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Cardiac magnetic resonance imaging of myocarditis and pericarditis following COVID-19 vaccination: a multicenter collection of 27 cases

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Abstract

Objectives To assess clinical and cardiac magnetic resonance (CMR) imaging features of patients with peri-myocarditis following Coronavirus Disease 2019 (COVID-19) vaccination.

Methods We retrospectively collected a case series of 27 patients who underwent CMR in the clinical suspect of heart inflammation following COVID-19 vaccination, from 16 large tertiary centers. Our patient's cohort was relatively young (36.6 ± 16.8 years), predominately included males (n = 25/27) with few comorbidities and covered a catchment area of approximately 8 million vaccinated patients.

Results CMR revealed typical mid-subepicardial non-ischemic late gadolinium enhancement (LGE) in 23 cases and matched positively with CMR T2 criteria of myocarditis. In 7 cases, typical hallmarks of acute pericarditis were present. Short-term follow-up (median = 20 days) from presentation was uneventful for 25/27 patients and unavailable in two cases.

Conclusions While establishing a causal relationship between peri-myocardial inflammation and vaccine administration can be challenging, our clinical experience suggests that CMR should be performed for diagnosis confirmation and to drive clinical decision-making and follow-up.

Key Points

- *Acute onset of dyspnea, palpitations, or acute and persisting chest pain after COVID-19 vaccination should raise the suspicion of possible myocarditis or pericarditis, and patients should seek immediate medical attention and treatment to help recovery and avoid complications.*
- *In case of elevated troponin levels and/or relevant ECG changes, cardiac magnetic resonance should be considered as the best non-invasive diagnostic option to confirm the diagnosis of myocarditis or pericarditis and to drive clinical decision-making and follow-up.*

Keywords Magnetic resonance imaging · COVID-19 · Vaccination · Myocarditis · Pericarditis

Abbreviations

AHA	American Heart Association
CDC	Centers for Disease Control and Prevention
Cine-SSFP	Cine steady-state free precession
CMR	Cardiac magnetic resonance
CMRI	Cardiac magnetic resonance imaging
COVID-19	Coronavirus disease 2019
ECG	Electrocardiogram
ECV_cmr	Myocardial extracellular volume fraction estimated by CMR

Position statement on COVID-19 vaccines: The authors are firm supporters of the COVID-19 vaccination campaign and vaccinated themselves as well.

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EF	Ejection fraction
FU days	Follow-up days from presentation
hs-cTnI	High-sensitivity cardiac troponin I
hs-cTnT	High-sensitivity cardiac troponin T
LGE	Late gadolinium enhancement
LGE segments (AHA)	LGE left ventricular distribution based on the "17 segments cardiac segmentation model" by the American Heart Association
LV	Left ventricular
LVEDVI	Indexed left ventricular end-diastolic volume
LVEDVI_cmr	LVEDVI estimated by CMR
LVEF	Left ventricular ejection fraction
LVEF_cmr	LVEF estimated by CMR
mRNA	Messenger ribonucleic acid
n.v.	Normal values
Pericarditis_cmr	Pericarditis detected by CMR
ROI	Region of interest
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
T2w-STIR	T2-weighted short-tau inversion recovery
VAERS	Vaccine Adverse Event Reporting System

Since the beginning of the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, an unprecedented massive effort has been carried out worldwide to rapidly provide acquired immunity against the development of the coronavirus disease 2019 (COVID-19) [1].

As of December 2021, over 8.2 billion doses of a range of different COVID-19 vaccines have been administered, prioritizing distribution to categories that are at highest risk of complications and/or transmission, such as the elderly and the healthcare workers.

While reported side effects following these vaccines have been mild and short-lasting in the overwhelming majority of cases, some series of rare but more significant complications have been collected in various international registries and databases [2].

Myocardial and/or pericardial inflammation is a rare yet known adverse event that has been described in relation to several vaccines (from influenza to smallpox) and also, in recent reports, following SARS-CoV-2 vaccine administration [3, 4].

