Cardiac MRI Findings in COVID-19 Vaccine-Related Myocarditis: A Pooled Analysis of 468 Patients

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Understanding the pattern and severity of myocarditis caused by the coronavirus disease 2019 (COVID-19) vaccine is imperative for improving the care of the patients, and cardiac evaluation by MRI plays a key role in this regard. Our systematic review and meta-analysis aimed to summarize cardiac MRI findings in COVID-19 vaccine-related myocarditis. We performed a comprehensive systematic review of literature in PubMed, Scopus, and Google Scholar databases using key terms covering COVID-19 vaccine, myocarditis, and cardiac MRI. Individual-level patient data (IPD) and aggregatedlevel data (AD) studies were pooled through a two-stage analysis method. For this purpose, all IPD were first gathered into a single data set and reduced to AD, and then this AD (from IPD studies) was pooled with existing AD (from the AD studies) using fixed/random effect models. l^2 was used to assess the degree of heterogeneity, and the prespecified level of statistical significance (P value for heterogeneity) was <0.1. Based on meta-analysis of 102 studies (n = 468 patients), 79% (95% confidence interval [CI]: 54%-97%) of patients fulfilled Lake Louise criteria (LLC) for diagnosis of myocarditis. Cardiac MRI abnormalities included elevated T2 in 72% (95% CI: 50%-90%), myocardial late gadolinium enhancement (LGE) in 93% (95% CI: 83%-99%; nearly all with a subepicardial and/or midwall pattern), impaired left ventricular ejection fraction (LVEF) (<50%) in 4% (95% CI: 1.0%–9.0%). Moreover, elevated T1 and extracellular volume fraction (ECV) (>30), reported only by some IPD studies, were detected in 74.5% (76/102) and 32% (16/50) of patients, respectively. In conclusion, our findings may suggest that over two-thirds of patients with clinically suspected myocarditis following COVID-19 vaccination meet the LLC. COVID-19 vaccine-associated myocarditis may show a similar pattern compared to other acute myocarditis entities. Notably, preserved LVEF is probably a common finding in these patients. **Evidence Level:** 4

Technical Efficacy: Stage 3

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be a global health challenge.¹ To end the ongoing pandemic, a growing number of countries adopted the mass vaccination program using newly approved vaccines against the virus; as of February 7, 2022, about half of the population around the world has been fully vaccinated.² Despite the undeniable efficacy of vaccines for decreasing the burden of disease in areas with high vaccination rates, some side effects, mainly related to the activation of local and/or systemic inflammation, have been identified for them.³

Several cases of clinically suspected myocarditis have been reported worldwide shortly after COVID-19 vaccination, mainly for messenger ribonucleic acid (mRNA)-based vaccines.⁴ Timely diagnosis and management are crucial for improving the prognosis of this complication.⁵ An increasing number of studies have utilized cardiac MRI, as the most important noninvasive diagnostic tool, to assess suspected myocarditis associated with COVID-19 vaccination.^{5–105}

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One narrative review article attempted to address the pattern of myocardial injury following COVID-19 vaccination based on cardiac MRI findings from 11 case series.⁴ Since the last review, a large number of case reports/series have been published. Hence, we conducted the present comprehensive systematic review and meta-analysis study to include all available case reports and case series evaluating cardiac MRI findings in patients with clinically suspected myocarditis following COVID-19 vaccination.

Materials and Methods

Our study was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As a systematic review and meta-analysis of published studies, it required no ethical approval. We included all eligible studies that reported cardiac MRI findings in patients with COVID-19 vaccineassociated myocarditis.

Search

A comprehensive search was performed on three databases, including PubMed, Scopus, and Google Scholar, on January 21, 2022 and updated on April 27, 2022, using a combination of the key terms in three domains: 1) COVID-19 vaccine, 2) myocarditis, and 3) cardiac MRI. Detailed search strings for each database are presented in the Supplementary Table S1.

