Clinical course and follow-up of pediatric patients with COVID-19 vaccine-associated myocarditis compared to non–vaccine-associated myocarditis within the prospective multicenter registry—"MYKKE"

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ABSTRACT

Background Since the onset of widespread COVID-19 vaccination, increased incidence of COVID-19 vaccine-associated myocarditis (VA-myocarditis) has been noted, particularly in male adolescents.

Methods Patients <18 years with suspected myocarditis following COVID-19 vaccination within 21 days were enrolled in the PedMYCVAC cohort, a substudy within the prospective multicenter registry for pediatric myocarditis "MYKKE." Clinical data at initial admission, 3- and 9-months follow-up were monitored and compared to pediatric patients with confirmed non–vaccine-associated myocarditis (NVA-myocarditis) adjusting for various baseline characteristics.

Results From July 2021 to December 2022, 56 patients with VA-myocarditis across 15 centers were enrolled (median age 16.3 years, 91% male). Initially, 11 patients (20%) had mildly reduced left ventricular ejection fraction (LVEF; 45%-54%). No incidents of severe heart failure, transplantation or death were observed. Of 49 patients at 3-months follow-up (median (IQR) 94 (63-118) days), residual symptoms were registered in 14 patients (29%), most commonly atypical intermittent chest pain and fatigue. Diagnostic abnormalities remained in 23 patients (47%). Of 21 patients at 9-months follow-up

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Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; BMI, body-mass index; BSA, body surface area; CMRI, cardiac magnetic resonance imaging; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECG, electrocardiogram; EMB, endomyocardial biopsy; GLM, generalized linear model; Hs-cTnT, high-sensitivity troponin T; HTX, heart transplantation; IL-1RA, interleukin-1 receptor antagonist; IQR, interquartile range; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVNC, left ventricular noncompaction cardiomyopathy; MACE, major adverse cardiovascular events; MCS, mechanical circulatory support; MRNA, messenger ribonucleic acid; NYHA, New York Heart Association; NSAIDs, nonsteroidal anti-inflammatory drugs; NSVT, nonsustained ventricular tachycardia; NT-proBNP, N-terminal prohormone of brain natriuretic peptide (BNP); NVA-myocarditis, non–vaccine-associated myocarditis; VA-myocarditis, vaccine-associated myocarditis.

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(259 (218-319) days), all were free of symptoms and diagnostic abnormalities remained in 9 patients (43%). These residuals were mostly residual late gadolinium enhancement in magnetic resonance imaging. Patients with NVA-myocarditis (n=108) more often had symptoms of heart failure ($P = .003$), arrhythmias ($P = .031$), left ventricular dilatation ($P = .045$), lower LVEF ($P < .001$) and major cardiac adverse events ($P = .102$).

Conclusions Course of COVID-19 vaccine-associated myocarditis in pediatric patients seems to be mild and differs from non–vaccine-associated myocarditis. Due to a considerable number of residual symptoms and diagnostic abnormalities at follow-up, further studies are needed to define its long-term implications. (Am Heart J 2024;267:101–115.)

Background

By February 2023 over 13 billion administered doses of coronavirus disease 2019 (COVID-19) vaccines were registered globally by the Center for Systems Science and Engineering at Johns Hopkins University.[1] An Israeli study published in August 2021 indicated that the messenger ribonucleic acid (mRNA) COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) comes with an elevated risk of myocarditis, particularly in people aged 16 to 39 years and in male subjects.[2] Since then, numerous case studies have been demonstrating an association between myocarditis and mRNA COVID-19 vaccines.[3-5] The general incidence of myocarditis does not significantly differ between patients receiving COVID-19 vaccines compared to those receiving a variety of non-COVID-19 vaccines (such as varicella, yellow fever, measles, mumps, rubella) and is even less significant compared to patients receiving smallpox vaccines.[6] Still, the analysis of subpopulations revealed an increased susceptibility to myocarditis in males and patients younger than 30 years.[6] A large-scale study in the United States indicated that the rates of mRNA COVID-19 vaccine-associated myocarditis (VA-myocarditis) were the highest after the second dose in adolescent males aged 12 to 17 years, and in young men aged 18 to 24 years.[7] In the European Union the mRNA COVID-19 vaccines BNT162b2 (Comirnaty, Pfizer-BioNTech) and mRNA-1273 (Spikevax, Moderna) obtained approval for children older than 5 years, whereas the US Food and Drug Administration (FDA) issued emergency use authorization of these vaccines in children down to 6 months of age.[8] Previous studies demonstrated that vaccination of children and adolescents was safe and reduced the risk of hospitalization and multisystem inflammatory syndrome (MIS-C).[9-11] It has recently been highlighted that myocarditis after COVID-19 vaccination was associated with a better clinical outcome compared to conventional myocarditis and myocarditis due to SARS-CoV-2 infection.[12] Nevertheless, data on COVID-19 VA-myocarditis in children are rare and even though the course of this type of myocarditis seems to be mild, little is currently known about the long-term effects on these patients.[13] Therefore, it was our aim to first characterize the clinical course of myocarditis following COVID-19 vaccination including follow-up data within the German registry for suspected myocarditis in children and adolescents "MYKKE." We then compared these patients to a pediatric cohort with non–vaccine-associated myocarditis (NVA-myocarditis) to examine differences in course and outcome.

Methods

"MYKKE" registry

"MYKKE" is a multicentered, prospective long-term registry for suspected pediatric myocarditis, which offers a research platform for clinical studies investigating epidemiology, clinical entity, diagnostic and therapeutic procedures as well as outcome of pediatric myocarditis. The registry is hosted and technically administered by the Competence Network for Congenital Heart Defects. Ethical approval was first obtained at the initiating center (Deutsches Herzzentrum Berlin, Berlin, Germany) from the ethics committee of the Charité - Universitätsmedizin Berlin (EA2/074/13) and subsequently confirmed by local authorities of all collaborating centers (ClinicalTrials.gov Identifier: NCT02590341). Since 2013, 29 medical centers in Germany, Switzerland and Austria became participating partners. Within the "MYKKE" registry we designed a substudy investigating clinical course of suspected COVID-19 VA-myocarditis in children and adolescents, named PedMYCVAC. Data were collected retrospectively and prospectively, from July 1st 2021 to December 1st 2022. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