In the USA, as of November 10, 2021, the Vaccine Adverse Event Reporting System (VAERS) has received 1793 reports of myocarditis or pericarditis happening after COVID-19 vaccination [2]. Of these, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) did confirm 1049 reports of myocarditis or pericarditis, particularly among male adolescents and young adults aged below 30 after messenger ribonucleic acid (mRNA) COVID-19 vaccination [2].

The underlying pathogenesis is reasonably considered to be multifactorial and likely dependent on the activation of an uncontrolled autoimmune response to the vaccine triggered by molecular mimicry and cross-reaction mechanisms occurring in genetically susceptible individuals [4].

While establishing a causal relationship between myocardial and/or pericardial inflammation and vaccine administration can be challenging, recognition of such a clinical entity can be relevant, not only for epidemiological purposes but also to define the appropriate clinical management and follow-up.

The diagnostic contribution of cardiac magnetic resonance (CMR) to non-invasively depict COVID-19–associated myocarditis and pericarditis has been already extensively described in the acute/active and chronic setting of the disease [5].

We retrospectively collected data from a series of 23 cases observed by 16 large tertiary centers in the period from March to July 2021, representing patients in which CMR was performed between 1 and 25 days after vaccination in the clinical setting of a suspected cardiac involvement. Four patients were scanned between 32 and 82 days after vaccination, due to clinical relapse of a previously documented acute myocarditis.

Diagnosis of acute myocarditis was established according to the updated Lake-Louise criteria [6].

Detailed clinical and imaging features of our patient cohort, composed of a total of 27 patients, are summarized in Table 1.

Briefly, our patient population was relatively young (average age 36.6 ± 16.8 years), mostly included males (n = 25/27) and with few comorbidities; notably, autoimmune disorders were observed in 3/27 cases. In addition to suspected post-vaccine forms of myocardial injury, all recruiting centers were also asked to collect data for all patients who received a CMR diagnosis of acute peri-myocarditis in the same observational period, for comparative purposes. With this regard, our consortium has observed overall 238 cases of myocarditis, including 27 cases in vaccinated patients and 211 in unvaccinated individuals (n = 14 cases with history of COVID-19 disease ; n = 197 unvaccinated without history of COVID-19 disease); a descriptive summary of patients' risk factors and comorbidities among these different groups is displayed in Table 2.

In vaccinated patients, CMR diagnosis of myocarditis and/or pericarditis more commonly followed immunization with mRNA vaccines (n = 24/27), after the second jab (n = 15/27), and within 10 days from administration (n = 22/27; average 8 ± 9 days). Clinical presentations included chest pain (n = 25/27), palpitations (n = 10/27), arthralgias and myalgias (n = 9/27), and dyspnea (n = 7/27). High-sensitivity cardiac troponin T (hs-cTnT) or high-sensitivity cardiac troponin I (hs-cTnI) levels were systematically elevated in 27/27 cases and associated with a variable spectrum of electrocardiogram

Table 1 Summary of clinical and CMRI features of the 27 cases. LVEF_cmr: LVEF estimated by CMR; LVEDVI_cmr: LVEDVI estimated by CMR