In addition, reference lists of the included articles and systematic reviews on similar topics were manually checked to identify any additional eligible studies. Citations from all retrieved articles were imported into EndNote X9 software (version EndNote X9.3.2, Captivate Analytics, California USA), and the duplicates were removed.

Study Inclusion

Two researchers (P.S. and E.J.A.), both with 2 years of experience in medicine independently screened the titles, abstracts, and full texts of retrieved studies to identify the eligible items. Any disagreement resolved by a third researcher (N.S.H., 13 years of experience in medicine or H.R., 11 years of experience in research) based on the topic.

Eligibility Criteria

We included all studies that met all our inclusion criteria as follows:

- Inclusion of patients with clinically suspected myocarditis following COVID-19 vaccination.
- 2. Cardiac evaluation by MRI.
- 3. Observational study design: cohort studies, case series, and case reports.
- 4. Written in English.

Data Extraction

Three out of four mentioned researchers (H.R., P.S., and E.J.A.) extracted the data from the full texts of the included studies into the "Data Extraction Form" produced using Microsoft Excel (*version 2016*, Microsoft Corp., Redmond, WA, *USA*). Extracted data were: first author's name, country, study design, sample size, age, sex, study population, time from vaccine to symptoms, time from

symptoms to MRI, symptoms type, elevated troponin, electrocardiogram (ECG) changes, echocardiography findings, and main cardiac MRI findings including myocardial and pericardial late gadolinium enhancement (LGE), T1, T2, extracellular volume (ECV), left ventricle (LV) ejection fraction (EF), pericardial effusion (PE), and wall motion abnormality (WMA).

Quality Assessment

Two trained researchers mentioned above (P.S. and E.J.A.) independently assessed the quality of the articles by the Joanna Briggs Institute (JBI) appraisal tool adapted for use in case series.²⁰ Furthermore, any disagreement was resolved through discussion with a third researcher (H.R. or N.S.H.). JBI's critical appraisal tool contained 10 items, and its total score ranged from 0 to 10.²⁰

Statistical Analyses

Data sets were classified as individual-level patient data (IPD) and aggregate-level data (AD). We collected available IPD from each case report/series of patients with clinically suspected myocarditis following the COVID-19 vaccine who underwent cardiac MRI. Characteristics of these patients were reported in terms of demographic/ clinical data, laboratory results including serum troponin, ECG findings, and imaging findings from echocardiography and cardiac MRI. We calculated percentages for categorical variables based on valid denominators (i.e. the number of patients with data for the characteristic of interest). Continuous data were summarized using median (interquartile range [IQR]) or mean and standard deviation (SD).

Then, summarized cardiac MRI findings from IPD were combined with findings from AD studies using both fixed and randomeffect models, which are standard AD meta-analysis methods. Based on the size of the observed heterogeneity, the values were derived either from the random or fixed-effect model. The chi-square test and I^2 statistic were used to measure the heterogeneity among the studies; if $I^2 > 75\%$ and the *P* value for heterogeneity < 0.1, it was considered that there was significant heterogeneity. Data were processed in SPSS (version 20; IBM Corp., Armonk, NY, USA) and analyzed using RStudio (version 1.4.1103, PBC, Boston, MA, USA).

Results

Our systematic literature search revealed 2543 citations through the initial search databases. After excluding duplications, 1997 publications remained for the title and abstract screening. Overall, 266 publications were retrieved for review of full-text articles. Finally, 102 publications, including 56 case reports^{12–50,52–58,92–94,97,98,101,102,105,106} and 46 case series^{5,7,10,23,35,45,51,59–91,95,96,100,103,104,107} fulfilled the inclusion criteria. Figure 1 shows the selection process in detail.

A total of 468 patients with suspected myocarditis and cardiac MRI findings were included in this study (n = 294 from case reports/case series with IPD^{5,7,9,11–66,68,70–73,75–87,89,91–95,97–107} and n = 174 from five case series^{67,69,74,88,90} with AD). Based on data provided by 100 out of 102 studies, all included patients met CDC criteria for suspected



FIGURE 1: PRISMA flowchart of literature search and selection process

myocarditis. Supplementary Table 2 shows the quality of the included case series; all studies scored eight or higher.

