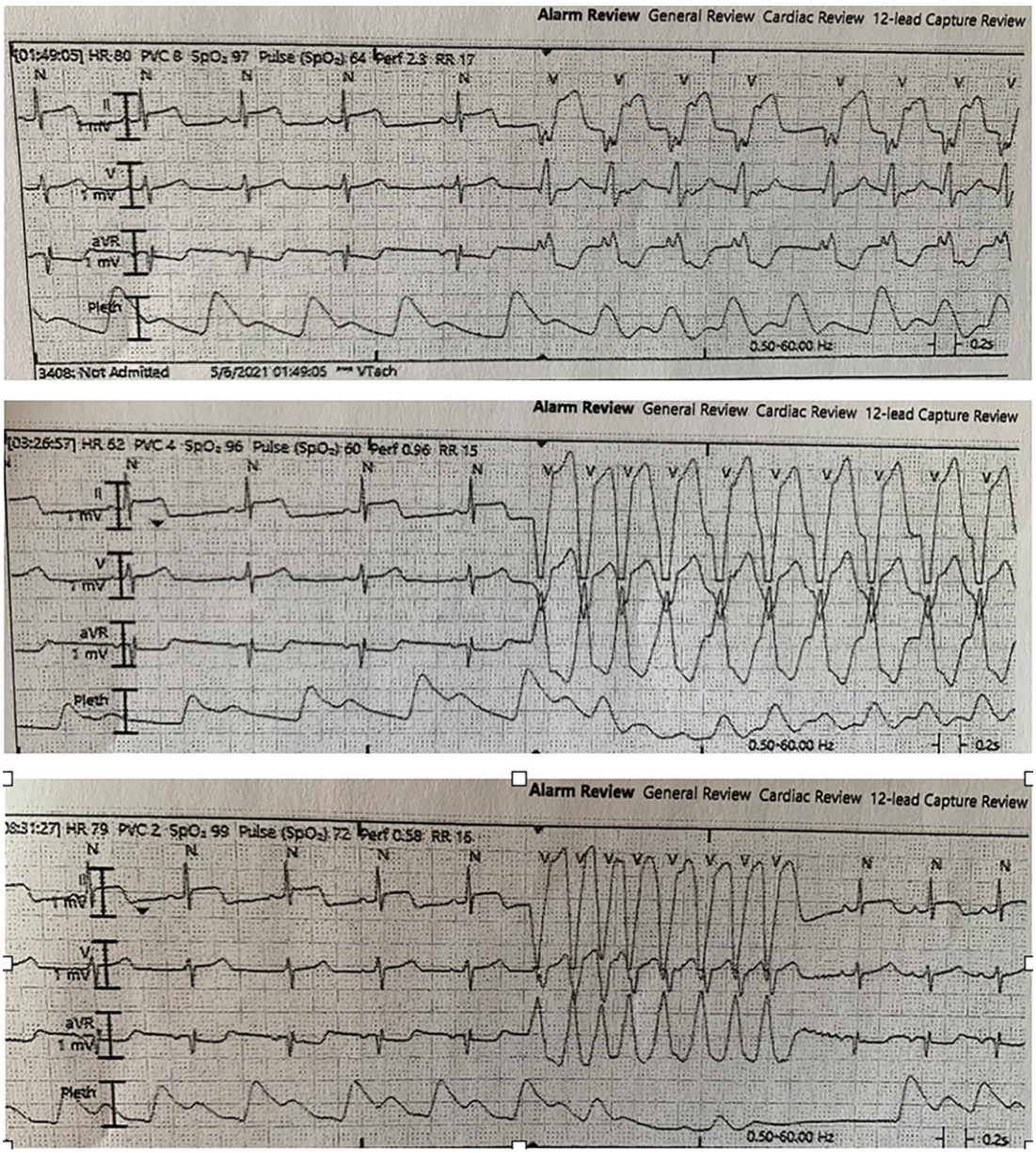

FIGURE 2

Strips from a telemetry unit showing multiple episodes of nonsustained ventricular tachycardia in a 16-year-old patient with myocarditis after COVID-19 vaccination. HR, heart rate; PVC, premature ventricular contraction; SpO_2, pulse oxygen saturation; RR, respiratory rate.