Case	No. of doses	Vaccine	Days from injection to presentation	Age	Sex	BMI	Autoimmunities	Fever (> 37.5 °C)	Chest pain	Palpitations	Myalgia	Dyspnea	Troponin (hs-cTnT/ cTnI) level baseline	Troponin lab cutoff value
Case 1	1	Vaxzevria (AstraZeneca)	19	20	M	24.07	0	0	1	0	0	0	593	cTnT < 14 ng/L
Case 2	1	Comirnaty (Pfizer/BioNTech)	1	43	M	25.95	0	0	1	1	1	0	706	cTnT < 14 ng/L
Case 3	1	Comirnaty (Pfizer/BioNTech)	8	41	F	31.22	1	0	1	1	0	1	676	cTnT < 14 ng/L
Case 4	2	Comirnaty (Pfizer/BioNTech)	3	44	M	28.4	0	0	1	0	1	1	7400	cTnT < 34.2 ng/L
Case 5	2	Comirnaty (Pfizer/BioNTech)	4	26	M	23.7	0	1	1	1	0	0	2500	cTnT < 57 ng/L
Case 6	2	Comirnaty (Pfizer/BioNTech)	9	41	M	27.6	0	1	1	1	0	0	5533	cTnT < 57 ng/L
Case 7	2	Spikevax (Moderna)	6	27	M	22.5	0	1	1	0	1	0	119	cTnT < 14 ng/L
Case 8	1	Spikevax (Moderna)	1	57	M	23.63	0	1	1	0	0	0	715	cTnT < 14 ng/L
Case 9	1	Comirnaty (Pfizer/BioNTech)	2	12	M	17.2	0	0	1	0	0	0	695	cTnT < 14 ng/L
Case 10	1	Comirnaty (Pfizer/BioNTech)	6	20	M	20.43	0	0	1	0	0	0	1406	cTnT < 14 ng/L
Case 11	2	Comirnaty (Pfizer/BioNTech)	14	18	M	22.09	0	1	1	0	0	0	427	cTnT < 14 ng/L
Case 12	1	Comirnaty (Pfizer/BioNTech)	3	33	M	28.3	0	1	1	0	0	0	27	cTnT < 19,8 ng/L
Case 13	2	Vaxzevria (AstraZeneca)	7	26	M	41.5	0	0	1	0	0	0	2500	cTnT < 14 ng/L
Case 14	2	Vaxzevria (AstraZeneca)	6	21	M	32	0	1	1	1	0	1	657	cTnT < 14 ng/L
Case 15	1	Spikevax (Moderna)	2	49	M	24.62	1	0	1	0	0	0	524	cTnT < 14 ng/L
Case 16	2	Comirnaty (Pfizer/BioNTech)	3	57	M	25.6	0	0	1	0	0	1	218	cTnT < 14 ng/L
Case 17	2	Comirnaty (Pfizer/BioNTech)	7	26	M	27.4	0	0	1	1	0	0	382	cTnT < 14 ng/L

Table 1 (continued)

Case 18	2	Comirnaty (Pfizer/BioNTech)	5	55	M	33.8	0	1	1	1	1	1	1790	cTnT < 14 ng/L
Case 19	2	Spikevax (Moderna)	4	29	M	28.1	0	1	1	0	1	0	516	cTnT < 14 ng/L
Case 20	2	Comirnaty (Pfizer/BioNTech)	3	51	M	26.22	0	1	1	0	0	0	270	cTnT < 14 ng/L
Case 21	2	Comirnaty (Pfizer/BioNTech)	2	31	M	23.67	0	1	1	0	0	0	378	cTnT < 14 ng/L
Case 22	1	Comirnaty (Pfizer/BioNTech)	10	32	M	21.39	0	1	1	1	1	0	639	cTnT < 14 ng/L
Case 23	1	Comirnaty (Pfizer/BioNTech)	23	19	M	24.62	0	1	1	1	1	0	587	cTnT < 14 ng/L
Case 24	1	Spikevax (Moderna)	4	20	M	20.76	0	0	1	0	0	1	1494	cTnT < 14 ng/L
Case 25	1	Comirnaty (Pfizer/BioNTech)	4	44	M	24	0	1	0	0	0	0	216	cTnT < 34.2 ng/L
Case 26	2	Spikevax (Moderna)	46	66	F	26	0	1	1	1	1	0	4209	cTnT < 14 ng/L
Case 27	2	Comirnaty (Pfizer/BioNTech)	20	80	M	26.4	1	1	0	0	1	1	562	cTnT < 14 ng/L
Mean			8.222222222	36.5926		25.96926	0.111111111	0.592592593	0.92592593	0.37037037	0.33333333	0.25925926		
Standard deviation			9.540735874	16.8163		4.792807	0.320256308	0.500711744	0.26688026	0.492102878	0.48038446	0.44657608		

