Outcome and Morphofunctional Changes on Cardiac Magnetic Resonance in Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination

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Messenger RNA (mRNA) COVID-19 vaccination has been associated with a higher-than-expected occurrence of acute myocarditis, although the benefits of the vaccine greatly outweigh the risk of myocarditis. Even if the short-term prognosis of mRNA vaccine–related myocarditis has been reported to be favorable, scarce information is available on midterm prognosis. The current series included 7 to 9 patients with baseline and follow-up cardiac magnetic resonance imaging (CMRI).[1,2] Questions on acute myocarditis following mRNA COVID-19 vaccination addressed by this study are the risk of adverse events after discharge and the extent of residual myocardial dysfunction and scar formation.

We conducted a retrospective, multicenter study involving 31 hospitals in Europe and the United States. The Niguarda Hospital in Milano, Italy, acted as the coordinating center. The Institutional Review Board in Milano, Italy (Ethics Committee Milano Area 3), approved this study during the session of May 2022 (identifier 395-18052022). Written consent was not necessary due to the nature of the study. The data will not be shared because the current ethics approval does not allow us to share these data. We identified 77 patients with a confirmed diagnosis based on consistent cardiac symptoms, which occurred within 30 days since an mRNA COVID-19 vaccination, significant elevation of troponin levels, and CMRI findings consistent with acute myocarditis according to the 2018 updated Lake Louise criteria. Among patients with available follow-up (n=75; 97.4%), none died or required further hospitalization after a median time of 147 (first to third quartile [Q1–Q3],

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Table. Clinical and Diagnostic Characteristics of Patients With mRNA COVID-19 Vaccine Myocarditis

	Baseline characteristics					Changes in imaging data between baseline and follow-up		
	No. of patients with available data	All patients	Patients without follow-up CMR	Patients with follow-up CMR	*P* value	Baseline imaging data	Follow-up imaging data	*P* value
N		77	28	49				
Demographics								
Age, y	77	25 (20–35)	25 (20–39)	25 (30–34)	0.771			
Women	77	15 (19)	6 (21.4)	9 (18.4)	1.000			
White ethnicity	77	70 (90.9)	26 (92.8)	44 (89.8)	1.000			
History of allergic reaction	77	3 (3.8)	1 (3.5)	2 (4.1)	1.000			
Previous myocarditis	77	7 (9.0)	2 (7.1)	5 (10.2)	1.000			
Prior exposure and vaccination								
Previous exposure to SARS-CoV2	76	8 (10.5)*	1 (3.5)	7 (14.6)*	0.245			
Previous COVID-19 hospitalization	76	2 (2.6)*	0	2 (4.2)*	0.528			
Type of mRNA vaccine								
BNT162b2 (Pfizer/BioNTech)	76	56 (73.7)*	20 (74.1)*	36 (73.5)*	1.000			
mRNA-1273 (Moderna)	76	20 (26.3)*	7 (25.9)*	13 (25.5)*	1.000			
Myocarditis after the first vaccine dose	72	21 (29.2)*	6 (24.0)*	15 (31.9)*	0.591			
Myocarditis after the second vaccine dose	72	36 (50.0)*	11 (44.0)*	25 (53.2)*	0.621			
Myocarditis after the third vaccine dose	72	15 (20.8)*	8 (32.0)*	7 (14.9)*	0.128			
Time between the vaccine dose and the onset of symptoms, d	72	3 (2–5)	3 (3–5)	3 (2–6)	0.981			
Time between the vaccine dose and hospitalization, d	72	3 (2–6)	3 (2–5)	3 (2–6)	0.771			
Presence of IgG anti-Spike protein (after vaccination)	22	18 (82)*	3 (75)*	15 (83)*	0.582			
Positive SARS-CoV-2 RT-PCR on nasopharyngeal swab	77	0	0	0				
Clinical presentation and hospitalization								
Need for hospitalization	77	77	28	49				
Prodromal symptoms								
Fever	77	28 (36.3)	5 (17.9)	23 (46.9)	0.014			
Flu-like symptoms	77	30 (39.0)	9 (32.1)	21 (42.8)	0.467			
Other	77	3 (3.9)	0	3 (6.1)	0.297			
Not reported	77	24 (31.1)	15 (53.6)	9 (18.3)	0.002†			
Presenting symptoms								
Chest pain	77	73 (94.8)	26 (92.8)	47 (95.9)	0.619			
Heart failure	77	4 (5.1)	3 (10.7)	1 (2.0)	0.134			
Cardiogenic shock/cardiac arrest	77	3 (3.9)	1 (3.6)	2 (4.1)	1.000			
Syncope	77	1 (1.3)	0	1 (2.0)	1.000			
Other	77	8 (10.4)	2 (7.1)	6 (12.2)	0.703			
Systolic blood pressure on admission, mm Hg	74	120 (110–132)	115 (106–135)	120 (110–130)	0.457			
Heart rate on admission, bpm	76	81 (70–90)	80 (70–92)	81 (72–90)	0.790			
Days in hospitals	73	6 (5–8)	6 (4–8)	7 (5–9)	0.220			