VAM with the MIS-C cohort (Table 3), the patients with MIS-C were sicker and had a longer ICU length of stay (7 days ± 5 [range 2–18]); 50% of them required inotropic support, including ECMO in one. C-reactive protein levels were higher and ventricular function was worse in patients with MIS-C when compared with patients with C-VAM. Serum troponin levels were higher and there was an increase in prevalence and extent of LGE in the C-VAM group when compared with the MIS-C cohort (Figs 4–6).

Follow-up

In patients with C-VAM, follow-up data until July 21, 2021, were reviewed. There was no significant difference in the follow-up, or short-term, outcomes between the younger and older pediatric age groups. Fifty-four patients (86%) were evaluated for follow-up at a mean of 35 days ± 25 (range 8–122) since their last vaccination. All were doing well clinically, with resolution of their symptoms in most. Seven patients (13%) reported nonspecific symptoms, including intermittent atypical chest pain (4), palpitations (2), and mild fatigue with minimal activity (1). All patients had normal ventricular function, based on echocardiography. The 4 patients

TABLE 2 Cardiovascular Testing and Imaging Findings in Children and Young Adults With Myocarditis After COVID-19 Vaccination

Findings	Overall (N = 63)	12–15 y (n = 31)	16–20 y (n = 32)	P
ECG, n (%)				
Abnormalities on ECG	44 (70)	19 (61)	25 (78)	.38
Complete heart block	1 (2)	0 (0)	1 (3)	.32
Nonsustained VT	3 (5)	1 (3)	2 (6)	.57
Echocardiography				
LV EF %	61 ± 6.5 (45–73)	61 ± 6 (45–73)	60 ± 7 (45–83)	.51
Reduced LV EF, n (%)				
Mild (EF: 45%–54%)	9 (14)	4 (13)	5 (16)	.80
Moderate (EF: 35%–44%)	0	—	—	—
Severe (EF <35%)	0	—	—	—
CMR				
Days from recent vaccination to CMR	4.9 ± 2.3 (2–15)	5.0 ± 2.8 (2–15)	5.2 ± 3.2 (2–15)	.68
Myocardial edema (T2-weighted imaging or T2 mapping), n/N (%)	50/56 (89)	24/28 (86)	26/28 (93)	.40
ECV %	32.6 ± 9	36.3 ± 11	28.9 ± 4	.05
Presence of LGE, n/N (%)	49/56 (88)	24/28 (86)	25/28 (89)	.69
LV EF %	58 ± 6 (46–73)	59 ± 6 (46–73)	57 ± 5 (47–64)	.21
Reduced LV EF, n/N (%)				
Mild (EF: 45%–54%)	13/56 (23)	6/28 (21)	7/28 (25)	.83
Moderate (EF: 35%–44%)	0	—	—	—
Severe (EF <35%)	0	—	—	—
LV EDV, mL/m^2	86 ± 12 (55–111)	85 ± 11 (57–105)	88 ± 14 (55–111)	.40
RV EF %	56 ± 9 (43–105)	56 ± 5 (47–65)	55 ± 12 (43–105)	.68
Reduced RV EF (EF <49%), n/N (%)	3/45 (7)	1/22 (5)	3/23 (13)	.58
RV EDV, mL/m^2	89 ± 15 (48–123)	87 ± 13 (56–107)	91 ± 16 (48–123)	.36

Data are reported as mean ± SD (range), unless specified. Percentages may not total 100 because of rounding. Unless otherwise specified, the denominator for calculation of percentages is the total sample size. EDV, end diastolic volume; LV, left ventricle; RV, right ventricle; VT, ventricular tachycardia; —, not applicable.

who had presented with arrhythmias earlier continue to be in normal sinus rhythm with no recurrence. Of the 60 patients with ECGs done at follow-up, 48 (80%) had normal ECG findings. Eight had persistent T-wave abnormality or inversion in inferior leads, 2 had inferior Q waves, and 2 had nonspecific ST-T changes. Holter information was available in 10 patients (19%) and revealed no abnormalities. Troponin levels were obtained in 27 patients (50%) and were normal, except that 3 individuals had borderline elevations. Two patients (4%) have had a follow-up CMR so far at 66 and 71 days, respectively, after the initial CMR. Both showed improvement in myocardial edema but had persistence of LGE, with mild improvement in 1 patient (Fig 7). Both patients continued to have normal biventricular function on CMR. Biventricular sizes were normal in both, including one who was noted to have mild right ventricular dilation at his initial CMR. Follow-up CMR studies have been scheduled and are pending, as of the time this article was submitted, for the rest of the patients. There were no acute events, rehospitalizations, or deaths reported.

