Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study

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Summary

Background We aimed to study the clinical characteristics, myocardial injury, and longitudinal outcomes of COVID-19 vaccine-associated myocarditis (C-VAM).

Methods In this longitudinal retrospective observational cohort multicenter study across 38 hospitals in the United States, 333 patients with C-VAM were compared with 100 patients with multisystem inflammatory syndrome in children (MIS-C). We included patients ≤30 years of age with a clinical diagnosis of acute myocarditis after COVID-19 vaccination based on clinical presentation, abnormal biomarkers and/or cardiovascular imaging findings. Demographics, past medical history, hospital course, biochemistry results, cardiovascular imaging, and follow-up information from April 2021 to November 2022 were collected. The primary outcome was presence of myocardial injury as evidenced by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging.

Findings Patients with C-VAM were predominantly white (67%) adolescent males (91%, 15.7 ± 2.8 years). Their initial clinical course was more likely to be mild (80% vs. 23%, p < 0.001) and cardiac dysfunction was less common (17% vs. 68%, p < 0.0001), compared to MIS-C. In contrast, LGE on CMR was more prevalent in C-VAM (82% vs. 16%, p < 0.001). The probability of LGE was higher in males (OR 3.28 [95% CI: 0.99, 10.6, p = 0.052]), in older patients (>15 years, OR 2.74 [95% CI: 1.28, 5.83, p = 0.009]) and when C-VAM occurred after the first or second dose as compared to the third dose of mRNA vaccine. Mid-term clinical outcomes of C-VAM at a median follow-up of 178 days (IQR 114–285 days) were reassuring. No cardiac deaths or heart transplantations were reported until the time of submission of this report. LGE persisted in 60% of the patients at follow up.

Interpretation Myocardial injury at initial presentation and its persistence at follow up, despite a mild initial course and favorable mid-term clinical outcome, warrants continued clinical surveillance and long-term studies in affected patients with C-VAM.

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Keywords: Myocarditis; COVID-19 vaccine-associated myocarditis; Cardiac MRI; Myocardial injury; LGE late gadolinium enhancement; MIS-C multisystem inflammatory syndrome in children

Introduction

Vaccination has been a public health cornerstone in the mitigation of the SARS-CoV-2 pandemic. Myocarditis is a rare complication of mRNA vaccines.[1–3] Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) imaging is increasingly used to characterize acute myocardial injury and chronic scarring in childhood myocarditis.[4] We previously reported a high rate of myocardial injury with COVID-19 vaccine-associated myocarditis (C-VAM) in a pediatric pilot cohort.[3] The natural history, implications of myocardial injury, and overall prognosis for young patients with C-VAM are insufficiently studied. In other conditions, including viral myocarditis, LGE can be a harbinger of heart failure, dilated cardiomyopathy, arrhythmias, and sudden cardiac death in the future.[5–9] The objectives of this study were to describe the initial clinical and cardiac imaging characteristics of C-VAM, explore possible risk factors for myocardial injury as evidenced by LGE on CMR imaging and evaluate cardiovascular outcomes, in a large cohort of children, adolescents and young adults diagnosed with C-VAM.

Methods

Study design and participants

This was a longitudinal multicenter retrospective observational study across 38 U.S. member institutions of the Myocarditis After COVID Vaccination (MACiV) study network of pediatric cardiologists and CMR experts. We included patients ≤30 years of age with a clinical diagnosis of acute myocarditis after COVID-19 vaccination based on clinical presentation, abnormal biomarkers and/or cardiovascular imaging findings, as per the Centers for Disease Control and Prevention

Research in context

Evidence before this study
In August 2021, we published the first report of a robust pediatric cohort with COVID-19 vaccine-associated myocarditis (C-VAM), systematically studied by cardiac magnetic resonance imaging (CMR) and demonstrating myocardial injury as evidenced by late gadolinium enhancement (LGE). A PubMed search from 03/01/2021 to 9/30/2021, using the terms "COVID-19 vaccine myocarditis" AND "late gadolinium enhancement" AND "outcome" produced only two results, including our study above. No literature existed on the sequelae of C-VAM or the prognosis of LGE in these patients. We thus embarked on a larger multicenter longitudinal study to comprehensively evaluate the cardiac manifestations and outcomes of C-VAM, especially the evolution of myocardial damage in children, adolescents, and young adults.

Added value of this study
This study not only provides a detailed phenotypic clinical characterization of C-VAM in 333 children, adolescents, and young adults, but also includes important longitudinal myocardial tissue information in vaccine-associated myocarditis and provides data on the cardiovascular outcomes of this complication in a large cohort of patients across 38 sites in the United States. This constitutes the hitherto largest longitudinal study in C-VAM that includes information on myocardial injury and scarring, along with its possible risk factors. The study contrasts C-VAM to multisystem inflammatory syndrome in children (MIS-C), a complication related to COVID-19 with cardiac manifestations.

Implications of all the available evidence
Myocardial injury as evidenced by LGE on CMR imaging is common in patients with myocarditis after mRNA COVID-19 vaccination who present to the hospital, especially in adolescent males. As the long-term significance of this myocardial damage is unclear, continued clinical surveillance of affected patients is warranted.

(CDC) criteria[1] (Appendix A). Patients with a plausible alternative etiology for their acute myocarditis, including a recent infectious cause, were excluded. Institutional research ethics boards approved the study at every participating site and waived informed consent requirements. Demographics, past medical history, hospital course, biochemistry results, cardiovascular imaging, and follow-up information from April 2021 to November 2022 were collected. Sex and race/ethnicity as reported by patients/parents were retrieved from the medical records. Patients were stratified into younger (5–15 years) and older (16–30 years) age groups, reflecting the sequential vaccine roll-out of the U.S Food and Drug Administration's Emergency Use Authorizations of mRNA vaccines. To gain a better perspective of the cardiac involvement in myocarditis associated with COVID-19 vaccination, we compared these patients with those who had multisystem inflammatory syndrome in children (MIS-C), based on CDC criteria[10] (Appendix B), an important complication of COVID-19 in the pediatric population with frequent cardiac manifestations that the vaccine seeks to prevent. Patients with MIS-C, who had CMR for myocarditis during the acute or subacute illness were included.

Clinical information and cardiovascular testing
Biomarkers of myocardial injury (troponin), heart failure (brain-natriuretic peptide BNP or NT-pro-BNP) and systemic inflammation (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) were collected. Troponin levels were standardized by dividing them by their respective upper limits of normal to account for assay variability across different institutions and to allow for comparison of different types of troponins (high sensitivity vs. regular). To compare clinical courses, greater than mild clinical severity was defined as ≥1 of the following: presence of ventricular arrhythmias, including ventricular tachy-arrhythmias and higher-grade atrioventricular conduction block, left ventricular (LV) systolic dysfunction on echocardiogram as defined by left ventricular ejection fraction (LVEF) <55%, need for inotropic medications, mechanical ventilation or invasive cardiac support, heart transplantation, or death.