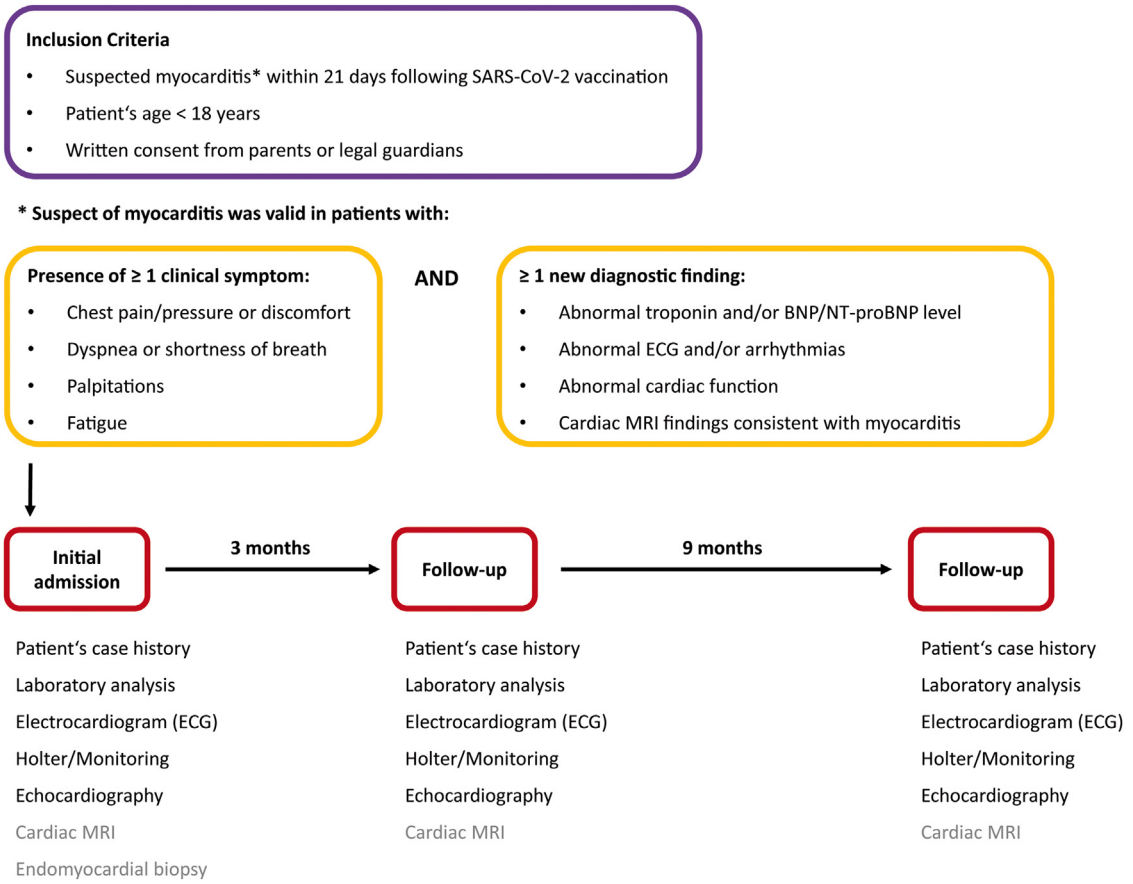
Inclusion criteria

We included patients who met the following criteria (Figure 1):

1. Suspected myocarditis within 21 days after COVID-19 vaccination.
2. Patient's age <18 years.
3. Written consent from parents or legal guardians.

In accordance with the US Centers for Disease Control and Prevention (CDC) case definition for probable cases

Figure 1



PedMYCVAC diagnostic workflow. Inclusion criteria and diagnostic workflow at initial admission and follow-ups. *BNP*, brain natriuretic peptide; *ECG*, electrocardiogram; *MRI*, magnetic resonance imaging; *NT-proBNP*, N-terminal prohormone of BNP.

of COVID-19 VA-myocarditis,[14] the suspect of myocarditis was valid in patients presenting:

≥1 new clinical symptom: chest pain/pressure or discomfort, dyspnea or shortness of breath, palpitations, fatigue

AND

≥1 new diagnostic finding: elevated serum levels of troponin or Brain Natriuretic Peptide (BNP)/N-terminal prohormone of BNP (NT-proBNP), abnormal electrocardiogram (ECG) or newly appeared arrhythmias, abnormal ventricular systolic function on echocardiogram, cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis or biopsy-proven myocarditis.[15]

Patient data and follow-ups

Clinical data at initial admission and at follow-up were entered in the online study database by the local physicians and monitored by the central "MYKKE" study team as described before[16] (Figure 1). Variables of interest included the vaccination data and patient's case history, symptoms and treatment, ECG, echocardiography, laboratory analysis, cMRI and endomyocardial biopsy (EMB). All diagnostic procedures were performed at the discretion of the local medical team. Laboratory-specific threshold values were accepted for all laboratory parameters. Monitored arrhythmias included abnormal amount of supraventricular and ventricular extrasystoles, supraventricular tachycardia with hemodynamic instability and ventricular tachycardia. Local protocols were used for cMRI analysis and image interpretation was performed by the respective centers. When EMB was conducted, samples were analyzed by 1 single accredited laboratory (Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tuebingen, Tuebingen, Germany) performing histopathology, immunohistochemistry and viral genome detection. The diagnosis of

myocarditis was confirmed according to the established criteria.[17,18]

In order to evaluate clinical impact of COVID-19 VA-myocarditis, pediatric patients with EMB- and/or cMRI-confirmed diagnosis of non–vaccine-associated myocarditis (NVA-myocarditis) were included for comparison and were adjusted in age, sex and body-mass index (BMI). Only patients aged 9 years and older were taken into account. Of those patients, all were diagnosed and enrolled in the "MYKKE" registry before the onset of the COVID-19 pandemic. Patients with primary cardiomyopathy, congenital heart disease or severe noncardiac diseases were excluded. Due to the small number of female patients with COVID-19 VA-myocarditis, female patients were excluded in both cohorts from the comparative statistical analysis. Major adverse cardiac events (MACE) were defined as malign arrhythmias (ventricular tachycardia, supraventricular tachycardia with hemodynamic instability), need for mechanical circulatory support (MCS), events of resuscitation, heart transplantation and/or death.

Statistical analysis

Data are presented as medians and interquartile ranges (IQR), or as counts and percentages where applicable. The percentages were always calculated based on the number of patients undergoing the specific test. High-sensitivity troponin T (hs-cTnT) and NT-proBNP values were used for statistical analysis since most patients had measured those instead of Troponin I and BNP. Regardless of the type of troponin measured, its elevation was generally assessed (yes/no). The same is valid for BNP and NT-proBNP. For comparison of clinical characteristics between different stays a likelihood ratio test for mixed models including the number of follow-up visit as factor was used. For comparing the proportion of sex between the stays a χ^2 test was used. Depending on the outcome variable, a linear or logistic model was used to compare patients with COVID-19 VA-myocarditis and patients diagnosed with confirmed NVA-myocarditis at initial admission. Both cohorts were preselected based on following baseline characteristics: male sex, age above 9 years, body-mass-index (BMI) above 13. Patient's BMI, age and an indicator variable for the cohort were further included as covariates in the model. For linear regression models, the regression coefficient for the cohort indicator is reported, whereas for logistic regression models the odds ratio is included in the table. P value of $<.05$ was considered statistically significant. Data were analyzed using R version 4.2.2.

Funding

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Results

From July 2021 to December 2022, 56 patients from 15 institutions were included in the analysis. Most patients were male ($n = 51$; 91%) and median (IQR) age at admission was 16.3 (15.4-16.9) years. In our cohort, 55 patients (98%) had received BioNTech-Pfizer's mRNA vaccine BNT162b2 (Comirnaty), only 1 patient (2%) had received Moderna's vaccine mRNA-1273 (Spikevax), following the national health institute's recommendation. Suspected myocarditis was most frequently observed after the second dose of mRNA vaccine ($n = 29$; 52%). In 17 patients symptoms occurred after the third dose (30%) and in 10 patients after the first dose (18%). Onset of symptoms followed the vaccine administration at a median (IQR) of 3 (2-6.3) days. Two patients tested positive for SARS-CoV-2 infection within 2 weeks after vaccination. Six patients had a notable past medical history including Wolff-Parkinson-White syndrome, Area postrema syndrome, type 1 diabetes, ventricular septal defect with surgical closure in early childhood, arterial hypertension, and bronchial asthma in 1 patient each. The cohort included 1 pair of monozygotic twins.