Characteristic and Cardiac MRI Findings of Patients in IPD Studies

Detailed characteristics and cardiac MRI findings of each included IPD study are presented in Supplementary Tables S3 and S4, respectively. Table 1 summarizes baseline characteristics and cardiac MRI findings in 294 patients. Overall, 89.8% (264/294) of the included patients were male with a mean age of 27.3 years ([SD]: 14.1 years). The 95.2% (280/294) of evaluated cases with suspected myocarditis had a recent history of an mRNA-based vaccination, mainly the second dose (78.2%).

Survival status was reported for 263 patients; death occurred in none of them and all were discharged in favorable clinical conditions. Overall, 95.4% (254/266) of patients presented with chest pain and 21.8% (58/266) with dyspnea. The median (IQR) time from vaccine to symptoms was 3.0 days (2.0–4.0 days). ECG data were available in 259 cases, and 221 (85.3%) of them had abnormal findings, mainly ST-segment elevations (75.7% [150/198]). An elevated troponin level was found in 276 of 278 evaluated cases. Echocardiography showed LVEF < 50% in 24.8% (34/137) of patients, PE in 7.3% (7/95), and WMA in 43.3% (49/113).

The median time from vaccine to MRI was 6.0 days (IQR: 5.0–8.8 days). On cardiac MRI, diagnosis of myocarditis was established in 99 (86.6%) of 114 patients using revised/old Lake Louise criteria (LLC). Myocardial LGE was detected in 94.0% (268/285) of patients, predominantly with a subepicardial and/or mid-wall pattern (99.0% [206/208]) and localized in the basal or mid inferolateral segment of the LV (61.4% [124/202]). Mean (SD) T2, reported in 69 patients, was 55.9 ms (9.5 msec). Abnormal T2, detected by quantitative or qualitative methods, was found in 81.9% (131/160). Mean (SD) T1 was 1083.91 msec (94.3 msec) (n = 73), and abnormal T1 was observed in 74.5% (76/102). Mean (SD) ECV was 29.61 (6.4), and in 32% (16/50) it was greater than 30%.

On cardiac MRI, regarding pericardial involvement, effusion was observed in 27.2% (40/147) of patients and enhancement in 32.8% (39/119). The mean (SD) LVEF was 56.7% (7.57%), and 16 out of 174 (9.2%) patients had an impaired LVEF (<50%). Overall, WMA was found in 29 out of 93 assessed patients (31.2%).

Characteristic and Cardiac MRI Findings of AD Studies

Six case series reported aggregated characteristic and cardiac MRI findings of 174 patients with suspected myocarditis following mRNA-based COVID-19 vaccines (Table 2). Sample sizes varied from 3 to 97 patients. Overall, patients were teenagers and young adults who presented with elevated troponin and chest pain. The reported mean/median time from symptoms to cardiac MRI was less than 7 days.

In summary, cardiac MRI findings in AD studies were as follows: myocarditis based on LLC in 65% (112/171), abnormal T2 in 66.6% (116/174), and LGE in 82.2%(143/174) of patients. The pattern of LGE was reported only