Results from electrocardiograms (ECGs), telemetry, Holter monitoring, echocardiography, and CMR were collected. The CMR findings were verified by site co-investigators with expertise with this modality. CMR information about myocardial edema, hyperemia, myocardial injury and scarring along with ventricular volumes were recorded. Myocardial edema was identified by prolonged T2 time on mapping or high T2 signal intensity visually or by a myocardial/skeletal muscle signal intensity ratio ≥2. Hyperemia was diagnosed by early gadolinium enhancement. The presence of LGE in the myocardium or elevated native T1 times or extracellular volume fraction (ECV) were regarded as markers of myocardial injury.[11–14] T2 and native T1 times as well as ECV values were compared to local or reported pediatric normal ranges.[15,16] To assess the severity of myocardial injury, patients were stratified based on LGE severity. Greater than mild LGE severity was defined as multifocal and/or transmural LGE or ≥4 American Heart Association (AHA) myocardial segments with LGE.[17]

Outcomes

The primary outcome was presence of myocardial LGE at initial presentation. Secondary outcomes included the following variables during follow-up: presence of myocardial LGE; presence of cardiovascular symptoms including chest pain, palpitations, shortness of breath, syncope; ventricular or supra-ventricular tachycardias; frequent premature ventricular contractions; second- or third-degree atrioventricular conduction block; LVEF <55% on echocardiogram; listing for heart transplantation; re-hospitalization and/or death attributable to cardiac causes.

Statistical analysis

Continuous data are reported as means and standard deviations, if normally distributed; otherwise as medians and interquartile ranges (IQR). Categorical results are displayed as frequencies and percentages, as appropriate. Only complete data were included for analyses. Pearson's correlation and Spearman's rank correlation were used to assess the strength and direction of the relationship between parametric and non-parametric data, respectively. Fisher's exact test was used for categorical variables; the student's t-test or the Mann–Whitney U test was used for continuous variables. Tukey's post-hoc testing was used to adjust for multiplicity. Candidate demographic characteristics were assessed for association with baseline LGE using simple logistic regression and tested for multicollinearity and interaction before being included in multivariable analyses using stepwise forward logistic regression. Relationships with LGE are reported as odds ratios (OR) with 95% Confidence Intervals (CI). The Likelihood ratio test, Hosmer–Lemeshow test, Link test, and receiver operating curves were used to assess model fit, linearity, and discriminatory power, respectively. p-values <0.05 were regarded as significant. All analyses were performed with Stata, v.18 statistical software (StataCorp. 2023. Stata Statistical Software: Release 18. TX: StataCorp LLC).

Role of the funding source

The funder of the study did not have any role in study design, data collection, data analysis, or writing of the report except for its interpretation, review, edit and decision to submit for publication.

Results

Four hundred and thirty-three patients were enrolled, including 333 with C-VAM and 100 with MIS-C. Baseline demographic, clinical characteristics and cardiac imaging findings are summarized in Table 1.

Initial clinical course in C-VAM

The initial presentation of 58 of the C-VAM patients (17%) had been reported in our prior study.[3] Ninety-five percent of patients (306 of 323) had been vaccinated with the monovalent Pfizer-BioNTech COVID-19 mRNA vaccine, 5% (n = 16) had received the monovalent Moderna COVID-19 mRNA vaccine and one patient was reported to have received the Johnson & Johnson vaccine. The mean age at presentation was 15.7 ± 2.8 years, the age distribution is depicted in Fig. 1. Eighty-four percent of patients (278 of 331) had symptoms following the 2nd dose, 10% (n = 33) after the 1st dose, and 6% (n = 20) after the 3rd dose (booster). Mean onset of symptoms was within 3.2 ± 5.2 days from the day of vaccination, with 96% patients (318 of 331) presenting within 7 days from vaccination. Most of the patients had chest pain (96%, 320 of 333) and elevated troponin (96%, 313 of 326). There was no history of preexisting hemodynamically significant heart disease in any of the patients. All 269 patients who underwent polymerase chain reaction investigation for SARS-CoV-2 tested negative for the virus. Two hundred and ninety-nine C-VAM patients (90%) were admitted to the hospital, for a mean length of stay of 2.8 ± 2.1 days. Six patients (2%) received inotropic support, two (1%) required mechanical ventilation, and one (0.3%) underwent extracorporeal membrane oxygenation (ECMO). No patient required a ventricular assist device, was listed for heart transplantation, or died during the acute illness.

Cardiovascular testing in C-VAM

Two hundred patients (60%) had abnormal ECGs, consisting of diffuse ST segment changes and/or T wave inversions. Frequent premature ventricular contractions were noted in 26 patients (8%). Seventeen patients (5%) had ventricular tachycardia, nine of whom (53%) were treated with anti-arrhythmic medications. One patient (0.3%) presented with complete heart block. He did not require pacing and regained normal conduction following admission. Seventeen percent of patients (53 of 307) had LV systolic dysfunction by echocardiography, all in the mild range except for nine patients (3%) in the moderate-severe range. Left ventricular ejection fraction correlated weakly inversely with patient age (r = −0.17, p = 0.002). No patient had more than mild valvar regurgitation. Small pericardial effusions were reported in nine patients (3%). Cardiac magnetic resonance imaging (CMR) was performed in 72% patients (232 of 324), with a mean time interval of 23 ± 39 days after COVID-19 vaccine administration. Forty-one percent of them (96 of 232) had evidence of myocardial edema based on T2-weighted imaging or T2 mapping on CMR. Eighty-two percent (177 of 216) demonstrated LGE, occurring in the sub-epicardium in 63% (135 of 214) and frequently involving the mid and basal inferolateral segments of the left ventricle (Figs. 2 and 3). Older patients (>15 years of age) were more likely to exhibit LGE (88% vs. 75%, p = 0.01) and to have > mild LGE severity as compared to the younger age group (57% vs. 40%, p = 0.01). Standardized