DISCUSSION

Although myocarditis after immunizations against smallpox, influenza, and tetanus is well recognized,[13–16] the experience in children with vaccine-associated myocarditis, other than after COVID-19 vaccination, is limited. Importantly, myocarditis was not reported after the clinical trials of mRNA COVID-19 vaccines.[17,18] This may be related to the limited number of patients in the clinical trials and reflective of the apparent rarity of this complication.[19]

On May 10, 2021, the US Food and Drug Administration (FDA) expanded the Emergency Use Authorization for the Pfizer-BioNTech vaccine to include adolescents 12 through 15 years age.[20] As of July 6, 2021, 594 cases of myocarditis and/or pericarditis reported to the Vaccine Adverse Event Reporting System have been confirmed by the CDC and FDA.[21] On the basis of the Advisory Committee on Immunization Practices notification from June 23, 2021, the highest reporting rates were among boys aged 12 to 17 years and those aged 18 to 24 years (62.8 and 50.5 reported myocarditis cases per million second doses of the mRNA COVID-19 vaccine administered, respectively).[22] At present, the CDC and FDA continue to recommend COVID-19 vaccination for all individuals aged ≥12 years.[22]

The current study adds the following information to our understanding of myocarditis related to the COVID-19 vaccine:

1. Myocarditis after mRNA vaccines is associated with acute myocardial injury and edema of

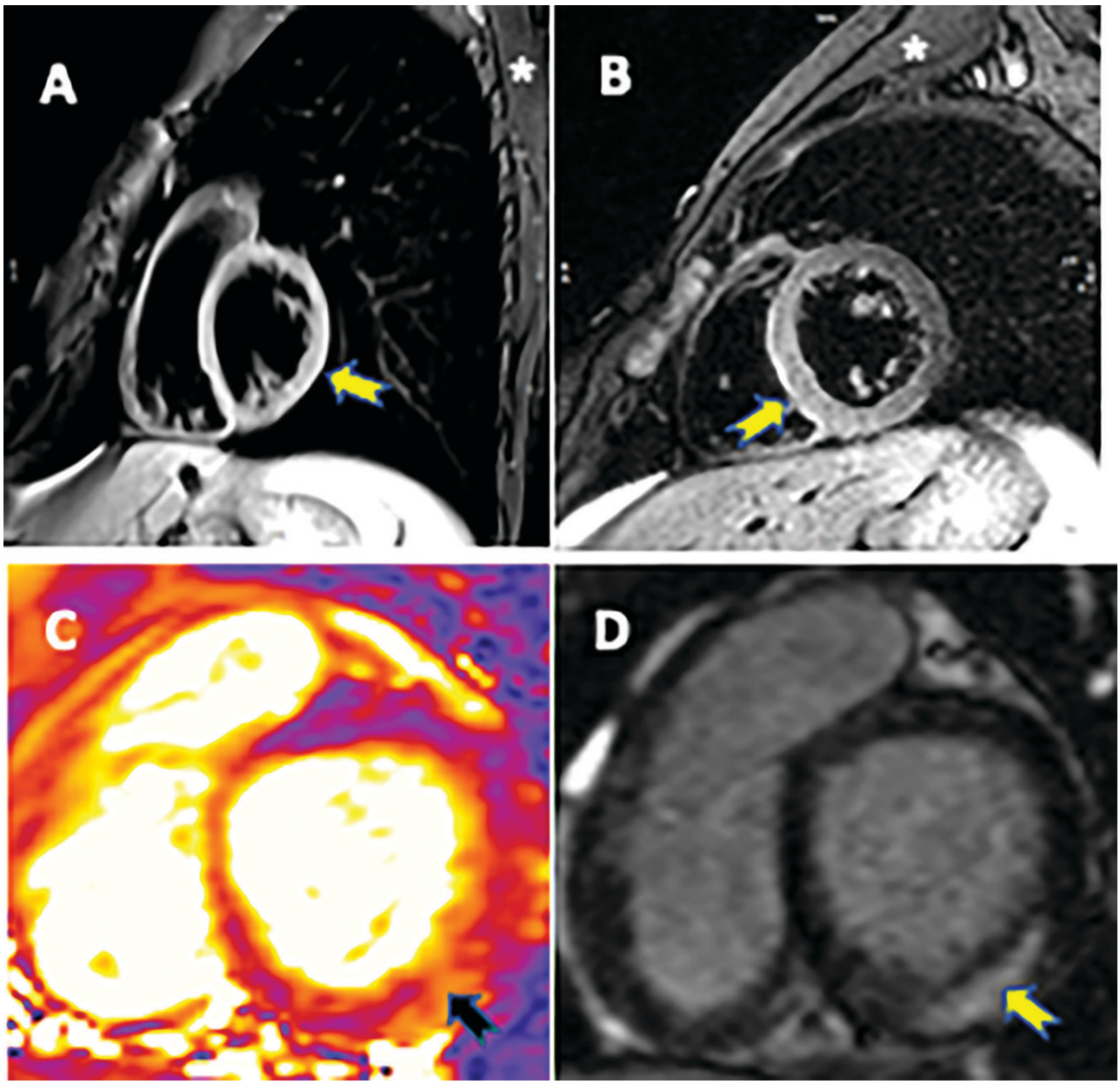

FIGURE 3

CMR examples of myocardial edema in the C-VAM cohort. A and B, T2-weighted images show high signal intensity in the myocardium (yellow arrow) compared with the skeletal muscle (*) in 2 patients. C and D, T2 mapping image demonstrates an area of elevated T2 (black arrow) in subepicardial and mid-myocardial regions (C) corresponding to an area of LGE (yellow arrow) (D).

the myocardium, in the presence of preserved ventricular function;

2. the initial clinical course and short-term outcomes are good and reassuring;
3. there is no apparent difference in clinical characteristics and outcomes between 12- to 15-year-olds and older adolescents; and
4. the clinical presentation is distinct from MIS-C and appears to be less severe.

Although endomyocardial biopsy remains the confirmatory test in the diagnosis of myocarditis, its invasive nature and the possibility of tissue sampling errors, along with risks of cardiac perforation and arrhythmias, limit its use, especially in children. Cardiac MRI has emerged as the modality of choice to evaluate the myocardium, including in myocarditis.[4,23] The CMR diagnosis of myocarditis by the Lake Louise criteria is based on the detection of myocardial edema and myocardial injury or necrosis.[4–6,23,24] The majority of our patients met these