(*Continued*)

Table. Continued

	Baseline characteristics					Changes in imaging data between baseline and follow-up		
	No. of patients with available data	All patients	Patients without follow-up CMR	Patients with follow-up CMR	*P* value	Baseline imaging data	Follow-up imaging data	*P* value
Days in intensive care unit	74	2 (0–3)	2 (0–4)	2 (0–3)	0.577			
Need for inotropes	75	4 (5.3)*	2 (7.4)*	2 (4.2)*	0.606			
Need for temporary mechanical circulatory support	75	3 (4.0)*	1 (3.7)*	2 (4.2)*	1.000			
ECG on admission								
Normal	75	14 (18.7)*	7 (25.9)*	7 (14.6)*	0.237			
ST-segment elevation	75	47 (62.7)*	14 (51.8)*	33 (68.7)*	0.214			
Other abnormal ST-T segment	75	13 (17.3)*	5 (18.5)*	8 (16.7)*	1.000			
QRS >120 ms	74	1 (1.3)*	0	1 (2.1)*	1.000			
ECG monitoring								
Nonsustained ventricular tachycardia	75	8 (10.7)*	5 (19.2)*	3 (6.1)	0.117			
VT/VF	75	1 (1.3)*	1 (3.8)*	0	0.347			
Sustained atrial arrhythmias	75	0	0	0				
Cardiac biomarkers								
Troponin increase on admission (×fold URL)	77	80 (27–238)	58 (24–171)	83 (33–330)	0.253			
Troponin increase at peak (×fold URL)	74	108 (50–357)	73 (39–243)	122 (67–522)	0.085			
Day of troponin peak after admission	18	1 (0–2)	1 (0–2)	2 (1–2)	0.216			
First CK-MB, µg/L	30	27 (10–45)	10 (8–29)	31 (14–62)	0.078			
Peak CK-MB, µg/L	32	31 (11–54)	10 (8–38)	34 (13–78)	0.122			
First NT-proBNP, ng/L	46	323 (136–610)	219 (139–688)	356 (125–571)	0.961			
First BNP	9	45 (17–87)	33 (12–81)	45 (42–46)	0.606			
Inflammatory biomarkers								
C-reactive protein increase on admission (×fold URL)	73	8 (2–16)	5 (2–11)	8 (3–19)	0.216			
Eosinophilia	75	4 (5.3)*	2 (7.7)*	2 (4.1)	0.606			
Echocardiography‡						Baseline echo (n=48 patients)	Follow-up echo (n=48 patients)	*P* value
Days after hospitalization							144 (59–197)	
LV EF on first echo, %	74	56 (50–60)	56 (52–62)	56 (50–60)	0.453	55 (84–60)	60 (60–64)	<0.001†
Presence of segmental hypokinesia	74	36 (48.6)*	12 (48.0)*	24 (49.0)	1.000	26 (54.2)	3 (6.2)	<0.001†
Inferior or lateral wall	74	33 (44.6)*	9 (36.0)*	24 (49.0)	0.331			
Anterior wall	73	9 (12.3)*	4 (16.0)*	5 (10.4)*	0.482			
Septal wall	73	8 (10.9)*	3 (12.0)*	5 (10.4)*	1.000			
LVEDD, mm	44	48 (45–52)	48 (45–50)	48 (45–52)	0.599	48 (46–52)	48 (45–50)	0.183
Dilated LV	73	6 (8.2)*	2 (8.3)*	4 (8.2)	1.000	5 (10.4)	0	0.056
Dilated RV	73	0	0	0		0	0	
RV-TAPSE <17 mm	73	2 (2.7)*	1 (4.2)*	1 (2.0)	1.000	2 (4.2)	0	0.242
Pericardial effusion	74	12 (16.2)*	3 (12.0)*	9 (18.4)	0.740	11 (22.9)	0	<0.001†
Lowest LV EF value, %	73	56 (50–60)	55 (51–61)	56 (50–60)	0.780			
Coronary angiography/CT scan excluding coronary artery disease	77	35 (45.4)	10 (35.7)	25 (51.0)	0.238			

(*Continued*)