Case	Elevated troponins	ECG baseline anomalies	CMR date	LVEF_cmr	LVEDVI_cmr	LGE	LGE segments (AHA)	LGE pattern	T1 mapping global	ECV_cmr	T2 mapping global	Pericarditis_cmr	FU days	At FU
Case 1	1	1	27/06/2021	47	89	1	11, 12, 16	Mid-epicardial	1026	26	48	0	44	0
Case 2	11	1	17/06/2021	50	73	1	5, 6, 11, 12, 13, 14, 15, 16	Mid-epicardial	1201	42	65	0	49	0
Case 3	1	1	21/05/2021	62	54	1	2, 3, 8, 9, 10	Mid-epicardial	Not performed	Not performed	Not performed	1	13	0
Case 4	1	1	25/07/2021	69	67	1	4, 5, 10, 15	Mid-epicardial	1280 (3T)	27 (3T)	56 (3T)	1	4	0
Case 5	1	1	18/03/2021	70	90	1	4, 5, 6, 10, 11, 12, 15	Mid-epicardial	Not performed	Not performed	Not performed	0	82	0
Case 6	1	1	05/08/2021	57	121 (dilated)	1	4, 5, 10, 11, 16	Mid-epicardial	1075	33	53	1	6	0
Case 7	1	0	15/06/2021	60	94	1	1, 4	Mid-epicardial	Not performed	Not performed	Not performed	0	4	0
Case 8	1	0	17/06/2021	70	76	1	6, 5, 11, 12	Mid-wall	Not performed	Not performed	Not performed	0	35	0

Table 1 (continued)

Case 9	1	1	14/07/2021	80	95	0		Pericardial	980	25	51	1	2	0
Case 10	1	0	07/07/2021	58	93.4	1	6	Mid-epicardial	Not performed	Not performed	Not performed	0	25	0
Case 11	1	1	18/06/2021	62	63	1	7	Mid-epicardial	1076	29	54	0	43	0
Case 12	1	1	01/04/2021	54	84	1	3, 4, 13, 16	Mid-epicardial	1110	Not performed	58	0	30	0
Case 13	1	0	16/06/2021	56	89.7	1	2, 3, 4, 5, 8, 9, 10, 11	Epicardial	1157	35	47	0	Unknown	Unknown
Case 14	1	1	23/06/2021	58	83	1	4, 5, 6, 11, 12	Epicardial	961	28	46	0	Unknown	Unknown
Case 15	1	1	18/05/2021	65	50	0			1045	Not performed	61	0	70	0
Case 16	1	1	21/06/2021	59	95.2	0			1037	25.32	50	1	26	0
Case 17	1	1	30/06/2021	61	81.3	0			987	24.28	48	1	9	0
Case 18	1	1	07/07/2021	64	60.9	1	10, 11, 15, 16	Mid-epicardial	1043	25.61	48	0	14	0
Case 19	1	1	23/07/2021	52	76.8	1	4, 5, 10, 11, 12, 15, 16, 17	Mid-epicardial	1021	31.13	55	0	25	0
Case 20	1	1	10/07/2021	61	67	1	5	Mid-epicardial	1022	Not performed	43	0	20	0
Case 21	1	1	25/05/2021	75	79	1	3	Mid-epicardial	1030	Not performed	38	0	62	0
Case 22	1	1	14/07/2021	61	75	1	8	Mid-epicardial	1075	Not performed	59	0	15	0
Case 23	1	0	19/07/2021	49	88	1	5	Mid-epicardial	1010	Not performed	54	0	13	0
Case 24	1	1	14/07/2021	62	86	1	10, 11, 15, 16	Mid-epicardial	Not performed	Not performed	Not performed	0	18	0
Case 25	1	1	14/07/2021	59	89.8	1	4.5	Mid-wall	1020	27	52	1	6	0
Case 26	1	1	28/07/2021	51	73	1	4, 5, 10, 11	Mid-epicardial	1175	38	62	0	14	0
Case 27	1	0	15/06/2021	62	111 (dilated)	1	3	Mid-wall	1060	31	55	0	76	0
Mean	1	0.777777778		60.5185185	78.924	0.851852			1055.55	30.02428571	52.35	0.259259259	Median = 20	0
Standard deviation	0	0.423659273		7.75772751	12.93980551	0.362014			63.66811563	5.357679914	6.690724137	0.446576085	Range = 2-82	0