	C-VAM				MIS-C				C-VAM vs. MIS-C
	Total (N = 333)	≤15 yrs. (N = 162)	>15 yrs. (N = 171)	p value	Total (N = 100)	≤15 yrs. (N = 68)	>15 yrs. (N = 32)	p value	p value
Demographics									
Age (years)	15.7 (2.8)	13.7 (1.8)	17.5 (2.3)	<0.0001	12.4 (4.4)	10.2 (3.6)	17.1 (1.0)	<0.0001	<0.001
Weight (kg)	72.6 (21.9)	69.3 (23.2)	75.7 (20.1)	0.008	58.3 (26.6)	48.5 (22.4)	79.3 (22.6)	<0.0001	<0.001
Sex	–	–	–	0.53	–	–	–	0.69	<0.001
Male	302/332 (91%)	149/162 (92%)	153/170 (90%)	–	66/100 (66%)	44/68 (64%)	22/32 (69%)	–	–
Female	30/332 (9%)	13/162 (8%)	17/170 (10%)	–	34/100 (34%)	24/68 (35%)	10/32 (31%)	–	–
Race	–	–	–	0.36	–	–	–	0.64	<0.001
White	208/310 (67%)	104/150 (69%)	104/160 (65%)	–	29/88 (33%)	18/58 (31%)	11/30 (37%)	–	–
Black	18/310 (6%)	6/150 (4%)	12/160 (8%)	–	42/89 (47%)	30/59 (51%)	12/30 (40%)	–	–
Asian	19/310 (6%)	10/150 (7%)	9/160 (6%)	–	2/89 (2%)	1/59 (2%)	1/30 (3%)	–	–
Hispanic	46/310 (15%)	19/150 (13%)	27/160 (17%)	–	13/89 (15%)	7/59 (12%)	6/30 (20%)	–	–
Other	19/310 (6%)	11/150 (7%)	8/160 (5%)	–	3/89 (3%)	3/59 (5%)	0	–	–
Ethnicity	–	–	–	0.52	–	–	–	0.86	0.14
Hispanic/Latino	80/308 (26%)	36/148 (24%)	44/160 (28%)	–	16/87 (18%)	10/56 (18%)	6/31 (19%)	–	–
Not Hispanic/Latino	228/308 (74%)	112/148 (76%)	116/160 (73%)	–	71/87 (82%)	46/56 (82%)	25/31 (81%)	–	–
Presenting symptoms									
Chest pain	320/333 (96%)	157/162 (97%)	164/171 (96%)	0.62	23/94 (24%)	17/63 (27%)	6/31 (19%)	0.42	<0.001
Shortness of breath	88/327 (27%)	43/158 (27%)	44/169 (26%)	0.81	26/92 (28%)	17/62 (27%)	9/30 (30%)	0.80	0.75
Palpitations	34/306 (11%)	18/148 (12%)	16/158 (10%)	0.57	10/82 (12%)	6/55 (11%)	4/27 (15%)	0.61	0.78
Fever	108/327 (33%)	62/158 (39%)	47/169 (28%)	0.04	91/98 (93%)	61/68 (90%)	30/30 (100%)	0.07	<0.001
GI symptoms	75/325 (23%)	41/158 (26%)	33/167 (20%)	0.23	67/96 (70%)	47/65 (72%)	20/31 (65%)	0.44	<0.001
Headache	83/319 (26%)	41/153 (27%)	42/166 (25%)	0.58	36/85 (42%)	22/57 (39%)	14/28 (50%)	0.32	0.003
Fatigue	87/312 (28%)	52/152 (34%)	37/160 (23%)	0.02	51/86 (59%)	31/58 (53%)	20/28 (71%)	0.11	<0.001
Rash	3/310 (1%)	2/148 (1%)	2/162 (1%)	0.51	37/95 (39%)	25/64 (39%)	12/31 (39%)	0.97	<0.001
Biomarkers of inflammation, cardiac injury, and heart failure									
Elevated CRP	224/273 (82%)	114/143 (80%)	111/130 (85%)	0.22	96/96 (100%)	66/66 (100%)	30/30 (100%)	–	<0.001
CRP value (mg/L)	6.7 (9.8)	7.7 (10.5)	5.7 (9.1)	0.13	29.4 (50.7)	27.7 (53.6)	33.2 (44.2)	0.63	<0.001
Elevated ESR (%)	69/223 (31%)	42/113 (37%)	28/110 (25%)	0.06	64/75 (85%)	44/51 (86%)	20/24 (83%)	0.74	<0.001
ESR value (%)	30.5 (21.0)	30.9 (24.0)	30.0 (15.7)	0.87	60.6 (31.9)	60.3 (33.5)	61.1 (28.8)	0.93	<0.001
Elevated troponin	313/326 (96%)	160/162 (99%)	153/164 (93%)	0.01	24/31 (77%)	18/23 (78%)	6/8 (75%)	0.85	<0.001
Standardized troponin (unitless)	251.6 (427.5)	216.6 (375.7)	289.3 (475)	0.14	79.8 (245.5)	94.9 (291.0)	44.8 (55.6)	0.43	0.001
hsTnI value (pg/mL)	3270 (4137)	3959 (4657)	2030 (2623)	0.04	1917 (5576)	2385 (6403)	515 (690)	0.48	0.19
Non- hsTnI value (ng/mL)	37.4 (388.7)	64.2 (558.5)	12.2 (15.7)	0.29	2.3 (6.0)	2.2 (6.9)	2.6 (4.0)	0.83	0.50
Elevated BNP or NTproBNP	99/236 (42%)	47/120 (39%)	51/116 (44%)	0.45	91/97 (94%)	64/67 (96%)	27/30 (90%)	0.29	<0.001
BNP value (pg/ml)	514 (867)	628 (1123)	379 (377)	0.34	5179 (11,243)	5185 (12,109)	5166 (9476)	0.99	0.006
NTproBNP value (pg/ml)	780 (691)	804 (634)	761 (742)	0.82	11,655 (15,717)	13,278 (17,441)	6965 (8125)	0.30	<0.001
Hospital course									
Hospital LOS (days)	2.8 (2.1)	2.8 (2.6)	2.8 (1.4)	0.88	8.7 (11.7)	9.8 (14.0)	6.5 (2.8)	0.18	<0.001
ICU LOS (days)	2.6 (2.2)	3.0 (3.0)	2.3 (1.4)	0.22	5.0 (3.4)	5.4 (3.7)	4.1 (2.3)	0.14	<0.001
ICU admission	75/299 (25%)	32/152 (21%)	43/147 (29%)	0.13	73/99 (74%)	51/67 (76%)	22/32 (69%)	0.43	<0.001
Mechanical ventilation	2/330 (1%)	2/161 (1%)	0	0.14	16/72 (22%)	12/51 (24%)	4/21 (19%)	0.67	<0.001
ECMO	1 (0.3%)	1/162 (0.6%)	0	0.30	2/72 (3%)	2/51 (4%)	0	0.35	0.03
VAD/transplant/death	0	0	0	–	0	0	0	–	–

(Table 1 continues on next page)