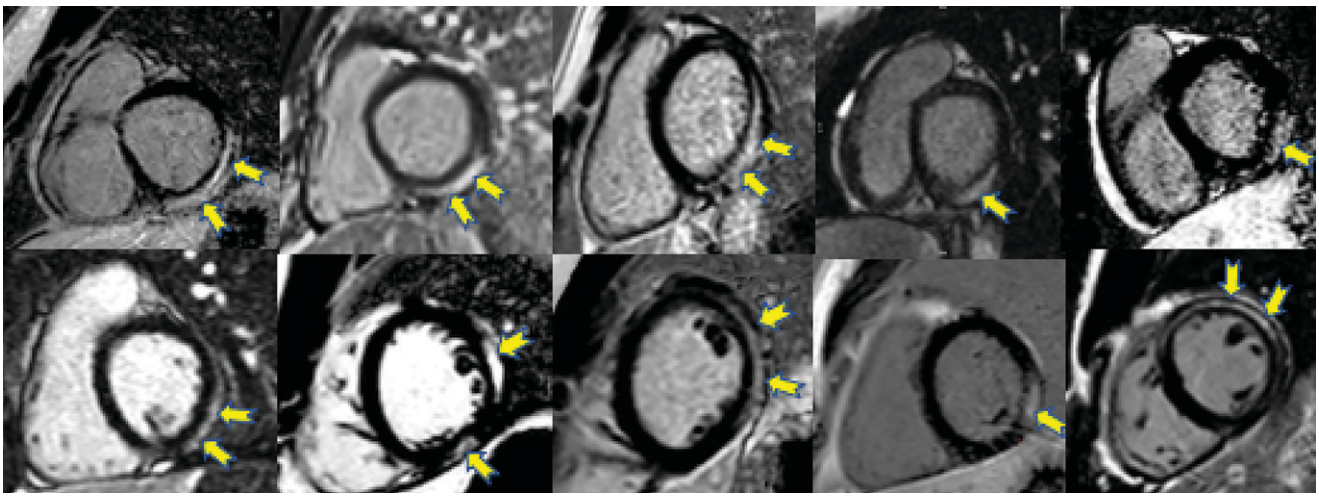

FIGURE 4
CMR examples illustrating LGE in the C-VAM cohort (short-axis view). The pattern of LGE is notably similar across all patients, with a subepicardial distribution along the lateral, inferolateral, and inferior walls in the basal and midmyocardium of the left ventricle (yellow arrows).

CMR criteria, and the rest were classified as having clinically suspected myocarditis.[23] Previous reports provided limited insights into the CMR findings in C-VAM. The myocardial tissue characteristics observed in our patients were like those seen in acute viral-mediated myocarditis.[4,23,24] Most patients presented with evidence of myocardial edema. Subepicardial LGE affecting the left ventricular lateral and inferior walls was present in nearly all patients. The high prevalence of LGE and, in some cases, its extent, along with consistency of the LGE pattern (Figs 4 and 5), was unexpected, especially given the relatively mild clinical symptoms in many patients, although it was in keeping with the elevated troponin levels that were observed in all patients. The relatively mild disease course of the patients reported here makes it tempting to speculate that many others go undetected, as was the case with the smallpox vaccine.[13–15]

In contrast, patients with MIS-C are often critically ill on presentation, requiring advanced support.[25–28] They have higher systemic inflammatory markers and imaging evidence of cardiodepression. The patients with C-VAM, with a milder