Clinical manifestation

Most common symptoms at initial admission were chest pain in 50 cases (89%), fatigue, shortness of breath and fever in 37 (66%), 16 (29%), and 15 (29%) patients, respectively (Table I). Eight patients (14%) reported palpitations. Most patients were hospitalized ($n = 50$; 89%). No incidents of severe heart failure, heart transplantation (HTX) resuscitation or death were registered. Patients were discharged after a median (IQR) stay of 5 (4.3-7) days and were advised to abstain from physical training till re-evaluation.

Laboratory findings

At initial presentation, 45 patients (82%) displayed elevated troponin levels, with a median (IQR) hs-cTnT value of 193 (10-646) ng/L. Of note, the median time interval between vaccination and first medical contact was significantly longer in patients without troponin elevation

Table I. Clinical characteristics in pediatric patients with COVID-19 vaccine-associated myocarditis at initial admission and at follow-ups.

Characteristics	Initial admission ($n = 56$)	Three-months follow-up ($n = 49$)	Nine-months follow-up ($n = 21$)	*P* value
Age, years	16.3 (15.4-16.9)	16.5 (15.7-17.2)	17.2 (16.6-17.9)	<.001
Weight, kg	65 (55.9-77.3)	66.6 (55.7-77)	69 (60-74.2)	<.001
Height, cm	176 (171-181)	176 (171-182)	178 (172-184)	.123
Male sex, *n* (%)	51 (91)	44 (90)	20 (95)	.759
Hospitalization, *n* (%)	50 (89)	5 (10)	0 (0)	**<.001**
Symptoms, *n* (%)		$n = 47$		
Chest pain	50 (89), $n = 55$	11 (22)	0 (0)	**<.001**
Fatigue	37 (66)	6 (13)	0 (0)	**<.001**
Shortness of breath	16 (29)	4 (9)	0 (0)	**<.001**
Fever	15 (29), $n = 52$	—	—	—
Palpitations	8 (14)	2 (4)	1 (5)	.168
Syncope	0 (0), $n = 55$	—	—	—
NYHA classification				.138
I	51 (91)	43 (91)	21 (100)	
II	2 (4)	1 (2)	0 (0)	
III	2 (4)	1 (2)	0 (0)	
IV	0 (0)	0 (0)	0 (0)	
n.a.	1 (2)	2 (4)	0 (0)	
Electrocardiogram, *n* (%)		$n = 47$		
ST-elevation	29 (52)	8 (17)	1 (5)	**<.001**
ST-depression	9 (16)	1 (2)	0 (0)	**<.001**
T-wave inversion	12 (21)	6 (13)	1 (5)	**<.001**
Laboratory analysis				
Leukocytes, $10^3/\mu L$	7.6 (6.4-10), $n = 56$	6.3 (5.7-7.3), $n = 25$	6.8 (5.3-7.6), $n = 11$	**.002**
C-reactive protein, mg/L	15.8 (4-41.5), $n = 56$	1.1 (0.5-2.3), $n = 47$	2.7 (1.2-9.2), $n = 20$	.061
Hs-cTnT, ng/L	193 (10-646), $n = 31$	7.5 (4.1-9.2), $n = 10$	4.6 (3.6-6), $n = 6$	**.035**
NT-proBNP, ng/L	157 (53.5-402), $n = 35$	34 (17.8-66.5), $n = 15$	27 (10.2-30), $n = 9$	**.004**
Cardiac MRI, *n* (%)		$n = 12$	$n = 11$	
LGE	35 (75), $n = 47$	9 (75)	6 (55)	.341
Edema	25 (54), $n = 46$	0 (0)	2 (18)	**<.001**
Medication, *n* (%)				
NSAIDs	11 (20)	1 (2)	0 (0)	**<.001**
Corticosteroids	2 (4)	1 (2)	0 (0)	.513
IVIG	1 (2)	0 (0)	0 (0)	**.015**
β-Blockers	13 (23)	12 (24)	3 (14)	**.015**
ACE inhibitors	7 (13)	5 (10)	3 (14)	.094
Diuretics	3 (5)	2 (4)	0 (0)	**.002**

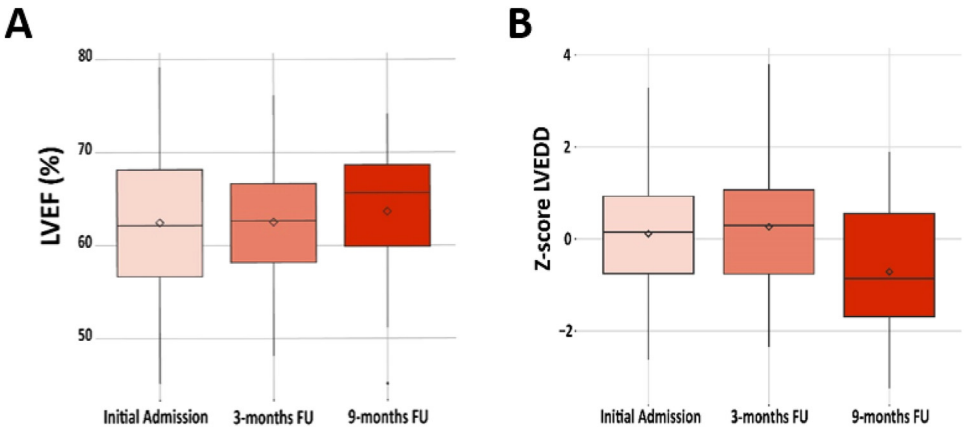
Data are reported as median (interquartile range), unless specified. Percentages are rounded. The denominator of percentages is the total sample size, unless specified. The *P* values are based on likelihood ratio tests of appropriate mixed models. A *P* value of <.05 was considered statistically significant and marked in bold. *ACE*, angiotensin-converting enzyme; *BSA*, body surface area; *Hs-TnT*, high-sensitivity troponin T; *IVIG*, intravenous immunoglobulins; *LGE*, late gadolinium enhancement; *MRI*, magnetic resonance imaging; *n.a.*, not applicable; *NT-proBNP*, N-terminal prohormone of brain natriuretic peptide; *NSAID*, nonsteroidal anti-inflammatory drug; *NYHA*, New York Heart Association.

than in patients with troponin elevation (median 17 (IQR 6-25) days, vs median 4 (IQR 3-5) days, $P = .002$). In 27 patients (59%) BNP or NT-proBNP was above laboratory-specific threshold with a median (IQR) NT-proBNP of 157 (53-402) ng/L. C-reactive protein (CRP) was abnormal in 39 patients (70%, median 15.8 (IQR 4-41.5) mg/L) and leukocytes were elevated in 10 patients (18%, median 7.6 (IQR 6.4-10.0) $\times$ $10^3/\mu L$).