Table. Continued

	Baseline characteristics					Changes in imaging data between baseline and follow-up		
	No. of patients with available data	All patients	Patients without follow-up CMR	Patients with follow-up CMR	*P* value	Baseline imaging data	Follow-up imaging data	*P* value
Available cardiac MRI‡						Baseline cardiac MRI (n=49 patients)	Follow-up cardiac MRI (n=49 patients)	*P* value
Days after hospitalization	77	4 (2–7)	3 (2–9)	4 (2–7)	0.697	4 (2–7)	137 (93–180)	
LV EF, %	76	59 (55–64)	60 (55–64)	59 (55–65)	0.556	59 (55–65)	60 (57–64)	0.507
LV EF <50%	76	5 (6.6)*	2 (3.6)*	3 (6.2)*	1.000	3 (6.2)*	0	0.117
LV EF <55%	76	14 (18.4)*	5 (17.8)*	9 (18.7)*	1.000	9 (18.7)*	3 (6.1)	0.071
Indexed LVEDV, mL/m^2	62	82 (72–88)	82 (70–89)	82 (73–88)	0.969	82 (73–88)	75 (65–84)	0.029†
Dilated LV	75	8 (10.6)*	3 (10.7)	7 (14.6)*	1.000	7 (14.6)*	5 (10.6)*	0.759
RV EF, %	73	57 (52–62)	58 (52–62)	56 (52–62)	0.740	56 (52–62)	57 (52–61)	0.563
Dilated RV	75	2 (2.7)*	1 (3.6)*	1 (2.1)*	1.000	1 (2.1)*	1 (2.1)*	1.000
Edema on T2-w imaging	77	75 (97.4)	28 (100)	47 (95.9)	0.531	47 (95.9)	10 (20.4)	<0.001†
Inferior	77	37 (48.0)	11 (39.2)	26 (53.0)	0.343	26 (53.1)	3 (6.1)	<0.001†
Inferolateral	77	63 (81.8)	21 (75.0)	43 (87.7)	0.207	43 (87.7)	4 (8.2)	<0.001†
Anterolateral	77	40 (51.9)	14 (50.0)	26 (53.1)	0.817	26 (53.1)	0	<0.001†
Anterior	77	20 (26.0)	4 (14.2)	16 (32.6)	0.105	16 (32.6)	1 (20.4)	<0.001†
Septal	77	9 (11.7)	3 (10.7)	6 (12.2)	1.000	6 (12.2)	2 (4.1)	0.159
Presence of LGE	77	77 (100)	28 (100)	49 (100)		49 (100)	39 (79.6)	0.001†
Inferior	77	37 (48.0)	11 (39.2)	26 (53.0)	0.343	26 (53.1)	8 (16.3)	<0.001†
Inferolateral	77	45 (58.4)	13 (46.4)	32 (65.3)	0.149	32 (65.3)	12 (24.5)	<0.001†
Anterolateral	77	40 (51.9)	14 (50.0)	26 (53.1)	0.817	26 (53.1)	8 (16.3)	<0.001†
Anterior	77	11 (14.3)	2 (7.1)	9 (18.4)	0.310	9 (18.4)	0	0.003†
Septal	77	7 (9.1)	2 (7.1)	5 (10.2)	1.000	5 (10.2)	3 (6.1)	0.715
Increased T1 mapping signal	31	22 (71.0)*	9 (75.0)*	13 (68.4)*	1.000	13 (68.4)*	4 (13.3)*	<0.001†
Increased T2 mapping signal	41	35 (85.3)*	14 (87.5)*	21 (84.0)*	1.000	21 (84.0)*	3 (10.3)*	<0.001†
Pericardial effusion	77	10 (13.0)	4 (14.3)	16 (32.6)	0.106	16 (32.6)	3 (6.1)	0.004†
Available histology, n (%)	77	9 (11.7)	3 (10.7)	6 (12.2)	1.000			
Active myocarditis	9	6 (66.7)*	2 (66.7)*	4 (66.7)*	0.774			
Treatments								
Corticosteroids	77	9 (11.7)	3 (10.7)	6 (12.2)	1.000			
Other immunosuppressive agents	77	11 (14.3)	4 (14.3)	7 (14.3)	1.000			
NSAIDs	77	40 (51.9)	11 (39.2)	29 (59.2)	0.104			
In-hospital outcome								
Live	75	75 (100)*	26 (100)*	49 (100)*				
Dead	75	0	0	0				
Transplanted/LVAD	75	0	0	0				

Data are reported as n (%) for categorical variables and as median (interquartile range, 1–3) for continuous variables. The Mann-Whitney *U* test was used to compare continuous variables of patients with or without follow-up CMR. The Wilcoxon matched-pair signed-rank test was used to analyze paired data of baseline vs follow-up CMR. Categorical variables were compared with the Fisher exact test. BNP indicates brain natriuretic peptide; bpm, beats per minute; CK-MB, creatine kinease-myocardial band isoenzyme; CMR, cardiac magnetic resonance; CMRI, cardiac magnetic resonance imaging; CT, computed tomography; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RT-PCR, real-time polymerase chain reaction; RV, right ventricle; T2-w, T2 weighted; TAPSE, tricuspid annular plane systolic excursion; URL, upper reference limit; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*The proportion of patients was calculated on the number of patients with available data.