	C-VAM				MIS-C				C-VAM vs. MIS-C
	Total (N = 333)	≤15 yrs. (N = 162)	>15 yrs. (N = 171)	p value	Total (N = 100)	≤15 yrs. (N = 68)	>15 yrs. (N = 32)	p value	p value
(Continued from previous page)									
Use of Inotropes	6/331 (2%)	3/162 (2%)	3/169 (2%)	0.95	57/97 (59%)	42/67 (63%)	15/30 (50%)	0.24	<0.001
Use of IVIG	47/332 (14%)	19/162 (12%)	27/170 (16%)	0.21	89/97 (92%)	61/67 (91%)	28/30 (93%)	0.70	<0.001
Use of steroids	43/331 (13%)	19/162 (12%)	24/169 (14%)	0.61	89/97 (92%)	63/67 (94%)	26/30 (87%)	0.22	<0.001
Use of NSAIDs	272/332 (82%)	135/161 (84%)	139/171 (81%)	0.45	53/94 (56%)	40/65 (62%)	13/29 (45%)	0.13	<0.001
>mild clinical severity	77/333 (23%)	39/162 (24%)	38/171 (22%)	0.68	80/100 (80%)	56/68 (82%)	24/32 (75%)	0.39	<0.001
Echocardiography									
LV EF (%)	60 (8)	60 (8)	59 (7)	0.35	48 (15)	51 (14)	44 (15)	0.03	<0.001
LV EF >55%	254/307 (83%)	131/157 (83%)	123/150 (82%)	0.62	30/94 (32%)	23/65 (35%)	7/29 (24%)	0.28	<0.001
LV dysfunction									
Mild (EF: 45–54%)	44/307 (14%)	20/157 (13%)	24/150 (16%)	0.41	27/94 (29%)	17/65 (26%)	10/29 (34%)	0.41	0.001
Moderate (EF: 30–44%)	8/307 (3%)	5/157 (3%)	3/150 (2%)	0.51	29/94 (31%)	22/65 (34%)	7/29 (24%)	0.34	<0.001
Severe (EF: <30%)	1/307 (0.3%)	1/157 (0.6%)	0	0.32	10/94 (11%)	4/65 (6%)	6/29 (21%)	0.03	<0.001
LVDd (mm)	48.5 (5.7)	47.9 (5.2)	49.0 (6.1)	0.08	45.1 (8.8)	42.5 (8.7)	51.1 (5.5)	<0.0001	<0.001
LVDd Z-score	–0.6 (1.4)	–0.7 (1.2)	–0.6 (1.6)	0.38	–0.6 (2.3)	–0.7 (2.6)	–0.3 (1.5)	0.42	0.63
Cardiac magnetic resonance (CMR)									
LV EDV (ml/m^2)	86 (17)	87 (19)	85 (15)	0.24	81 (18)	78 (18)	88 (15)	0.008	0.02
LV ESV (ml/m^2)	36 (12)	37 (14)	36 (9)	0.34	35 (13)	34 (12)	39 (14)	0.05	0.40
RV EDV (ml/m^2)	89 (22)	90 (22)	88 (22)	0.55	85 (18)	83 (18)	90 (15)	0.07	0.08
RV ESV (ml/m^2)	42 (13)	42 (14)	41 (12)	0.85	39 (13)	39 (15)	40 (9)	0.57	0.14
Presence of myocardial edema	96/232 (41%)	42/111 (38%)	54/121 (45%)	0.29	12/100 (12%)	6/68 (9%)	6/32 (19%)	0.19	<0.001
Elevated T2 time	45/146 (31)	20/74 (27)	25/72 (35)	0.31	10/71 (14)	5/48 (10)	5/23 (22)	0.19	0.008
T2 value (ms.)	56 (8)	54 (7)	55 (7)	0.38	49 (5)	49 (6)	49 (4)	0.87	<0.001
Elevated T1 time	75/157 (48%)	37/79 (47%)	39/78 (50%)	0.69	27/66 (41%)	21/43 (49%)	6/23 (26%)	0.07	0.30
T1 value (ms.)	1081 (94)	1071 (95)	1091 (115)	0.24	1070 (127)	1096 (138)	1023 (86)	0.02	0.51
Elevated ECV	54/136 (40%)	32/72 (44%)	22/64 (34%)	0.23	12/58 (21%)	9/36 (25%)	3/22 (14%)	0.29	0.01
ECV value (%)	29 (6)	30 (7)	28 (5)	0.12	26 (3)	27 (3)	26 (3)	0.28	0.001
Presence of late gadolinium enhancement (LGE)	177/216 (82%)	78/104 (75%)	99/112 (88%)	0.01	10/64 (16%)	6/44 (14%)	4/20 (20%)	0.51	<0.0001
No. of LGE + myocardial segments	3.6 (2.2)	3.3 (2.1)	3.2 (2.1)	0.74	1.4 (2.0)	1.6 (2.4)	1.2 (0.8)	0.68	0.0005
>mild LGE severity	105/216 (48%)	42/105 (40%)	63/111 (57%)	0.01	5/74 (7%)	4/48 (8%)	1/26 (4%)	0.46	<0.00001

Data are reported as mean (±SD) or n/N (%) where applicable. Abbreviations: C-VAM, COVID-19 vaccine-associated myocarditis; MIS-C, Multisystem inflammatory syndrome in children; SD, standard deviation; GI, gastrointestinal; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; hsTnl, High sensitivity troponin; non-hsTnl, High sensitivity troponin; BNP, B-type natriuretic peptide; LOS, length of stay; ICU, intensive care unit; IVIG, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; > Mild clinical severity (see methods section); CMR, cardiovascular magnetic resonance; LV, left ventricle; EF, ejection fraction; LVDd, left ventricular end-diastolic diameter; EDV, end-diastolic volume; ESV, end systolic volume; ms., milliseconds; ECV, extracellular volume; LGE, late gadolinium enhancement; RV, right ventricle; > mild LGE severity (see methods section).

Table 1: **Demographic, clinical and cardiac imaging characteristics in patients with COVID-19 vaccine-associated myocarditis (C-VAM) vs. multisystem inflammatory syndrome in children (MIS-C) at initial presentation.**
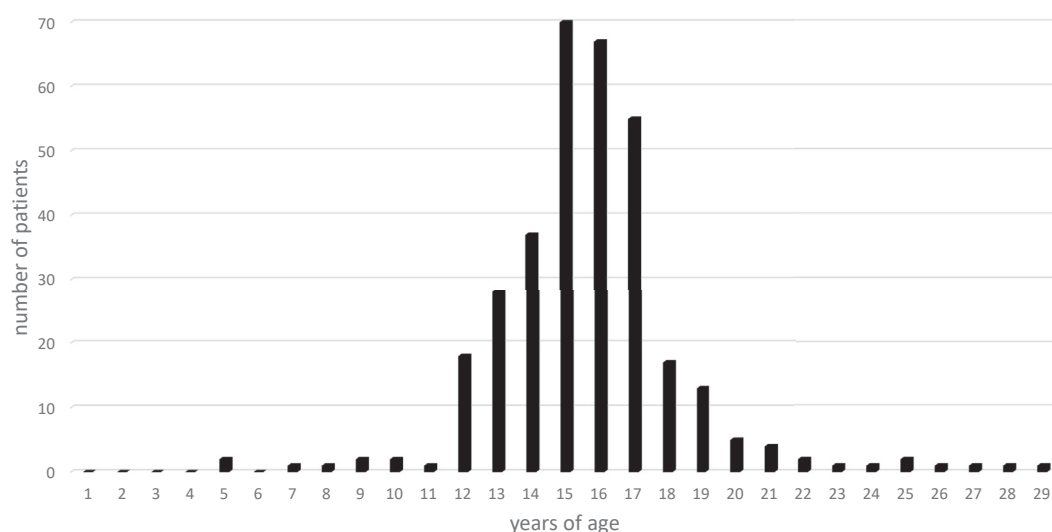
Fig. 1: Histogram of the age distribution within the cohort with COVID-19 vaccine-associated myocarditis.