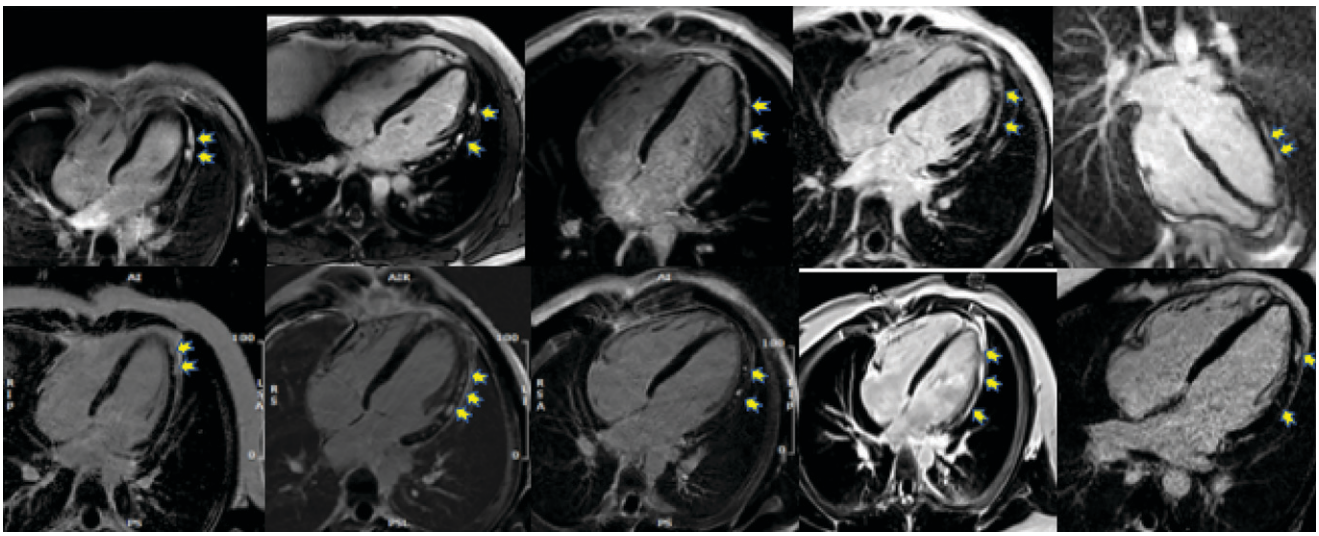

FIGURE 5
CMR examples illustrating LGE in the C-VAM cohort (4-chamber view). The pattern of LGE is notably similar across all patients, with enhancement in a subepicardial and midmyocardial pattern noted along the lateral and inferior walls (yellow arrows).

TABLE 3 Comparison Between Patients With C-VAM and MIS-C

	C-VAM (n = 63)	MIS-C (n = 16)	P
Age, y	15.6 ± 1.8	13.3 ± 4.3	.05
Wt, kg	73.3 ± 19.4	57.1 ± 20.8	.01
Troponin, ng/mL	8.78 ± 9.15	0.67 ± 1.10	<.0001
C-reactive protein, mg/L	37.0 ± 35.4	151.1 ± 119.5	.002
Intensive care length of stay	2.5 ± 1.5	6.6 ± 4.6	.004
LVEF % (echocardiography)	60.9 ± 6.5	45.1 ± 9.5	<.0001
LGE, n (%)	49 (88)	3 (20)	.0005
Myocardial edema,[a] n (%)	47 (83.9)	4 (28.6)	<.0001

Data are reported as mean ± SD, unless specified. LVEF, left ventricular ejection fraction.
[a] As evidenced by CMR parametric mapping or T2-weighted imaging.

presentation and hospital course and relatively preserved ventricular function, appear to have increased prevalence of LGE in comparison with those with MIS-C. This raises the question of whether differing pathomechanisms of cardiac involvement are at play in C-VAM versus MIS-C. Although it has been hypothesized that the acute ventricular dysfunction complicating MIS-C may be related to the systemic cytokine storm that is present during this overwhelming inflammatory condition,[25–28] the mechanism of cardiac injury in C-VAM appears more targeted to the cardiomyocyte. The pathophysiology of the myocardial injury in these patients is not well understood. One proposed mechanism is through molecular mimicry[29–31]: Myocardial proteins may resemble those that are expressed after mRNA vaccination, to which the body mounts an antibody response, possibly leading to myocardial injury or inflammation. The spike glycoprotein of SARS-CoV-2 attaches to the myocardial type 2 angiotensin-converting enzyme (ACE2) receptor expressed by cardiomyocytes, directly causing cell membrane disruption, even at a low viral load.[32,33] Thus, as an alternative explanation of vaccine-related injury, it is conceivable that in patients with C-VAM, the myocardial injury may be the result of the SARS-CoV-2 spike protein encoded by the mRNA vaccine and its binding to the host cell ACE2 receptor,[34] even in the absence of a live virus. Lastly, it is possible that the complex of the mRNA vaccine–induced spike protein and the myocardial ACE2 receptor presents an immunologic target. In this context, the striking predilection for boys, which is a consistent element of previous reports and corroborated by our results, is noteworthy: <10% of our patients were female. Estrogen is known to upregulate ACE2,[35] which has been proposed as a protective mechanism against organ damage by SARS-CoV-2, including in the heart. An increased genetic susceptibility in some patients has been discussed[36] and may explain the recurrent myocarditis in 2 of our patients who had a previous episode and potentially in a third patient with a family history of viral myocarditis.