Cardiovascular diagnostics

Initial electrocardiogram (ECG) revealed abnormal ST-segment elevation in 29 patients (52%) and T-wave inversion in 12 patients (21%). In 9 of 46 patients with Holter and/or cardiorespiratory monitoring, arrhythmias were registered (20%). No bradyarrhythmias including atrioventricular blockages were observed. Four patients (9%) presented nsVT without hemodynamic instability. Among those, 1 patient fulfilled the cMRI minor criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC). Abnormal amount of supraventricular and ventricular extrasystoles were noted in 4 and 3 patients (9%; 7%), respectively. All patients underwent echocardiographic examination. Median (IQR) left ventricular ejection fraction (LVEF) at initial examination was 62 (57-68)%. Median (IQR) *Z*-score of left ventricular end-diastolic diameter (LVEDD) was 0.15 (−0.75 to 0.93) (Figure 2). Only 1 patient (2%) displayed a dilated left ventricle with a *Z*-score of the LVEDD of 3.3, which was

Figure 2



Echocardiographic parameters LVEF and LVEDD in patients with VA-myocarditis over time. Echocardiographic parameters left ventricular ejection fraction (LVEF) (A) and *Z*-score of the left ventricular end-diastolic diameter (LVEDD) (B) in patients with COVID-19 vaccine-associated myocarditis at initial admission and at follow-ups (FU) after 3 months and 9 months. The boxplot displays the median values of the variables by the horizontal lines, the mean values by the diamonds.

further accompanied by global left ventricular hypokinesia, mildly reduced LVEF and echocardiographic characteristics of left ventricular noncompaction (LVNC). CMRI was performed in 49 patients (88%) at a median (IQR) of 9 (6-17) days after vaccination. Among those, late gadolinium enhancement (LGE) and myocardial edema were detected in 35 (74%) and 25 cases (54%), respectively. Median (IQR) LVEF obtained at cMRI was 60 (56-63)%, median (IQR) left ventricular end-diastolic volume (LVEDV) indexed for body surface area (BSA) was 82 (72-89) mL/m^2. Twenty-nine patients (83%) in our cohort were found to have a left ventricular inferior, inferolateral and/or anterolateral LGE distribution. In only 2 patients (6%), LGE was localized in septal segments. In 4 cases there were no further information on the LGE distribution.

Overall, 11 patients (20%) had mildly reduced systolic function defined as LVEF ranging from 45% to 54% on echocardiogram and/or cMRI.

Endomyocardial biopsy (EMB) was conducted in 11 patients (20%) at initial admission at a median (IQR) of 8 (6-10) days after vaccination (Table II). Myocarditis was confirmed in 7 of those patients (64%): healing/chronic lymphocytic myocarditis ($n = 6$, 55%) and healed myocarditis ($n = 1$, 9%) were diagnosed. Two biopsies (18%) showed low-grade myocardial damage with an increase in activated macrophages but without a complete picture of myocarditis. In 1 patient (9%) myocardial damage without inflammation was detected. Another biopsy did not show any evidence of myocardial damage or immunohistochemical signs of inflammation. A low viral load of Parvovirus B19 (377 copies/µg isolated myocardial deoxyribonucleic acid) was detected in 1 specimen. Coronary angiographies performed during cardiac catheterization revealed no obstructive coronary artery diseases. There were no periprocedural events in our cohort.

Therapy

Anti-inflammatory treatment included nonsteroidal anti-inflammatory drugs (NSAIDs) in 11 patients (20%), corticosteroids in 2 (4%) and intravenous immunoglobulin in 1 patient (2%). Heart failure medication included ß-blockers ($n = 13$; 23%), ACE inhibitors ($n = 7$; 13%), diuretics ($n = 3$; 5%) and antiarrhythmic sodium channel blocker in 1 patient (2%) with nsVT. In 33 patients (60%) no specific pharmaceutical treatment was administered. No patient required inotropic or vasoactive support, mechanical ventilation, or mechanical circulatory support (MCS).

Three-months follow-up

According to the study protocol, 3-months follow-up was achieved in 49 patients (88%) at a median (IQR) of 94 (63-118) days after initial presentation (Table I). Seven patients were lost to follow-up. Whereas most patients were free of symptoms, a considerable amount of 14 patients (28%) reported residual complaints: typical and/or atypical intermittent chest pain in 11 patients (22%), symptoms of fatigue in 6 patients (13%) and ongoing limitations and shortness of breath during physical activity in 2 patients (4%). Two patients (4%) reported palpitations and presented with an abnormal amount of ventricular extrasystoles registered by 24-hour Holter

Table II. Results of endomyocardial biopsies in patients with clinically suspected COVID-19 vaccine-associated myocarditis.

Patient no. (age, sex)	Diagnosis in EMB	Inflammation	Fibrosis	Viral PCR
1 (15 yrs, male)	Mild chronic myocardial damage with interstitial fibrosis	–	++	Negative
2 (17 yrs, male)	Healing/chronic lymphocytic myocarditis	++	+	Negative
3 (16 yrs, male)	Healing/chronic lymphocytic myocarditis	+	++	Negative
4 (15 yrs, male)	Healing/chronic lymphocytic myocarditis	+	++	Negative
5 (15 yrs, male)	Healing/chronic lymphocytic myocarditis	++	+	Negative
6 (17 yrs, female)	No evidence of myocarditis	–	+	Negative
7 (17 yrs, male)	Healing/chronic lymphocytic myocarditis	++	++	PVB19 377 copies/μg DNA
8 (17 yrs, male)	Healed myocarditis	+	++	Negative
9 (15 yrs, male)	Healing/chronic lymphocytic myocarditis	+	+	Negative
10 (16 yrs, male)	Healed myocarditis	+	++	Negative
11 (16 yrs, male)	Chronic myocardial damage with moderate increase in activated macrophages	++	+	Negative
12 (17 yrs, male)	Chronic myocardial damage with mild increase in activated macrophages	+	++	Negative

Diagnosis of myocarditis was confirmed by established criteria and grouped according to the World Health Organization's definition.[17,18] Inflammation was assessed by the extent of immunohistochemical detection of CD3+ T lymphocytes and CD68+ macrophages. Interstitial fibrosis was graded in Masson's trichrome stained sections.[19,20] Grade of inflammation and fibrosis: – none; + mild, ++ moderate; *DNA*, deoxyribonucleic acid; *EMB*, endomyocardial biopsy; *PCR*, polymerase chain reaction; *PVB19*, parvovirus B19.

ECG. One of them had recurrent episodes of nsVT on antiarrhythmic medication, which were terminated by electrophysiological intervention. According to that patient, episodes of intermittent palpitations were known from early childhood. Two patients (4%) were rehospitalized at follow-up due to ongoing symptoms, including the above-mentioned patient with recurrent episodes of nsVT. The remaining patients were in outpatient care.

ECG at 3-months follow-up showed normal findings in 37 out of 47 cases (79%). ST-segment elevation and T-wave inversion were recorded in 8 (17%) and 6 patients (13%), respectively. Troponin levels were analyzed in 23 patients (47%) and marginally elevated in 5 of them (22%). Of 20 patients with NT-proBNP or BNP analyzed at follow-up (41%), only 1 patient with recurrent pericardial effusion showed persistent increase (5%). Based on echocardiography, median (IQR) LVEF at 3-months follow-up was 63 (58-67)%. Median (IQR) *Z*-score of LVEDD was 0.3 (−0.8 to 1.1). Only 1 patient displayed ongoing dilatation of the left ventricle and fulfilled diagnostic criteria for LVNC. CMRI at 3-months follow-up was conducted in 12 patients (25%). Among those, 9 patients (75%) had persistence of LGE, with improvement in all, whereas myocardial edema completely resolved in all. Median (IQR) LVEDV indexed for BSA was normal with 80 (72-83) mL/m^2, median (IQR) LVEF based on cMRI was 63 (59-64)%. At 3-months follow-up, 3 patients (6%) still had mildly impaired systolic function with LVEF below 55% on echocardiogram and/or cMRI. Of 22 patients undergoing exercise testing at 3-months follow-up (45%), all showed normal cardiopulmonary exercise testing without occurrence of arrhythmias. EMB was performed in 1 patient with ongoing symptoms at follow-up and confirmed diagnosis of myocarditis (Table II).