TABLE 1. Characteristics and Cardiac MRI Findings of Patients in Studies With Individual-Level Patient Data								
Characteristics		Data Availability (n)	Findings					
Age (years), mean (SD)		274	27.3 (14.1)					
Male, <i>n</i> (%)		294	264 (89.8%)					
Survived, n (%)		263	263 (100%)					
Vaccine type, n (%)	Pfizer (BNT162b2)	294	213 (72.4%)					
	Moderna (mRNA-1273)		67 (22.8%)					
	Janssen (ad26.COV2.S)		4 (1.4%)					
	AstraZeneca (chAdOx1-SARS-COV-2)		9 (3.1%)					
	Covaxin (BBV152)		1 (0.3%)					
Vaccine dose, n (%)	First dose	293	54 (18.4%)					
	Second dose		230 (78.2%)					
	Third dose		9 (3.1%)					
Time from vaccine to symp	ptoms (day), median (IQR)	282	3 (2.0 to 4.0)					
Symptom type, n (%)	Chest pain	266	254 (95.4%)					
	Dyspnea		58 (21.8%)					
Abnormal ECG		259	221 (85.3%)					
ST segment elevation		198	150 (75.7%)					
Diffuse PR depression			32 (16.1%)					
Nonspecific ST-T chang	ges		41 (20.7%)					
Elevated troponin, n (%)		278	276 (99.3%)					
Echocardiography findings								
LVEF (%), mean (SD)		137	53.70 (9.4)					
LVEF < 50%, n (%)		137	34 (24.8%)					
LVEF < 55%, n (%)		203	63 (31%)					
Pericardial effusion, n (%	%)	95	7 (7.3%)					
Wall motion abnormalit	y, n (%)	113	49 (43.3%)					
Cardiac MRI findings								
Time from vaccine to M	IRI (day), Median (IQR)	68	6.0 (5 to 8.8)					
Lake louise criteria, n (%	6)	114	99 (86.8%)					
Native T1 (msec), Mear	n (SD)	73	1083.91 (94.3)					
Elevated T1, n (%)		102	76 (74.5%)					
Native T2 (msec), Mear	n (SD)	69	55.9 (9.5)					
Elevated Native T2, n (9	%)	102	62 (60.8%)					
T2 weighted or T2 STII	R or T2 mapping abnormality, n (%)	160	131 (81.9%)					
Myocardial LGE, n (%)								
Positive LGE		285	268 (94%)					
LGE Pattern								

Characteristics	Data Availability (n)	Findings
Subepicardial + & Mid wall -, n (%)	208	137 (65.9%)
Subepicardial – & Mid wall +, <i>n</i> (%)		23 (11.1%)
Subepicardial + & Mid wall +, <i>n</i> (%)		46 (22.1%)
Subepicardial + Mid wall +, n (%)		206 (99.0%)
Subepicardial – & Mid wall –, <i>n</i> (%)		2 (0.9%)
Subepicardial/Mixed LGE	208	183 (88.0)
Mid wall/Mixed LGE	208	69 (33.2%)
Nonischemic pattern of myocarditis, <i>n</i> (%)	214	214 (100%)
Involved segment, n (%)		
Basal or mid inferolateral, n (%)	202	124 (61.4%)
Other segments, n (%)	202	78 (38.6%)
ECV (%), Mean (SD)	50	29.61 (6.04)
ECV > 30%, n (%)		16 (32%)
LVEF (%), Mean (SD)	155	56.7 (7.57)
LVEF <55%, n (%)	177	58 (32.8%)
LVEF <50%, n (%)	174	16 (9.2%)
Wall motion abnormality, <i>n</i> (%)	93	29 (31.2%)
Pericardial enhancement, n (%)	119	39 (32.8%)
Pericardial effusion, n (%)	147	40 (27.2%)

TABLE 1. Continued

ECV = extracellular volume; ECG = electrocardiography; IQR = interquartile range; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; mRNA = messenger ribonucleic acid; <math>N = number; SD = standard deviation; STIR = short-tau inversion recovery.

in four studies with 21 patients and it was subepicardial and/or mid-wall in all of them.