†$P<0.05$.

‡Presented CMRI and echocardiographic data are not obtained from a centralized revision of the original exams but are based on the available reports from each institute.

74–215) days, and none of these patients experienced myocarditis recurrence. None of these patients received a further vaccination after the episode of myocarditis. Five patients (6.7%) had a subsequent SARS-CoV-2 infection without recurrent myocarditis.

In 49 (63.6%) patients, a follow-up CMRI was available (median age, 25 [Q1–Q3, 30–34] years; female sex, 18.4%). There were no significant differences between patients with or without CMRI at follow-up (Table). The follow-up CMRI was performed at a median time of 137 days (Q1–Q3, 93–180) after hospitalization. Compared with the baseline CMRI, there were no changes in the left ventricular (LV) ejection fraction and right ventricular ejection fraction, with a median value of 60% and 57%, respectively. A dilated LV in the follow-up was observed in 5 cases (10.6%), with a median indexed LV end-diastolic volume of 97 (Q1–Q3, 95–112) mL/m^2. The proportion of patients with persistent edema at follow-up based on conventional T2-weighted imaging was 20.4% (n=10), a figure significantly lower compared with the presence of edema at baseline (95.9%; n=47; in 2 patients, the presence of edema was based on T2 mapping imaging). LV segments with edema mainly involved the inferior or the inferolateral walls. Thirty-nine patients (79.6%) had a residual scar based on late gadolinium enhancement (LGE) on the follow-up CMRI, while on baseline CMRI, LGE was present in 100% of cases. Similarly, we observed a significant reduction of LGE-positive segments from a median of 4 (Q1–Q3, 3–7) to 2 (Q1–Q3, 1–4; $P<0.001$) at follow-up. LGE generally spared the anterior wall and the septum (only 3 patients; 6.1% had a residual septal LGE). Finally, pericardial effusion decreased from 16 (32.6%) to 3 (6.1%) patients (Table). No difference was found in the main morphofunctional CMRI parameters at follow-up depending on the type of vaccine administered, that is, BNT162b2 (Pfizer/BioNTech, n=36, 73.5%) or mRNA-1273 (Moderna, n=13, 26.5%). Furthermore, 48 (63.3%) patients had at least 1 echocardiogram after discharge, including 15 (31.2%) without follow-up CMRI, and all had preserved biventricular function without ventricular dilation (Table). When these data were compared with 105 (23.7%) of 443 acute myocarditis patients identified from the Lombardy registry with 2 CMRI scans within 1 year (median age, 32 [Q1–Q3, 23–40] years; women, 19.0%; median interval between the scans of 149 [Q1–Q3, 97–213] days),[3] we observed a similar proportion of patients with LV ejection fraction <55% (n=10, 9.5%; $P=0.55$), residual edema (n=16, 15.2%; $P=0.487$), and LGE (n=96, 91.4%; $P=0.062$) on follow-up CMRI compared with acute myocarditis after the mRNA COVID-19 vaccine.

In conclusion, we observed that in the midterm follow-up, patients who had acute myocarditis after the mRNA COVID-19 vaccine had preserved biventricular function, while 79.6% of patients had a residual scar and 20.4% had persistent edema. These figures are in line with CMRI finding in patients with other forms of myocarditis: after 6 months, edema based on T2-weighted imaging was present in 16% and LGE in 86% of the patients,[4] also in agreement with our data derived from a subanalysis of the Lombardy registry of acute myocarditis. No clinical events were reported in the follow-up, and the few patients with COVID-19 after vaccination did not develop recurrent myocarditis. Longer follow-up is needed, even if published long-term data suggest that patients with preserved biventricular ejection fraction without septal LGE involvement have low rates of adverse clinical events.[5] As a study limitation, we underline that the causal link between COVID-19 vaccination and myocarditis remains uncertain, albeit the short median time (3 days) from vaccination to symptom onset suggests causality.

The observed CMRI findings at baseline and morphofunctional changes over time align with those of classic viral acute myocarditis with a good prognosis.[5] This new information should further reassure patients who experience acute myocarditis after the mRNA COVID-19 vaccination.

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