Fourteen patients were still prescribed heart failure medication at 3-months follow-up including ß-blockers (n = 12; 24%), ACE inhibitors (n = 5; 10%), diuretics (n = 2; 4%) and antiarrhythmic sodium channel blocker was continued in the same patient with nsVT (2%). One patient with recurrent pericardial effusion and ongoing symptoms received NSAIDs and steroids (2%).

Overall, residual symptoms were reported by 14 patients (29%), in 23 patients (47%) diagnostic findings revealed persistent abnormalities and in 10 (20%) both was true at 3-months follow-up.

Nine-months follow-up

Data on 9-months follow-up of 21 patients (38%) were collected at a median (IQR) of 259 (218-319) days after initial presentation. All but 1 patient (95%), who reported intermittent palpitations at follow-up since SARS-

CoV-2 infection 2 weeks prior, were symptom-free at 9-months follow-up (Table I).

Overall, diagnostic abnormalities were detected in 9 patients (43%). ECG was conducted in all and showed persistent ST-segment elevation and T-wave inversion in 1 patient each (5%). No severe arrhythmias were monitored at the time of data analysis. Of the 2 patients with rhythm abnormalities at 3-months follow-up, 1 underwent successful electrophysiological intervention and subsequently had neither symptoms nor monitored arrhythmias. The remaining patient had ongoing ventricular extrasystoles at 9-months follow-up and an electrophysiological intervention planned for the near future. Laboratory analysis did not reveal any abnormalities. All but 1 patient (95%) underwent echocardiographic imaging. Median (IQR) LVEF was 66 (60-69)% and median (IQR) *Z*-score of LVEDD was −0.9 (−1.69 to 0.6). Of 11 patients (52%) with cMRI done at 9-months follow-up, 6 (55%) showed persistent LGE with further improvement. Two patients (18%) without cMRI done at 3-months follow-up displayed persistence of myocardial edema, though with significant regression. Three patients (14%) continued to present mildly reduced systolic function demonstrated by LVEF on echocardiogram and/or cMRI between 45% to 54%. Seven patients underwent exercise testing with normal findings in 6 of them (86%). One had a mildly reduced exercise capacity with a corresponding peak oxygen uptake (VO_2max) of 24 mL/min*kg. This patient reported mild exercise intolerance ever since a SARS-CoV-2 infection 4 weeks prior to follow-up, but was asymptomatic previously. Heart failure medication was continuously administered in 4 patients (19%), including ß-blockers and ACE inhibitors in 3 cases each. No MACE were observed.

Comparison between COVID-19 vaccine-associated myocarditis and non–vaccine-associated myocarditis

Table III shows differences in clinical characteristics and diagnostic findings in pediatric patients with COVID-19 VA-myocarditis ($n = 50$) compared to those with NVA-myocarditis ($n = 108$) at initial presentation. While patients with VA-myocarditis were more likely to present with chest pain ($P = .013$), patients with NVA-myocarditis tended to symptoms of heart failure ($P = .003$). Accordingly, patients with NVA-myocarditis had lower LVEF on echocardiogram ($P < .001$, Figure 3A) and were more likely to have LV dilatation ($P = .045$, Figure 3A). Also, arrhythmias occurred more frequently in the NVA-myocarditis group ($P = .031$). There were no significant differences between the 2 cohorts in ECG findings, frequency of LGE and edema on cMRI, or laboratory analysis. Out of 61 NVA-myocarditis patients undergoing EMB, 54 patients fulfilled histopathological criteria for myocarditis (acute lymphocytic myocarditis $n = 13$; healing/chronic lymphocytic myocarditis $n = 27$; healed myocarditis $n = 14$). In NVA-myocarditis patients, the requirement of MCS ($n = 5$, 5%), need for HTX ($n = 4$, 4%) and events of cardiorespiratory resuscitation ($n = 4$, 4%) and death ($n = 2$, 2%) were more probable. There were no such severe events in patients with COVID-19 VA-myocarditis.

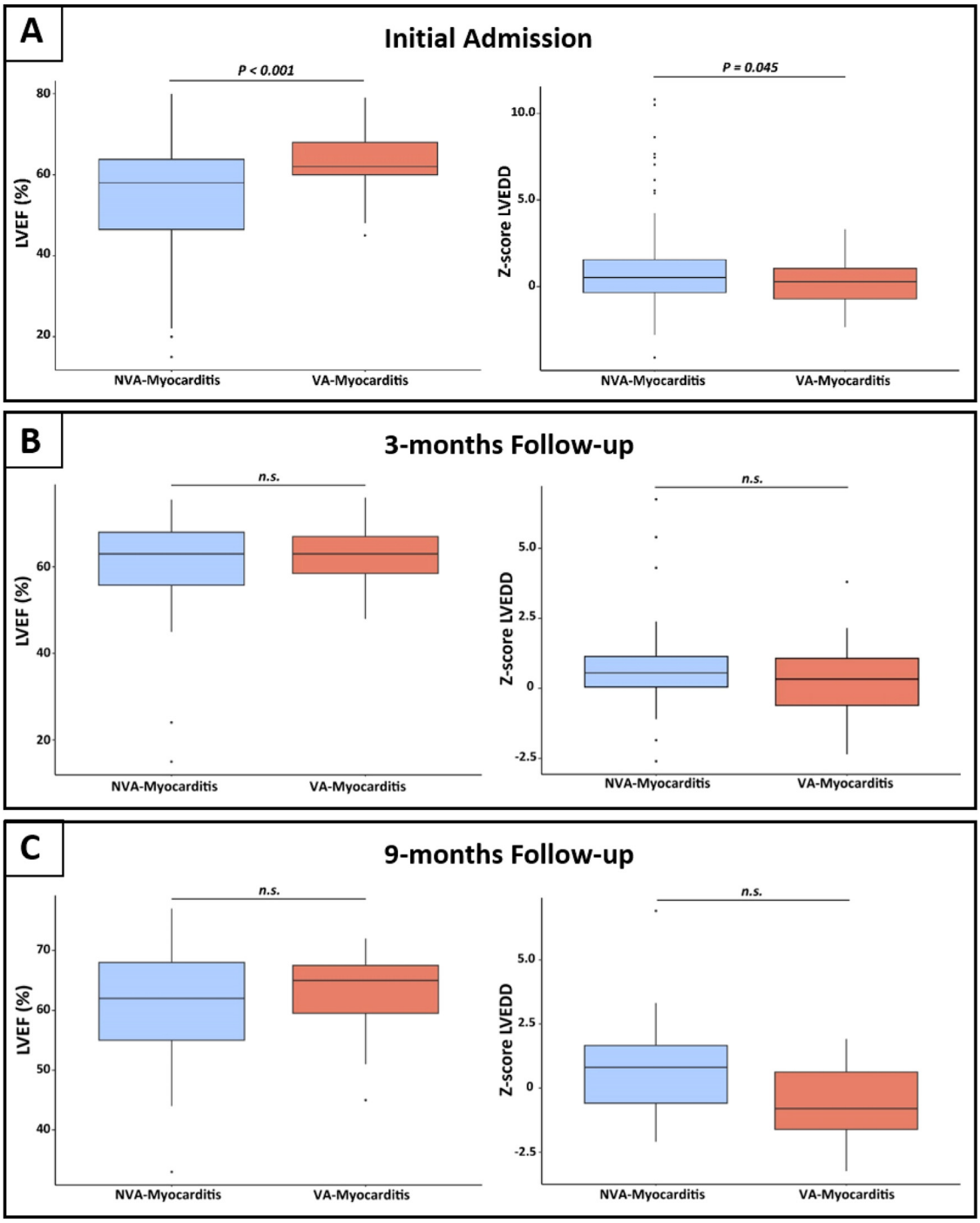
Tables IV and V show, by analogy, the clinical and diagnostic features of the 2 cohorts compared at 3- and 9-months follow-up. There were no statistically significant differences in symptoms and diagnostic findings between the 2 entities at follow-up. Notably, 3 patients with NVA-myocarditis experienced MACE at 9-months follow-up, of which all were heart transplanted due to severe heart failure at time of follow-up. In accordance, echocardiographic parameters LVEF and LVEDD had few outliers in this group, whereas the median values did not differ significantly between the cohorts (Figure 3B, C).