1 = true ; 0 = false

Table 2 Descriptive table reporting prevalence of cardiovascular risk factors and main comorbidities among consecutive patients with a CMR diagnosis of myocarditis and/or pericarditis, observed in the period March–July 2021. Our cohort is categorized into 3 groups: vaccinated: n = 27 vaccinated patients, COVID-19+ (unvaccinated): n = 14 unvaccinated patients with diagnosis of acute or healed COVID-19 disease (based on clinical presentation and PCR confirmation), and COVID-19− (unvaccinated): n = 197 patients, unvaccinated and without history of COVID-19 disease. Definitions of listed risk factors and comorbidities: hypertension = systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg or current medical treatment for hypertension; diabetes = fasting glucose > 126 mg/dL or current treatment; smoking = current smoker or ex-smoker with suspension less than 5 years before observation; hyperlipidemia = LDL > 130 mg/dL or current treatment; moderate/high physical activity = at least 150 min per week of moderate-intensity aerobic activity or 75 min per week of vigorous aerobic activity, or a combination of both; autoimmunities = history of autoimmune diseases

	Age years, (mean)	Gender (%male)	BMI (kg/m^2) (mean)	Hypertension (%)	Diabetes (%)	Smoking (%)	Moderate/high physical activity (%)	Hyperlipidemia (%)	Autoimmunities (%)
Vaccinated	36.6	92.6	25.9	22.8	6.2	20.4	35.7	22.6	11.1
COVID-19+ (unvaccinated)	46.2	84.8	26.2	25.5	13	29.7	22.4	44.8	9.8
COVID-19− (unvaccinated)	38.2	82.5	24.3	20	10.1	26.5	33.8	29.1	7.2

(ECG) abnormalities including ST–segment elevation and T-wave inversion (n = 21/27).

CMR revealed typical mid-subepicardial non-ischemic late gadolinium enhancement (LGE) in 23 cases and matched positively with CMR T2 criteria of myocarditis (Fig. 1). In 7 cases, CMR showed typical hallmarks of acute pericarditis (effusion with thickening and/or enhancement of pericardial layers).

Left ventricular (LV) systolic function was mildly reduced in 3/27 cases and normal in the remaining population (average ejection fraction: 60.5 ± 7.7%); indexed LV end-diastolic volume (LVEDVI) was normal in all cases (79 ± 13 mL/m^2), except for an 80-year-old male and a 41-year-old male presenting with a mildly dilated LV cavity (111 and 121 mL/m^2, respectively).

Short-term follow-up from presentation was uneventful for 25/27 patients (median = 20 days; range = 2–82 days) and unavailable in two cases.

We collected a case series from the joint efforts of 16 tertiary referral centers, roughly covering a catchment area of approximately 8 million patients vaccinated with at least one dose in the period from March to July. We could therefore estimate an incidence of approximately 3.4 observed cases of myocarditis per million administered doses. Our incidence is significantly lower as compared to most international registries, in which a range of 8.3–34 cases per million was reported (see Fig. 2) [2, 7–9].