Myocarditis after COVID-19 vaccination has been noted predominantly in White patients, in contrast to the Black and ethnic minority groups frequently reported in MIS-C.[25,27,28] Possible

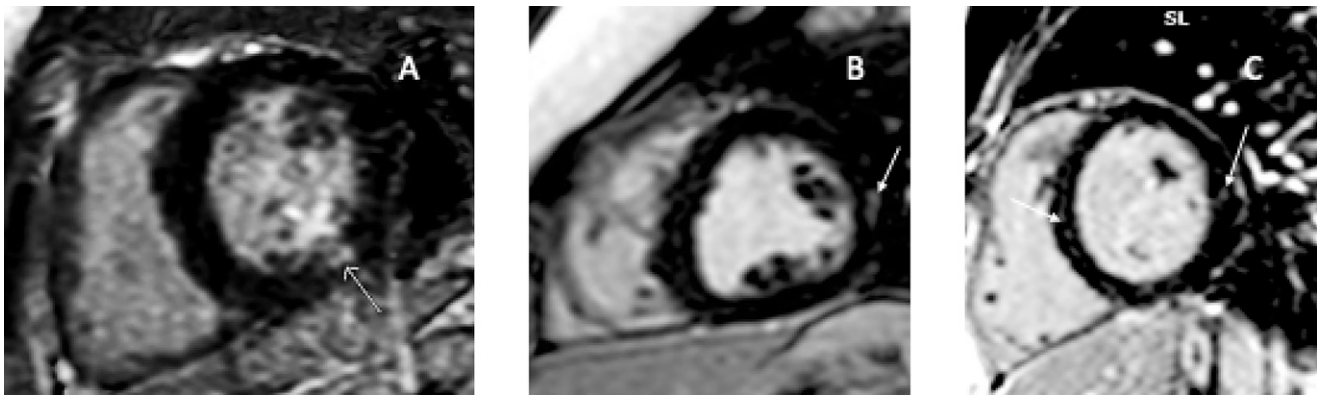

FIGURE 6
A–C, CMR images in 3 children hospitalized for MIS-C revealing trivial, focal subepicardial or midmyocardial LGE (white arrows). All 3 patients presented with at least moderate ventricular dysfunction and required inotropic support, including one needing ECMO (B).