Discussion

The PedMYCVAC study describes a multicentric cohort of 56 patients aged under 18 years with suspected myocarditis following mRNA SARS-CoV-2 vaccination. Our data are coherent with previous research in finding a predominance of male adolescents with onset of symptoms within a few days after the second dose of mRNA COVID-19 vaccine.[21,22] The susceptibility of young males for such a condition might be related to higher levels of androgens promoting a more extensive immune and inflammatory response.[23] Further, Cheng et al described phenotypic differences between sexes. Whereas males initially tended to show higher levels of troponin indicating more pronounced myocardial damage, females claimed longer duration of symptoms.[24] In our cohort 5 subjects were female, of which all reported ongoing or intermittent symptoms at 3-months follow-up. Of 51 male patients, only 9 had residual symptoms. This observation may also support the potential impact of hormonal factors on pathophysiology of COVID-19 VA-myocarditis. Further, potential underdiagnosis of myocarditis in females with various cardiac symptoms must be considered. The question of genetic variants predisposing for COVID-19 vaccine-associated myocarditis follows, since our sample included 1 pair of monozygotic twin boys. Certain cardiac genotypes have been associated with increased risk for viral myocarditis, which may only be assumed for COVID-19 VA-myocarditis.[25] A recently published case report of 13-year-old twins with myocarditis after mRNA COVID-19 vaccination strongly suggests genetic susceptibility pending genetic analysis.[26]

Clinical and diagnostic findings at initial presentation are largely concordant with results of previous case studies.[22,24,27] The proportion of VA-myocarditis patients with elevated troponin was much higher (98%) in a cohort reported by Oster et al.[7] In our cohort, patients without elevated troponin had a significantly longer interval between vaccination and first medical examination

Figure 3



Echocardiographic parameters LVEF and LVEDD in VA-myocarditis compared to NVA-myocarditis. Comparison of echocardiographic parameters left ventricular ejection fraction (LVEF) and *Z*-score of the left ventricular end-diastolic diameter (LVEDD) between male patients with COVID-19 vaccine-associated myocarditis (VA-myocarditis) and non–vaccine-associated myocarditis (NVA-myocarditis) at initial admission (A), 3-months follow-ups (B), and 9-months follow-up (C). The calculated *P* value corresponds to the regression coefficient of the cohort indicator in a linear model adjusted for age and body-mass index. The boxplot displays the median values of the variables by the horizontal lines. *N.s.*, nonsignificant.

Table III. Comparison of pediatric, male patients with COVID-19 vaccine-associated myocarditis and non–vaccine-associated myocarditis at initial admission while adjusting for body-mass index and age.

Characteristics	COVID-19 vaccine-associated myocarditis ($n = 50$)	Non–vaccine-associated myocarditis ($n = 108$)	Regression coefficient	*P* value
Age, years	16.3 (15.5-16.9)	16.1 (14.5-16.9)		
Weight, kg	68.2 (57-78)	71.8 (59-82)		
Height, cm	174.5 (171-182)	175.8 (169-181)		
Symptoms, *n* (%)				
Angina pectoris	43 (88), $n = 49$	74 (69)	3.405	**.013**
Fatigue	33 (66)	75 (70)	0.888	.753
Shortness of breath	15 (31), $n = 49$	33 (31)	0.965	.925
Palpitations	5 (10)	15 (14)	0.694	.515
Syncope	0 (0)	9 (8)	0.000	.991
NYHA classification > I	4 (8)	36 (33)	0.187	**.003**
Electrocardiogram, *n* (%)				
ST elevation	28 (56)	58 (54)	1.146	.699
ST depression	9 (18)	10 (10)	1.990	.177
T-wave inversion	11 (22)	33 (31)	0.592	.202
Monitored arrhythmias, *n* (%)	5 (10)	26 (24)	0.317	**.031**
Echocardiography				
LVEF (%)	62 (60-68)	58 (47-64)	9.060	**<.001**
LVEDD, *Z*-score	0.28 (−0.71 to 1.05), $n = 42$	0.52 (−0.35 to 1.55), $n = 102$	−0.871	**.045**
Laboratory analysis				
Hs-cTnT, ng/L	254 (31.9-709.8), $n = 26$	664 (28-1243), $n = 58$	−160.7	.429
NT-proBNP, ng/L	213 (56-402), $n = 29$	468 (128-1841), $n = 59$	−1485.6	.175
Cardiac MRI, *n* (%)				
LGE	34 (81), $n = 42$	74 (82), $n = 90$	1.067	.897
Edema	22 (52), $n = 42$	45 (54), $n = 83$	0.914	.821
MACE, *n* (%)	3 (6)	18 (17)	−1.078	.102

Data are reported as median (interquartile range), unless specified. Percentages are rounded. The denominator of percentages is the total sample size, unless specified. A *P* value of <.05 was considered statistically significant and marked in bold. *Hs-TnT*, high-sensitivity troponin T; *LGE*, late gadolinium enhancement; *LVEDD*, left ventricular end-diastolic diameter; *LVEF*, left ventricular ejection fraction; *MACE*, major cardiac adverse events including malign arrhythmias, requirement of mechanical circulatory support, resuscitation, heart transplantation and/or death; *NT-proBNP*, N-terminal prohormone of brain natriuretic peptide; *NYHA*, New York Heart Association. Monitored arrhythmias included abnormal amount of supraventricular and ventricular extrasystoles, supraventricular tachycardia, and ventricular tachycardia.

than patients with elevated troponin. Therefore, an increase in troponin may have been missed in some cases.