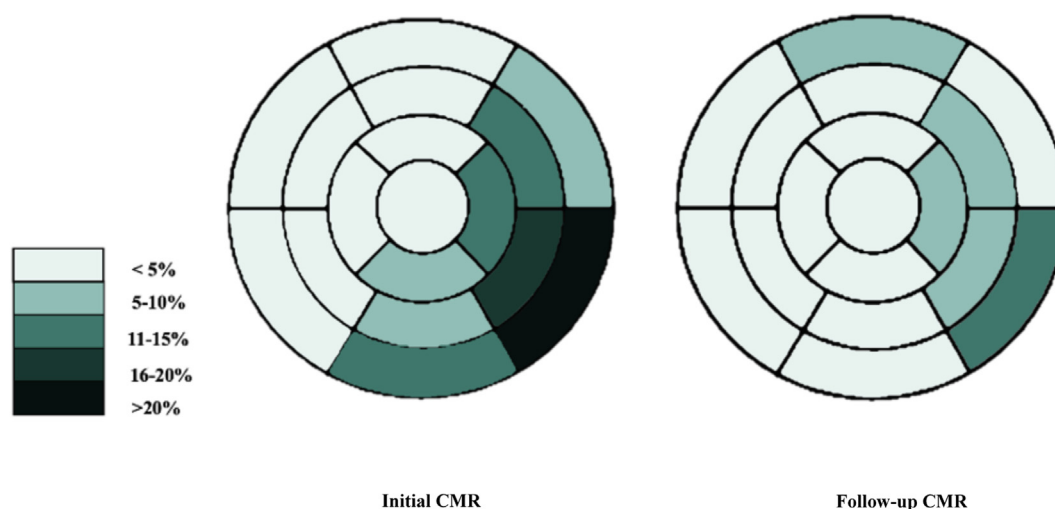Initial CMR   Follow-up CMR

Fig. 2: Distribution pattern and frequency of myocardial late gadolinium enhancement (LGE) in COVID-19 vaccine-associated myocarditis (based on the American Heart Association left ventricular myocardial 17-segment model)[17] at initial presentation (left) and at follow-up (right). The percentages indicate the frequency of LGE involvement in each of the myocardial segments, with darker colors corresponding to greater prevalence. LGE was common in the basal and mid inferolateral segments with an improvement demonstrated at follow-up.

troponin correlated weakly with the number of LGE positive segments ($r = 0.29$, $p = 0.0004$), with T1 time ($r = 0.23$, $p = 0.005$), with T2 time ($r = 0.18$, $p = 0.04$) and inversely with LVEF ($r = -0.17$, $p = 0.005$). C-reactive protein, but not ESR, correlated with the number of LGE segments ($r = 0.28$, $p = 0.002$) and inversely with LVEF ($r = -0.16$, $p = 0.02$).

Risk factors for LGE in C-VAM
On investigation of the possible risk factors for LGE in C-VAM, based on the multivariable model that included important demographic variables such as age, sex and vaccine dose, the odds of having LGE in C-VAM were 2.74 times higher (95% CI: 1.28, 5.83, $p = 0.009$) for older adolescents (>15 years) compared to younger patients, 3.28 times higher (95% CI: 0.99, 10.6, $p = 0.052$) for males compared to females, 7.18 (95% CI: 1.05, 49.09, $p = 0.045$) times higher after the first dose and 4.5 (95% CI: 1.23, 16.44, $p = 0.023$) times higher after the second dose compared to the third dose of the mRNA vaccine (Fig. 4).

Comparison with multisystem inflammatory syndrome in children (MIS-C) secondary to COVID-19
In comparison with MIS-C patients (Table 1), C-VAM patients were older (15.7 ± 2.8 years vs. 12.4 ± 4.4 years, $p < 0.0001$) and included a higher proportion of males
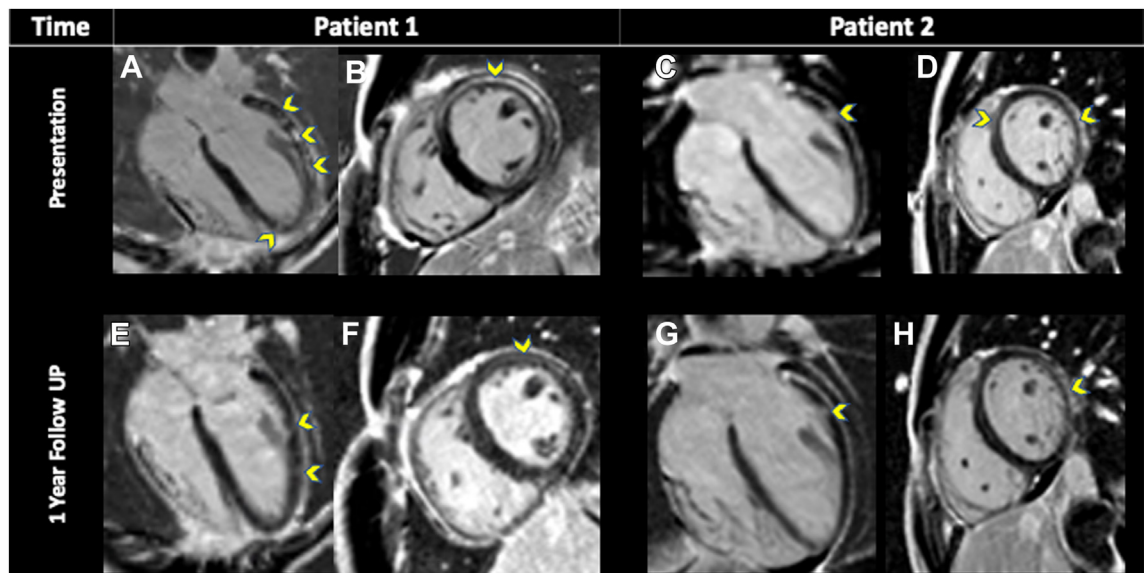
Fig. 3: **Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) imaging of the left ventricle in two patients with COVID-19 vaccine-associated myocarditis (CVAM) at presentation and at one year follow-up.** Patient 1 demonstrates marked multifocal LGE (A and B, yellow arrow heads) at presentation with notable improvement after one year (E and F, yellow arrows). Patient 2 shows LGE at presentation (C and D, yellow arrows) with persistence at one year (G and H, yellow arrows).
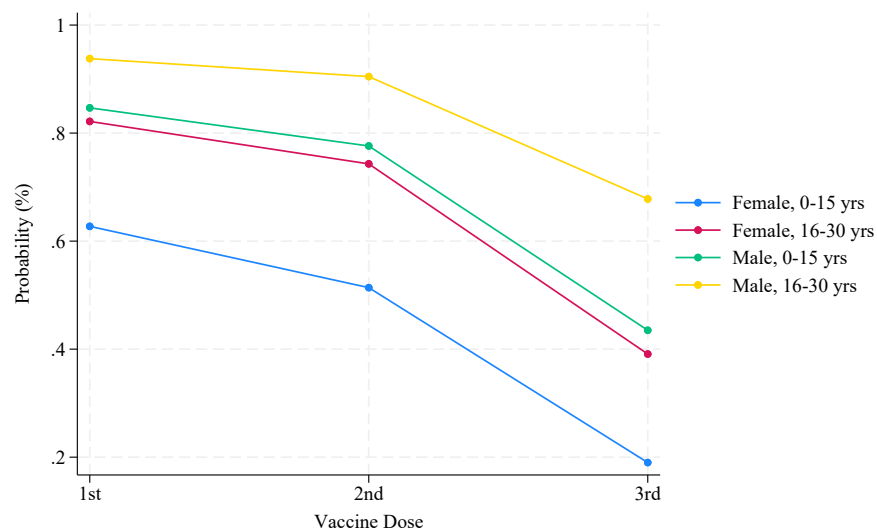
Fig. 4: **Risk factors for late gadolinium enhancement (LGE) in COVID-19 vaccine-associated myocarditis.** The likelihood of LGE was highest in adolescent or young adult males and in those who presented after the first or second dose (vs. the third dose) of the mRNA vaccine.