Pooled Analyses of Individual and Aggregated-Level Cardiac MRI Data

Data heterogeneity, described by I^2 , was high in all parameters, except for LVEF. Hence, we reported results of the random effects model for these variables (Fig. 2). In our pooled analyses, 79% (95% confidence interval [CI]: 54%–97%; I^2 : 91%) of patients with suspected clinical myocarditis met the LLC. Elevated T2 measured by a qualitative or quantitative method was found in 72% (95% CI: 50%–90%; I^2 : 89%) and elevated quantitative native T2 in 69% of cases (95% CI: 37%–95%; I^2 : 89%). Myocardial LGE was detected in 93% (95% CI: 83%–99%; I^2 : 73%) of patients (subepicardial/mid-wall pattern: 206/208 [99.0%]). In addition, LVEF less than 55% and 50% was observed in 28% (95% CI: 22%–35%; I^2 : 38%, P value = 0.20) and 4% (95% CI: 1%–9%; I^2 : 0.0%, P value = 0.85) of patients, respectively. Pooled mean LVEF was 58.35% (95% CI: 56.57–60.14%; I^2 : 83.0%) (Fig. 2 and Supplementary Fig. S1).

Discussion

Based on our systematic review and meta-analysis approach, cardiac MRI diagnosis of myocarditis was established in three-quarters of patients presenting with suspected clinical myocarditis following the COVID-19 vaccine according to the LLC. Elevated T2, assessed by a qualitative or quantitative method, was detected in 72% of patients (50%–90%). Also, 93% (83%–99%) had myocardial LGE, predominantly located in the basal inferolateral wall with a subepicardial and/or mid-wall pattern. Most patients (96%) had a preserved LVEF (LVEF > 50%). In addition, elevated T1 and ECV > 30% were found in 74.5% (76/91102) and 32% (16/50) of patients, respectively. Less than one-third of patients had WMA.

8	E 2. Study Character	ristics and	Cardiac MRI	Findings in Ca	se Series Wi	th Aggregated	-Level Data			
	Author N	Male/ Female	Age (Years)	Type of Vaccine	First/ SeconD dose	Time From Vaccine to Symptom (Days)	Cardiac Symptoms and Biomarkers and ECG	Echocardiography Findings	Time From Vaccine to MRI (Day)	Cardiac MRI Findings
	Jain et al 56 (2021)	NR	12–20	mRNA (NR)	0/56	0-7	Chest pain: 56/56 Elevated troponin: 56/56	NR	4.9 (2.3) ^a	Abnormal T2: 50/56 (89%) LGE: 49/56 (88%) Inferolateral or lateral: 49/49 ECV: 32.6 (9) ^a LLC: 49/56 (88%) LVEF: 58 (6) ^a Abnormal LVEF: 13/56 (23%) Others: NR
	Montogomery 8 et al (2021)	8/0	NR	mRNA (NR)	NR	<4 days	Elevated troponin: 8/8 Chest pain: 8/8 ECG: NR	NR	NR	Abnormal T2: 8/8 (100%) LGE: 8/8 (100%) Subepicardial: 8/8 (100%) LLC: 8/8 (100%) Others: NR
	Troung et al 97 (2021)	NR	Adolescents and young adults	mRNA (Pfizer)	NR	NR	Elevated troponin: 8/8	NR	5 (3–17) ^b	Abnormal T2: 54/97 (55.4%) LGE: 74/97 (76.3%) LLLC: 49/97 (50.5%) LVEF: 60% (55%– 62.7%) ^b Others: NR