Although endomyocardial biopsy (EMB) represents the gold standard in diagnosis of myocarditis, due to its invasive nature it is rarely performed in pediatric patients with COVID-19 VA-myocarditis and preserved LVEF.[28] Therefore, little is currently known about the pathohistological findings in children and adolescents with

COVID-19 VA-myocarditis. EMB confirmed the diagnosis of myocarditis after COVID-19 vaccination in 8 of 12 patients. Notably, 2 patient's specimens showed an increase in macrophages without fulfilling full pathohistological criteria for diagnosis of myocarditis. Infiltrating cells were predominantly T lymphocytes and macrophages, which is supported by a recently published case reports.[29,30] The predominance of macrophages in myocarditis following COVID-19 vaccination has been noted previously and may suggest a different immune-mediated mechanism compared with NVA-myocarditis.[31] Further, high amounts of mononuclear cell infiltrates and fibrosis in EMB of pediatric patients with NVA-myocarditis were previously associated with severe heart failure.[20] EMB in VA-myocarditis patients showed a mild to moderate grade of inflammation and fibrosis without signs of severe myocardial damage. The pathohistological findings may therefore support the clinically mild disease course. In all but 1 patient, who had low myocardial viral load of parvovirus B19, no other causes were identified by viral genome detection. However, this low viral load suggests myocardial persistence of the viral genome after PVB19 infection rather than acute myocardial inflammation.[20] The absence of exogenous agents may support an immune-mediated mechanism in these patients, although sampling errors must be considered, especially in right ventricular EMB.

The numbers of cMRI-confirmed myocarditis and its LGE distribution resemble those of Jain et al, although myocardial edema was detected more frequently in their cohort. This may be due to the shorter interval between cMRI scan and date of vaccination, since cMRI studies were all performed within 1 week after COVID-19 vaccination.[27] Myocardial edema might usually resolve fast

Table IV. Comparison of pediatric, male patients with COVID-19 vaccine-associated myocarditis and non–vaccine-associated myocarditis at 3-months follow-up while adjusting for body-mass index and age.

Characteristics	COVID-19 vaccine-associated myocarditis ($n = 44$)	Non–vaccine-associated myocarditis ($n = 39$)	Regression coefficient	*P* value
Age, years	16.6 (15.8-17.2)	16.1 (14.9-16.8)		
Weight, kg	68.6 (58-78.6)	67 (61.5-83.9)		
Height, cm	177.5 (172.8-183)	175 (167.5-181.5)		
Symptoms, *n* (%)	$n = 42$	$n = 38$		
Angina pectoris	6 (14)	5 (13)	1.130	.863
Fatigue	3 (7)	4 (11)	0.459	.353
Palpitations	2 (5)	1 (3)	1.000	1.000
NYHA classification > I	3 (7)	2 (5)	2.047	.517
Electrocardiogram, *n* (%)	$n = 42$	$n = 33$		
ST elevation	8 (19)	4 (12)	1.210	.784
ST depression	1 (2)	1 (3)	0.843	.910
T-wave inversion	5 (12)	9 (27)	0.285	.055
Monitored arrhythmias, *n* (%)	0 (0), $n = 42$	1 (3), $n = 38$	0.000	.997
Echocardiography				
LVEF (%)	63 (59-67), $n = 35$	63 (56-68), $n = 32$	2.639	.305
LVEDD, *Z*-score	0.32 (−0.61 to 1.07), $n = 36$	0.55 (0.04-1.14), $n = 35$	−0.413	.284
Laboratory analysis				
Hs-cTnT, ng/L	7.5 (4.7-9.1), $n = 8$	6.2 (3.6-8), $n = 10$	−4.351	.538
NT-proBNP, ng/L	28 (17-59), $n = 14$	49 (42-57), $n = 11$	1.753	.962
Cardiac MRI, *n* (%)				
LGE	9 (75), $n = 12$	7 (70), $n = 10$	1.273	.852
Edema	0 (0), $n = 11$	1 (11), $n = 9$	0.000*	.996*
MACE, *n* (%)	0 (0), $n = 43$	0 (0)	n.a.	n.a.

Data are reported as median (interquartile range), unless specified. Percentages are rounded. The denominator of percentages is the total sample size, unless specified. *Hs-TnT*, high-sensitivity troponin T; *LGE*, late gadolinium enhancement; *LVEDD*, left ventricular end-diastolic diameter; *LVEF*, left ventricular ejection fraction; *MACE*, major cardiac adverse events including malign arrhythmias, requirement of mechanical circulatory support, resuscitation, heart transplantation and/or death; *n.a.*, not applicable; *NT-proBNP*, N-terminal prohormone of brain natriuretic peptide; *NYHA*, New York Heart Association. Monitored arrhythmias included abnormal amount of supraventricular and ventricular extrasystoles, supraventricular tachycardia, and ventricular tachycardia.

* *Note:* The generalized linear model (GLM) did not converge due to perfect separation, resulting in unreliable coefficient estimates.

after the acute phase. The predominance of LGE localized in the inferior and lateral LV segments, as reported before, may support the mild disease course since septal LGE was previously associated with worse prognosis in viral myocarditis.[32,33] A notable number of patients showed persistence of LGE at 3- and 9-months follow-up, though with significantly reduced extent over time. A few studies confirm persistence of residual LGE despite resolution of edema at mid-term follow-up.[34-36] While the clinical course of our cohort was benign, presence of LGE in NVA-myocarditis has been an indicator of poor outcome and long-term cardiac risk, especially in case of increasing LGE and absence of edema.[37-39] Less data on the persistence of LGE and its prognostic value in COVID 19 VA-myocarditis are available, especially in children. Therefore, long-term follow-ups in patients with COVID-19 VA-myocarditis are necessary.

Given the relatively recent implementation of COVID-19 vaccines, follow-up data are still limited and data on long-term outcome in children and adolescents are missing. In our cohort, evaluation at 3-months follow-up revealed residual symptoms in 29% of patients, most commonly intermittent atypical chest pain and fatigue. Chain et al describe similar symptoms in 50% of adolescents diagnosed with probable or definitive COVID-19 VA- myocarditis at 1-month follow-up.[24] In our study, about a quarter were prescribed daily heart failure or antiarrhythmic medication at 3-months follow-up. These findings are in line with a 90-days follow-up surveillance study considering young adults and adolescents with COVID-19 VA-myocarditis published by Kracalik and coauthors. Interestingly, in their study, quality-of-life measures of patients at follow-up were comparable to healthy controls in prepandemic population of similar age.[40] At 9-months follow-up, persistence of diagnostic abnormalities was seen in 9 patients (43%), including mildly reduced left ventricular function in echocardiogram or cMRI in 3 cases. Importantly, due to loss of follow-up or lack of testing, less than 50% of the cohort was included at the 9-months follow-up. However, even if all remaining subjects had normalized, a substantial proportion of 16% still had diagnostic residuals. Of the 3 patients with mildly reduced LVEF, 1 reported exercise intolerance ever since SARS-CoV-2-infection 4 weeks prior to follow-up, which

Table V. Comparison of pediatric, male patients with COVID-19 vaccine-associated myocarditis and non–vaccine-associated myocarditis at 9-months follow-up while adjusting for body-mass index and age.