(91% vs. 66%, p < 0.001). They were predominantly white (67% vs. 33%, p < 0.001), in contrast to MIS-C patients who were more likely to be black (47% vs. 6%, p < 0.001). While MIS-C patients had higher CRP, ESR and BNP levels (p < 0.001), troponin levels were higher in C-VAM patients (p = 0.001). On average, LVEF in MIS-C patients was lower and a greater proportion of them had reduced LVEF (68% vs. 17%, p < 0.0001). Patients with MIS-C were likely to experience > mild

clinical severity (80% vs. 23%, p < 0.001), require intensive care unit admissions (74% vs. 25%, p < 0.001), inotropic support (59% vs. 2%, p < 0.001) and a longer hospital stay (8.7 ± 11.7 days vs. 2.7 ± 2.1 days, p < 0.001) in comparison with C-VAM patients. Conversely, LGE was less common in MIS-C patients compared with C-VAM patients (16% vs. 82%, p < 0.0001). Patients with C-VAM were more likely to have > mild LGE severity (48% vs. 7%, p < 0.00001) with

a higher number of LGE positive AHA segments (3.6 ± 2.2 vs. 1.4 ± 2.0, p = 0.0005). They were more likely to have myocardial edema (41% vs. 12%, p < 0.001), as evidenced by elevated T2 (31% vs. 14%, p = 0.008) and higher T2 times (56 ± 8 ms vs. 49 ± 5 ms, p = 0.001). Myocardial ECV was more likely to be elevated in C-VAM than in MIS-C patients (40% vs. 21%, p = 0.01) with higher ECV values in the C-VAM cohort (29 ± 6% vs. 26 ± 3%, p = 0.001). These differences persisted when comparing the younger and the older age groups of both MIS-C and C-VAM patients separately.

Outcomes in C-VAM

Follow-up information was available in 307 C-VAM patients (92%), for a median follow-up duration of 178 days (IQR 114–285 days). There were no cardiac related deaths or need for heart transplantation in any of our patients, confirmed at the time of submission of this report. Four patients were re-hospitalized for recurrent chest pain, including one with ventricular tachycardia and one for a recurrence of myocarditis with chest pain, palpitations, elevated troponin, and ST segment changes. Eighty-nine patients (28%) reported cardiac symptoms at a median follow up of 91 days (IQR 25–186 days) since receiving the vaccine. Arrhythmias such as atrial or ventricular tachycardia and frequent premature ventricular contractions were noted in 4% of the patients (11 of 272) at a median follow up duration of 31 days (IQR 23–230 days). EKG abnormalities including ST and T wave abnormalities occurred in 23% patients (48 of 206) at a median follow up of 35 days (IQR 18–98 days). The prevalence of LV dysfunction and myocardial edema decreased from 17% to 4% and from 41% to 4%, respectively (p < 0.001 for both). Although the severity and prevalence of LGE decreased during follow up (Figs. 2 and 3), 60% (98/161) patients had persistence of LGE at the time of their follow-up CMR examination at a median follow up of 159 days (IQR 78–253 days). Five patients (5%) among those that continued to be LGE positive at follow-up were reported to have worsening of LGE, including three patients with recurrence of cardiac symptoms including chest pain, palpitations, dizziness or fatigue. One patient required re-hospitalization with elevated troponin as described above, two had T-wave inversions on follow-up ECGs and one patient experienced ventricular tachycardia and mild LV systolic dysfunction. On average, the number of myocardial segments with LGE decreased from 3.6 ± 2.2 to 2.5 ± 1.8 (p < 0.001, Fig. 2). Myocardial T1, ECV, and T2 decreased from 1081 ± 94 ms to 998 ± 46 ms (p < 0.001), from 29 ± 6% to 25 ± 4% (p < 0.0001), and from 56 ± 8 ms to 49 ± 4 ms (p < 0.001), respectively. There were no significant differences in signs and symptoms at follow-up between younger (<15 years) or older (>15 years) C-VAM patients.

Discussion

Certain vaccines, including those against smallpox and, more recently, COVID-19, have been associated with myocarditis, but myocardial health in vaccine-associated myocarditis has not been extensively studied.[18] This report describes the largest longitudinal study in COVID-19 vaccine-associated myocarditis to date that provides detailed phenotypic clinical characterization along with important CMR information on myocardial tissue health. It also explores risk factors for myocardial injury and evaluates cardiovascular outcomes in children, adolescents, and young adults affected with this rare complication. Specifically, the study adds the following to our understanding of C-VAM (Fig. 5).

1. Despite a mild initial clinical course and low prevalence of cardiac dysfunction, myocardial injury as evidenced by higher troponin and LGE on CMR is common in C-VAM.
2. The likelihood for developing LGE is higher in males than in females, older adolescents than younger patients, and in those who developed C-VAM after the first or second dose of the mRNA vaccine compared to after the booster or third dose.
3. The mid-term clinical outcomes after C-VAM are reassuring, with no reported cardiac related deaths or need for heart transplantations.
4. Myocardial scarring persists during convalescence in most patients, but at a lower severity.