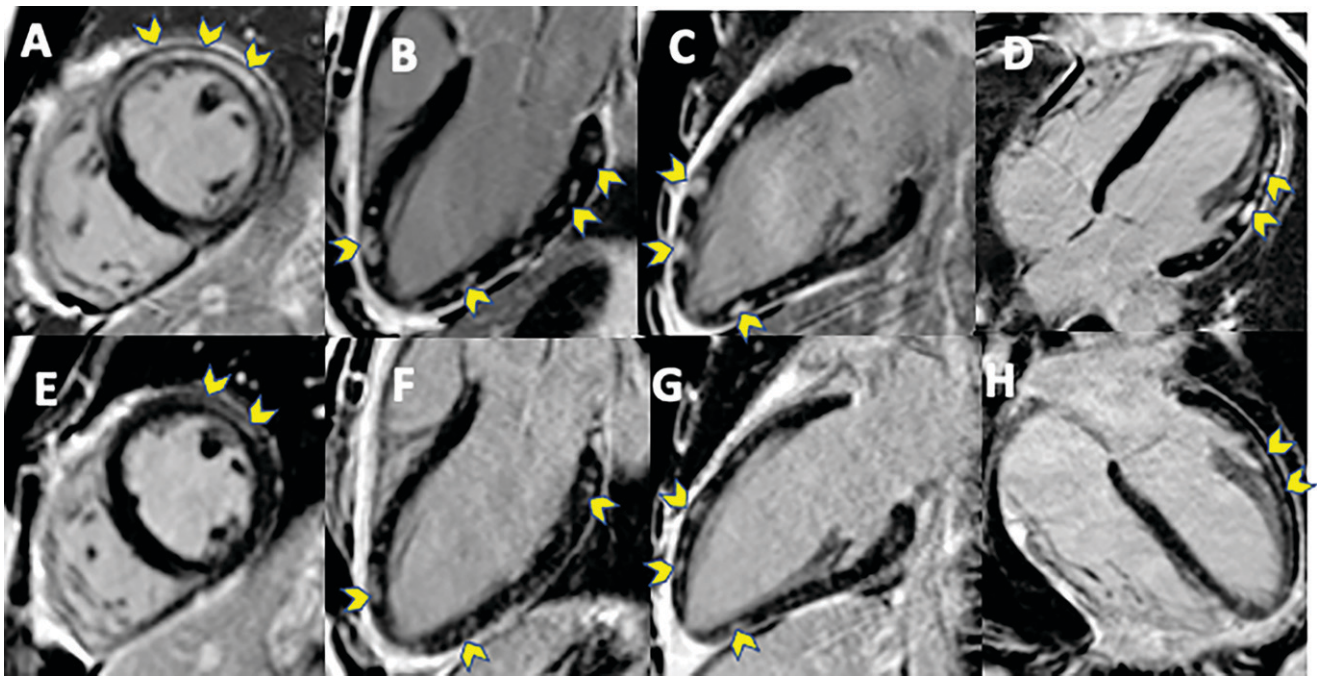

FIGURE 7
A–E, CMR in a patient with C-VAM at the time of diagnosis (A–D) and 8 weeks post diagnosis (E–H). There is notable persistence of myocardial LGE (yellow arrows), with mild improvement.

explanations for this ethnic discrepancy may include socioeconomic disparities seen in COVID-19 infections,[37] variation in vaccination rates,[38] and susceptibility to the infection itself and/or its complications.

Ten percent of our patients were initially worked up and treated for myocardial infarction. As awareness of vaccine-related myocarditis increases, we expect that more practitioners will consider the possibility of C-VAM, and the diagnosis will be made earlier.

A selection bias in the C-VAM cohort toward LGE-positive patients cannot be ruled out in our study, given that LGE was likely used to establish a diagnosis of myocarditis in some individuals. In fact, a similar selection bias is likely present in most, if not all, CMR-based studies of myocarditis. The true and independent prevalence of LGE is therefore unknown, and we are unable to speculate whether LGE is more prevalent after vaccination as compared with viral myocarditis.

The prognostic significance of prevalent LGE in asymptomatic patients with C-VAM is unclear at this time. The follow-up CMR in 2 of our patients has revealed persistence of LGE, albeit mildly decreased in one. Some reports have suggested a contraction of LGE during follow-up of acute viral myocarditis.[39,40] Follow-up CMR, hence, appears warranted to depict the extend of myocardial and ventricular remodeling or resolution of LGE. In the absence of guidelines for return to sports after myocarditis after COVID-19 vaccination, our findings make it seem reasonable to apply the recommendations available for acute viral myocarditis, which include refraining from sports for at least 3 to 6 months as well as close observation and monitoring for any dysrhythmias.[41]