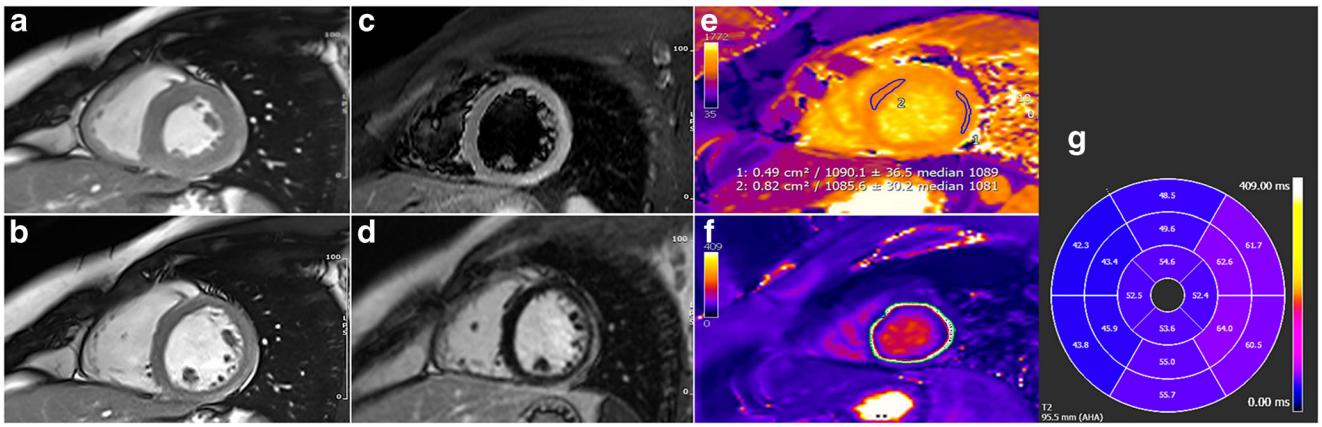

Fig. 1 Acute myocarditis 4 days after Spikevax (Moderna) vaccine administration in a 29-year-old patient (images refer to patient n. 19 from Table 1) presenting with infarct-like symptoms of acute chest pain, with ECG ST-elevation changes and troponin rise. End-systolic and end-diastolic cine-SSFP frames (**a** and **b**) show a non-dilated and functionally preserved left ventricular cavity (EF 61%; LVEDVI: 76.8 mL/m^2). Typical CMR hallmarks of an acute myocarditis can be observed in "edema-weighted" T2w-STIR short axis plane (**c**), consisting of the presence of a non-ischemic epicardial stria of high signal intensity involving the anterior- and infero-lateral mid-basal wall (arrows) and closely matching with LGE findings (**d**) (mid-ventricular level shown). Acute inflammation was also confirmed at myocardial mapping images showing focally increased native T1 mapping (1090 ms of a ROI on the middle-apical lateral wall; n.v. 950–1000 ms; **e**) and T2 mapping values (avg. 55 ms; n.v. < 50 ms; **f**) (AHA segments T2 mapping values shown in **g**). The patient's clinical course was benign and uneventful at 25 days follow-up