Characteristics	COVID-19 vaccine-associated myocarditis ($n = 20$)	Non–vaccine-associated myocarditis ($n = 24$)	Regression coefficient	*P* value
Age, years	17.1 (16.6-17.9)	16.1 (14.8-17.3)		
Weight, kg	69.5 (63.5-74.6)	66.9 (56.1-87.2)		
Height, cm	178 (173.5-184.8)	175.5 (171.5-180.5)		
Symptoms, *n* (%)				
Angina pectoris	0 (0)	0(0)	n.a.	n.a.
Fatigue	0 (0)	2 (8)	0.000	.996
Palpitations	1 (5)	1 (4)	1.878	.753
NYHA classification > I	0 (0)	1 (4) $n = 22$	$5 \cdot 10^{12}$*	.999*
Electrocardiogram, *n* (%)				
ST elevation	1 (5)	1 (5)	1.190	.915
ST depression	0 (0)	3 (14)	0.000	.996
T-wave inversion	1 (5)	4 (18)	0.114	.109
Monitored arrhythmias, *n* (%)	0 (0)	1 (4)	0.000*	.999*
Echocardiography				
LVEF (%)	65 (60-68), $n = 11$	62 (55-68), $n = 19$	0.299	.945
LVEDD, *Z*-score	−0.81 (−1.62 to 0.61), $n = 16$	0.8 (−0.6 to 1.65), $n = 21$	−1.096	.069
Laboratory analysis				
Hs-cTnT, ng/L	4.6 (3.6-6), $n = 6$	n.a., $n = 0$	n.a.	n.a.
NT-proBNP, ng/L	27 (10-30), $n = 9$	n.a., $n = 0$	n.a.	n.a.
Cardiac MRI, *n* (%)	$n = 11$			
LGE	6 (55)	4 (57), $n = 7$	1.467	.749
Edema	2 (18)	1 (20), $n = 5$	5.705	.444
MACE, *n* (%)	0 (0)	3 (13)	0.000	.996

Data are reported as median (interquartile range), unless specified. Percentages are rounded. The denominator of percentages is the total sample size, unless specified. *Hs-TnT*, high-sensitivity troponin T; *LGE*, late gadolinium enhancement; *LVEDD*, left ventricular end-diastolic diameter; *LVEF*, left ventricular ejection fraction; *MACE*, major cardiac adverse events including malign arrhythmias, requirement of mechanical circulatory support, resuscitation, heart transplantation and/or death; *n.a.*, not applicable; *NT-proBNP*, N-terminal prohormone of brain natriuretic peptide; *NYHA*, New York Heart Association. Monitored arrhythmias included abnormal amount of supraventricular and ventricular extrasystoles, supraventricular tachycardia, and ventricular tachycardia.

* *Note*: The GLM did not converge due to perfect separation, resulting in unreliable coefficient estimates.

was objectified by cardiopulmonary exercise testing. Another was suspected to suffer from left ventricular noncompaction cardiomyopathy (LVNC), which led to initiation of genetic testing. Given these overlaps, long-term impact of COVID-19 VA-myocarditis on left ventricular dysfunction is difficult to define. As of today, no connection has been made between COVID-19 vaccination and clinical onset of cardiomyopathies in genetically susceptible subjects. The question of whether the vaccination might trigger a clinical appearance of an underlying cardiomyopathy is unclear and needs further investigation. However, most of the few data published to date show complete resolution of left ventricular dysfunction in all pediatric patients with COVID-19 VA-myocarditis at short- to mid-term follow-up.[27,41,42]

In line with previously published studies, the clinical course of COVID-19 VA-myocarditis was mild and no incidents of severe heart failure, inotropic or mechanical circulatory support, HTX or death were observed.[27] In contrast, NVA-myocarditis in pediatric patients is reported to cause more frequently acute heart failure, requirement of MCS, HTX or death, especially in young children.[43] In our age- and sex-adjusted comparison, patients with COVID-19 VA-myocarditis were more likely to present with chest pain, whereas patients with NVA-myocarditis more frequently had symptoms of heart failure with lower LVEF, higher *Z*-score of LVEDD and recorded arrhythmias. Though statistically significant, the difference in median LVEF (58% vs 62%) has little clinical relevance but there were some cases of severe heart failure in the

NVA-myocarditis cohort. Further, there was a 17% chance for MACE at first admission, whereas in the COVID-19 VA-myocarditis cohort only 6% had MACE, all with nsVT. Three patients (13%) with NVA-myocarditis were heart transplanted at time of 9-months follow-up due to severe heart failure. In accordance, 2 recently published cohort studies found a lower risk of heart failure and death in patients with COVID-19 VA-myocarditis when compared to NVA-myocarditis at 90 and 180 days of follow-up.[12,44] These differences may lead to the assumption of different pathophysiologic mechanisms. Previously, proposed mechanisms in COVID-19 VA-myocarditis mainly included molecular mimicry between viral and self-antigens, the recognition of the mRNA itself as an antigen and as mentioned above genetic and sex predispositions.[31] Lately, evidence for alternate mechanisms such as cytokine-dependent tissue-damaging is growing.[45] Furthermore, neutralizing antibodies targeting the endogenous interleukin-1 receptor antagonist (IL-1RA) and a hyperphosphorylated IL-1RA isoform were detected in young male patients with EMB-confirmed myocarditis after the receipt of mRNA COVID-19 vaccines. These antibodies impaired IL-1RA bioactivity in vitro, were associated with low circulating levels of IL-1RA, and were found in patients with obvious cardiac damage and inflammation.[46] The retrospective cohort study of Patel et al confirms mild course in patients with COVID-19 VA-myocarditis compared to NVA-myocarditis and multisystem inflammatory syndrome in children (MIS-C)-related myocarditis. Though there was no significant difference in symptoms between patients with NVA-myocarditis and COVID-19 VA-myocarditis. This may be due to the small number of COVID-19 VA-myocarditis patients included ($n = 9$). Whereas all these patients had preserved LVEF, only 73% of patients with NVA-myocarditis had a LVEF above 55% at the time of discharge with longer duration of hospitalization and higher rates of heart failure medication.[47] Our study presents an in-depth phenotyped pediatric cohort of COVID-19 vaccine-associated myocarditis in comparison to non–vaccine-associated myocarditis. It is the first to highlight detailed differences in clinical and diagnostic findings between those 2 entities at initial presentation and during follow-up.

Limitations

Some limitations to this study must be addressed. The assumption that mRNA vaccination caused the myocarditis is based on the temporal correlation. We cannot demonstrate causality with certainty. Diagnostic and therapeutic procedures were managed by the local medical team and did not follow a standardized study protocol. While this reflects clinical practice, it comes with a certain risk of variability in findings, its interpretation and implication. Most patients included were initially hospitalized in a MYKKE medical center with expertise in pediatric cardiology. That may exclude less affected patients, who were only screened as outpatients. In addition, and importantly, 9-months follow-up was only obtained in 21 patients at time of analysis. Consequently, more than 50% of the cohort remained unconsidered in this regard. Although inpatient and outpatient caregivers and patient's families were actively contacted to obtain follow-up data, the available data may more likely come from patients with persistent symptoms or diagnostic abnormalities and thus may once again neglect the less affected patients. Restricting the NVA-myocarditis control cohort to only those with EMB- or cMRI-confirmed myocarditis does increase validity but also causes a potential selection bias as not all VA-myocarditis patient had confirmation via EMB or cMRI.

Conclusions

Overall, the outcome of COVID-19 VA-myocarditis in children and adolescents was good and absence of severe heart failure was observed. . In our comparative analysis between patients with COVID-19 VA-myocarditis and those with NVA-myocarditis, we found differences in clinical manifestation, diagnostic findings and a better outcome in favor of patients with COVID-19 VA-myocarditis. These differences might indicate different pathophysiologic mechanisms. Nevertheless, a substantial number of patients with COVID-19 VA-myocarditis showed residual symptoms and/or persistence of diagnostic abnormalities at follow-up. Further studies are needed to investigate its clinical significance and association with adverse events.

Disclosures

None reported.

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