COVID-19 vaccine-associated myocarditis patients in our cohort were predominantly males who presented with chest pain and elevated troponin. While their clinical course was nearly always mild with a low prevalence and extent of cardiac dysfunction, myocardial injury was common as evidenced by higher troponin levels and LGE in 82%. This is comparable to the prevalence of LGE detected in adult (95–96%) and childhood myocarditis (82%), albeit in selected populations.[5–8,19] The LGE pattern and distribution in C-VAM resembled those in viral myocarditis, in contrast to MIS-C where LGE was rare and, when present, mild in comparison. In a variety of cardiac conditions, including non-ischemic cardiomyopathies, LGE is associated with a propensity for arrhythmias, heart failure, and sudden cardiac death.[5–9] In adults with viral myocarditis, LGE at presentation is a predictor of long-term major adverse cardiovascular events, even if cardiac function is preserved.[6] A greater extent of LGE confers a higher risk for adverse outcomes.[7–9] Among those in our C-VAM cohort who were LGE positive, almost half had > mild LGE severity. We speculate that, given that LGE is common in C-VAM, along with elevated troponin but with a relatively modest systemic immune response based on lower levels of systemic inflammatory markers as compared to MIS-C, the

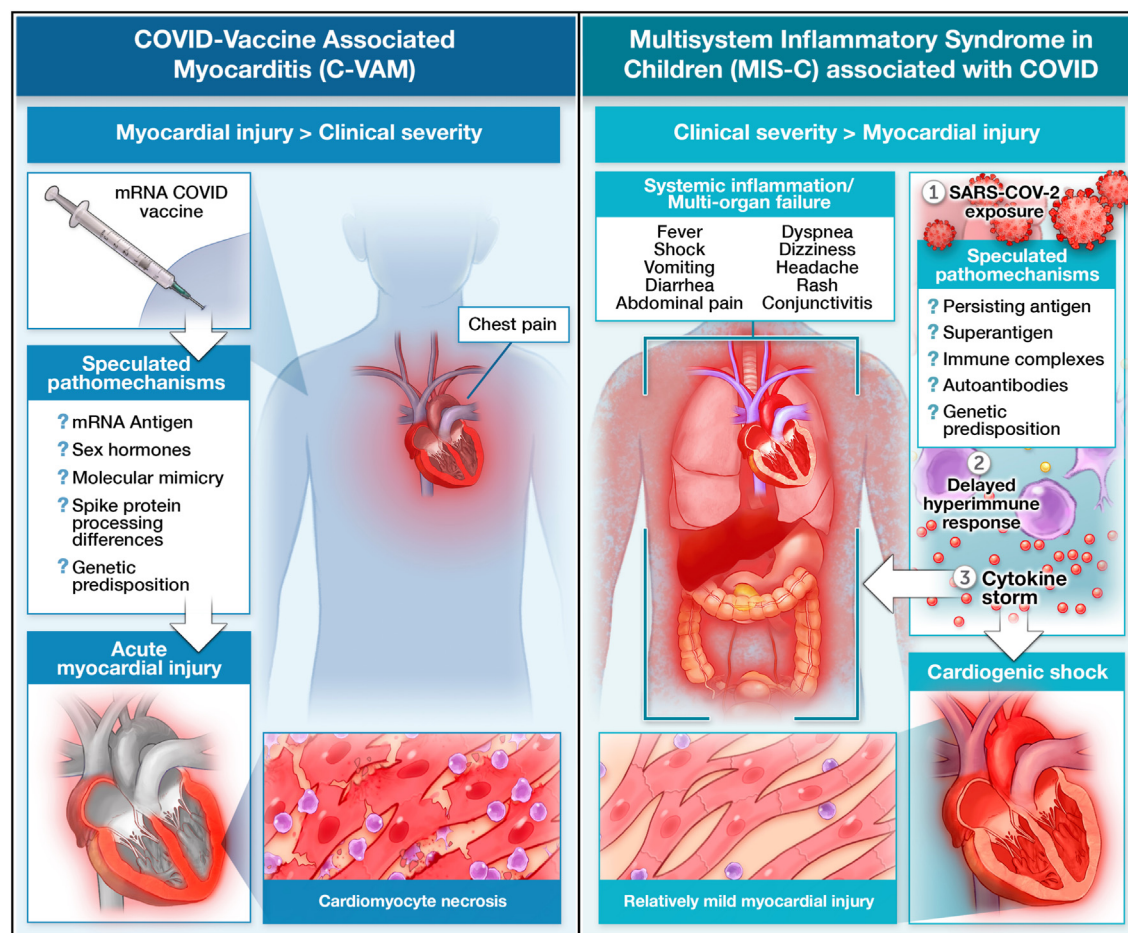## Cardiac manifestations and sequelae in COVID-19 Vaccine-associated Myocarditis
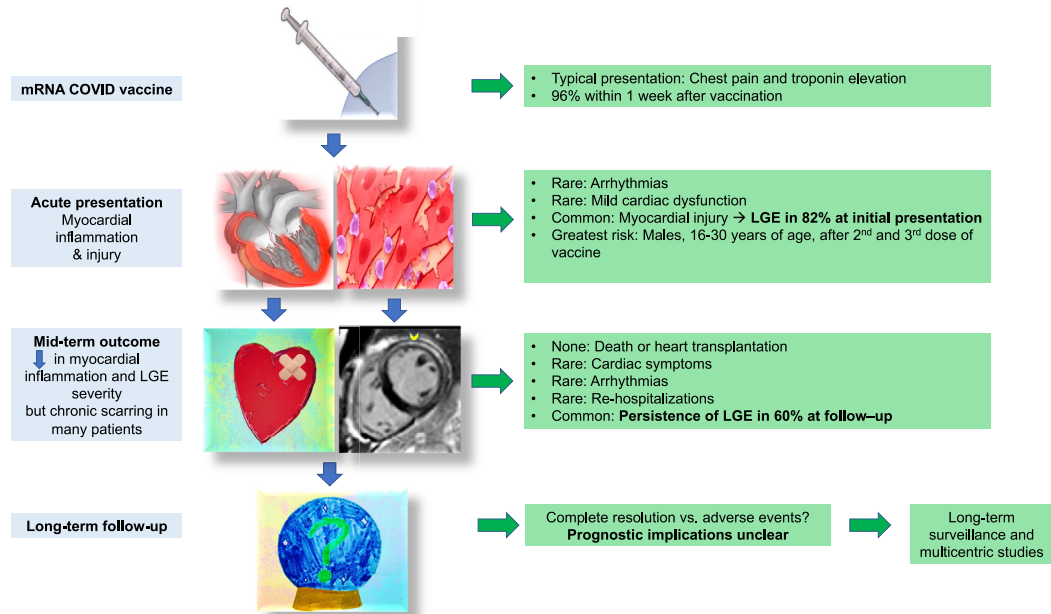
Fig. 5: **Key illustration:** Initial presentation, myocardial injury and outcomes, in young patients with COVID-19 vaccine associated myocarditis.

myocardial damage in C-VAM may be due to a process that specifically targets cardiomyocytes, leading to injury (Fig. 6). Imaging markers of cardiomyocyte necrosis and edema, including LGE, native T1, and T2, correlated with troponin levels, all serving as indicators of myocardial injury. C-reactive protein was more likely to be elevated compared to ESR and it correlated with both LGE severity and lower LVEF during the initial presentation in C-VAM; hence CRP may be of greater diagnostic yield as an inflammatory marker than ESR in the work-up of C-VAM patients.