Limitations of our study include its retrospective nature, combining patients from 16 different institutions that used similar but not identical approaches during the workup and management of childhood myocarditis. Our patients represent a selected cohort that may not necessarily be representative of the general pediatric population.

CONCLUSIONS

We report the largest study that we are aware of describing myocardial tissue characteristics in detail, as noted on CMR, with clinical features and early outcomes in pediatric patients with acute myocarditis after mRNA COVID-19 vaccination in the United States. Comparison with MIS-C improves our understanding of both the disease processes. Most patients with C-VAM had evidence of myocardial edema and of myocardial injury, as evidenced by LGE, which was out of keeping with the mild clinical presentation and

normal or quickly recovered ventricular function in most. Early clinical outcomes in these patients have been reassuring so far. The prognostic significance, long-term implications, and mechanism of this myocardial injury needs to be studied further, especially as vaccination efforts are rolled out to younger children.

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ABBREVIATIONS

ACE2: type 2 angiotensin-converting enzyme
CDC: Centers for Disease Control and Prevention
CMR: cardiovascular magnetic resonance
COVID-19: coronavirus disease 2019
C-VAM: coronavirus disease 2019 vaccination–associated myocarditis
ECG: electrocardiogram
ECMO: extracorporeal membrane oxygenation
ECV: extracellular volume
EF: ejection fraction
EGE: early gadolinium enhancement
FDA: US Food and Drug Administration
LGE: late gadolinium enhancement
MIS-C: multisystem inflammatory syndrome in children
mRNA: messenger RNA
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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Address correspondence to Supriya S. Jain, MD, Division of Pediatric Cardiology, Department of Pediatrics, New York Medical College and Maria Fareri Children's Hospital at Westchester Medical Center, 40 Sunshine Cottage Road, Valhalla, NY 10595. E-mail: sjain7@nymc.edu

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