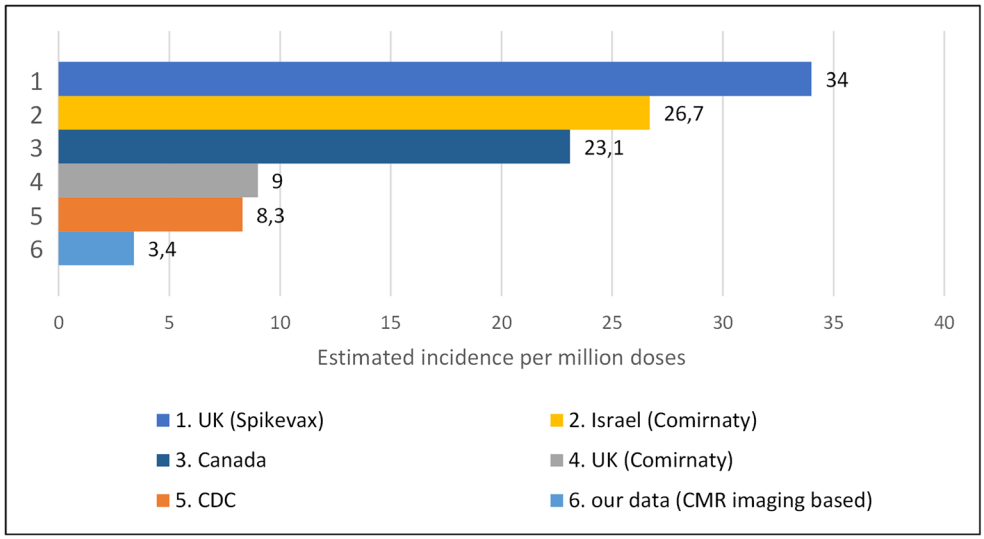

Fig. 2 Estimated incidences of myocarditis after COVID-19 vaccine administration derived from our data and as reported in the following government registries or studies: UK (Spikevax) = reported incidence of myocarditis (34 per million doses) after Spikevax (Moderna) vaccine administration in the UK (government report) [7]; Israel (Comirnaty) = reported incidence of myocarditis (26.7 per million doses) after Comirnaty (Pfizer-BioNTech) vaccine administration in Israel (observational retrospective study based on Ministry of Health database) [8]; Canada = reported incidence of myocarditis (23.1 per million doses) after COVID-19 vaccine administration in Canada (government report) [9]; UK (Comirnaty) = reported incidence of myocarditis (9 per million doses) after Comirnaty (Pfizer-BioNTech) vaccine administration in the UK (government report) [7]; CDC = reported incidence of myocarditis (8.3 per million doses) after COVID-19 vaccines administration in the USA (CDC report) [2]; current research = estimated incidence (3.4 per million doses) from CMR data reported in the present study

This reflects an intrinsic selection difference of our study, in which diagnosis was established with a non-invasive gold standard technique as CMR instead of using clinical diagnostic criteria, like in the Vaccine Adverse Event Reporting System (VAERS), for the CDC, which is a passive reporting system that relies on individuals to send in reports of their experiences [2].

Our findings need to be cautiously contextualized and commented on, because of their potential implications on the perception of vaccine safety by the general population.

A clear causative relationship cannot be established as we only referred to a post-vaccination temporal criterion; moreover, the background prevalence of myocarditis remains uncertain but is likely to be ~ 22 per 100,000 [10]. Finally, myocarditis and pericarditis are also both recognised complications of SARS-CoV-2 and it is entirely plausible that there are overlapping mechanisms involved in both natural infection and vaccine-mediated autoimmunity [11].

Even though we discussed about suspected cardiac side effects of the vaccine, the benefits of the immunization in preventing severe morbidity and mortality from SARS-CoV-2 infection still outweigh the risks of complications after vaccine administration [12].

Further work is required to establish whether there are any adverse sequelae associated with the cases of acute myocarditis observed in this case series; however, the largely preserved LV function and pattern of late enhancement may portend a good prognosis, although the presence of LGE highlights the need for careful surveillance.

Acute onset of dyspnea, palpitations, or acute and persisting chest pain after vaccination should raise the suspicion of possible myocarditis or pericarditis, and patients should seek immediate medical attention and treatment to help recovery and avoid complications. In case of elevated troponin levels and/or relevant ECG changes, CMR should be considered as the best non-invasive diagnostic option to confirm the diagnosis and to drive clinical decision-making and follow-up.

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Declarations

Guarantor The scientific guarantor of this publication is Prof. Marco Francone, MD, PhD.

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Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and Biometry No complex statistical methods were necessary for this paper.

Informed Consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical Approval Ethical approval was obtained from IRB on 25th May 2021, number 2551.

Methodology

- retrospective
- observational
- multicenter study

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