On exploration of demographic risk factors for LGE, males compared to females, older adolescents, and young adults >15 years of age compared to younger patients and those who developed C-VAM after the 1st and 2nd dose of the mRNA vaccine compared to the booster or 3rd dose had a higher likelihood to have LGE. Our finding that younger children were somewhat less likely to develop LGE and/or cardiac dysfunction along with the observation that older adolescents and young adult males are at the greatest risk for C-VAM supports the hypothesis of the influence of sex hormones in the pathogenesis.[20] Estrogen appears to have a protective effect in myocarditis while testosterone increases the risk of myocardial inflammation. Whether estrogen and testosterone are associated with better and worse prognosis, respectively, once C-VAM has occurred, is not currently known. Potential age-related differences in the processing and clearance of vaccine-derived spike protein have also been proposed as the etiology for the different

susceptibilities.[21] Other hypothesized patho-mechanisms for the cardiac involvement in C-VAM include an immunogenicity of mRNA or of the delivery lipid nano-particle vector, molecular mimicry between the mRNA-induced viral spike protein and myocardial antigens, and a dysregulated immune response in genetically predisposed individuals.[20]

To gain a better perspective of the severity of cardiac involvement and myocardial injury in myocarditis associated with the COVID-19 vaccine in the pediatric population, we compared it with MIS-C, a serious complication of COVID-19 with common cardiac dysfunction.[10,22–24] In order to contrast two conditions in young individuals during the pandemic, we focused on MIS-C rather than SARS-CoV-2 myocarditis as a comparison cohort, as the latter is relatively rare in children. MIS-C is due to a delayed hyperimmune response, occurring several weeks after exposure to SARS-CoV-2 virus and mediated by a non-targeted pro-inflammatory cascade leading to dysfunction of multiple systems, including the heart. The racial differences between C-VAM and MIS-C in our cohort with a greater proportion of whites in the C-VAM group and blacks in the MIS-C group could reflect the differences in immunization rates and/or an increased susceptibility to developing these complications.[25,26] MIS-C patients were younger and sicker, were more likely to require intensive care management and had higher prevalence and degree of systemic inflammatory markers and cardiac dysfunction. However, the lower troponin levels, rapid

COVID-Vaccine Associated Myocarditis (C-VAM)

Myocardial injury > Clinical severity

mRNA COVID vaccine

Chest pain

Speculated pathomechanisms

? mRNA Antigen
? Sex hormones
? Molecular mimicry
? Spike protein processing differences
? Genetic predisposition

Acute myocardial injury

Cardiomyocyte necrosis

Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID

Clinical severity > Myocardial injury

Systemic inflammation/ Multi-organ failure

Fever / Shock / Vomiting / Diarrhea / Abdominal pain / Dyspnea / Dizziness / Headache / Rash / Conjunctivitis

① SARS-COV-2 exposure

Speculated pathomechanisms

? Persisting antigen
? Superantigen
? Immune complexes
? Autoantibodies
? Genetic predisposition

② Delayed hyperimmune response

③ Cytokine storm

Cardiogenic shock

Relatively mild myocardial injury

Fig. 6: **Presumed pathophysiology of cardiac involvement in COVID-19 vaccine-associated myocarditis (C-VAM) and multi-system inflammatory syndrome in children (MIS-C).** In C-VAM, the mRNA vaccine induces an immunologic process that targets the myocardium, resulting in cardiomyocyte necrosis. In MIS-C, the body mounts an overwhelming inflammatory response to a preceding infection with SARS-CoV-2, affecting multiple organ systems, including the heart. This may result in transient cardiac dysfunction with a relatively mild myocardial injury.

resolution of cardiac dysfunction after immunomodulatory therapies as well as the observation that LGE was less prevalent in MIS-C compared to C-VAM suggest that cardiac function was affected non-specifically due to the severe systemic immune response in MIS-C, rather than a focused injury to the heart as in C-VAM (Fig. 6). The low prevalence of LGE in MIS-C noted in our study corroborates frequencies reported in other studies.[27]

The initial clinical presentation of C-VAM was mild in the majority of the patients, akin to the milder cases of classic viral or lymphocytic myocarditis. In fact, the acute clinical course of C-VAM may be more favorable than that of viral myocarditis.[28] The clinical outcomes in our C-VAM cohort are consistent with those reported in the literature in that C-VAM patients recovered swiftly from the initial episode, although recently, a Korean study reported a more guarded initial course.[29,30] Information on longer-term outcomes is still scarce. Most of

our patients had a favorable mid-term clinical outcome with no cardiac deaths or need for heart transplantation so far. While cardiac symptoms were uncommon, and clinically important arrhythmias were rare during follow-up, a few patients had recurrence of chest pain, ventricular tachycardia, T wave inversions on ECG and/or worsening LGE at follow-up, some requiring rehospitalization. Larger and longer-term studies are needed to determine the long-term clinical prognosis of C-VAM. At the mid-term mark, LVEF had normalized in nearly everyone. Likewise, CMR parameters of myocardial inflammation had decreased on the follow-up studies. In the acute setting of myocarditis, a rise in T1 and ECV may denote edema and myocardial injury but in the chronic, non-inflammatory state these markers signal diffuse myocardial fibrosis.[12–14] Their decline during follow-up, along with a decrease in T2 times, indicated improving inflammation, although

further follow-up will be needed to rule out diffuse myocardial fibrotic remodeling, in which case T1 and ECV may rise again over time. Among the patients who had LGE on their initial CMR, more than half of them had persistence of LGE on their follow-up CMR. In a longitudinal study of adult myocarditis patients who underwent serial CMRs, the persistence of LGE in the absence of myocardial edema, suggesting myocardial fibrotic remodeling, were harbingers of poor clinical outcomes.[8] This is consistent with animal models of myocarditis which demonstrated subsequent development of dilated cardiomyopathy.[9] Longitudinal studies are necessary to understand the long-term clinical significance of LGE in this population. Longer-term monitoring with clinical visits, serial echocardiograms and heart rate monitoring, to assess for signs of ventricular dysfunction, the development of heart failure and/or arrhythmias, at least in LGE positive patients, seems warranted.

Limitations of our study include those inherent to a retrospective design, such as variability in diagnostic testing and follow-up. Our C-VAM and MIS-C cohorts may have selection bias as sicker patients were more likely to be hospitalized and have CMR. However, most C-VAM patients had a mild illness, and our MIS-C findings match the literature. While CMR has largely replaced endomyocardial biopsy in pediatric myocarditis,[4] the latter remains the gold standard test to detect inflammation and characterize the type and extent of cellular infiltration. This direct tissue characterization was not available in our patient cohort.

In conclusion, COVID-19 vaccine-associated myocarditis has a mild initial clinical course but myocardial injury as evidenced by LGE on CMR at initial presentation is common, especially in older adolescent males who present after their first or second dose of mRNA vaccines. While mid-term clinical sequelae are rare and LGE severity decreases over time, the persistence of LGE at follow-up in most patients warrants continued clinical surveillance, additional research and longer-term studies in this subset of patients.

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