TAB	E 2. Continue	þ									
A	Author	N	Male/ Female	Age (Years)	Type of Vaccine	First/ SeconD dose	Time From Vaccine to Symptom (Days)	Cardiac Symptoms and Biomarkers and ECG	Echocardiography Findings	Time From Vaccine to MRI (Day)	Cardiac MRI Findings
4	Viskin et al (2021)	М	6/1	20-34	mRNA (Pfizer)	0/7	3-7	Chest pain: 7/7 Elevated troponin: 7/7 Abnormal ECG: 4/7 Hospitalized: 7/7	LVEF < 55%: 2/7	NR	Abnormal T2: 1/7 (14%) LGE: 6/7 (86%) Subepicardial: 1/6 (17%) Subepicardial and midwall: 5/6 (83%) LLC: 6/7 (86%) Others: NR
Ś	Pfajfer et al (2021)	ŝ	3/0	17 [17] ^a	mRNA (Pfizer)	2/1	1-10	Chest pain: 3/3 Elevated troponin: 3/3 Abnormal ECG: 1/3 ST-Elevation: 0/3 Hospitalized: 3/3	LVEF < 55%: 0/3 WMA: 0/3 Pericardial Effusion: 0/3	5-10	Abnormal T2: 0/3 LGE: 3/3 Subepicardial: 2/3 Midwall: 1/3 LLC: 0/3 Precardial Effusion: 1/3 Abnormal LVEF: 0/3 Others: NR
9	Lyengar et al (2022)	$\tilde{\mathbf{w}}$	NR	27	NR	0/3	ŝ	Chest pain: 3/3 Elevated troponin: 3/3 Abnormal ECG: 2/3 ST-Elevation: 2/3 Hospitalized: 3/3	LVEF < 55%: 2/3	с С	Abnormal T2: 3/3 (100%) LGE: 3/3 (100%) Subepicardial: 2/3 (66%) Subepicardial and Midwall: (33%) LLC:NR Others: NR
ECV ribon ^a Mea. ^b Med	= extracellular v ucleic acid; NR = 1 (standard devia ian (inter quarrik	olume; E = not rep .tion). e range).	CG = elect orted; WM	rocardiography A = wall motic	; LGE = late gad on abnormality.	olinium enha	ncement; LLC =	Lake Louise criteria;	LVEF = left ventricula	r ejection fractio	n; mRNA = messenger

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			Weight	Weight					
Study	Events	Total	(common)	(random)	IV, Fixed + Random, 95% CI	IV, Fiz	xed + Ra	ndom,	95% CI
Lyengar et al. 2022	3	3	1.2%	10.5%	1.00 [0.29; 1.00]				+
Montogomery et al. 2021	8	8	3.0%	15.3%	1.00 [0.63; 1.00]			_	
Troung et al. 2021	49	97	34.3%	21.4%	0.51 [0.40; 0.61]			· · · · ·	-
Pfajfer et al. 2021	0	3	1.2%	10.5%	0.00 [0.00; 0.71]	+			
Jain et al. 2021	49	56	19.9%	20.8%	0.88 [0.76; 0.95]				- -
Aggregated Individual Patient Data	99	114	40.3%	21.5%	0.87 [0.79; 0.92]				+
Total (fixed effect, 95% CI)		281	100.0%		0.79 [0.73; 0.84]				+
Total (random effects, 95% CI)				100.0%	0.79 [0.54; 0.97]				-
Heterogeneity: Tau ² = 0.0645; Chi ² =	54.76, df	= 5 (P <	< 0.01); I ² = 91	1%			1	1	1
						0 0.2	0.4	0.6	0.8

Meeting the Lake Louise Criteria (%)

			Weight	Weight	
Study	Events	Total	(common)	(random)	IV, Fixed + Random, 95% CI
Montogomery et al	8	8	1.8%	9.5%	1.00 [0.63; 1.00]
Troung et al. 2021	74	97	21.1%	23.9%	0.76 [0.67; 0.84]
Pfajfer et al. 2021	3	3	0.8%	4.9%	1.00 [0.29; 1.00]
Lyengar et al. 2022	3	3	0.8%	4.9%	1.00 [0.29; 1.00]
Viskin et al. 2021	6	7	1.6%	8.8%	0.86 [0.42; 1.00]
Jain et al. 2021	49	56	12.2%	21.6%	0.88 [0.76; 0.95]
Aggregated Individual Patient Data	268	285	61.7%	26.4%	0.94 [0.91; 0.96]
Total (fixed effect, 95% CI)		459	100.0%		0.95 [0.92; 0.97]
Total (random effects, 95% CI)				100.0%	0.93 [0.83; 0.99]
Heterogeneity: Tau ² = 0.0153; Chi ² =	21.83, df	= 6 (P <	< 0.01); I ² = 73	3%	Г
					0



Weight Weight Study Events Total (common) (random) IV, Fixed + Random, 95% CI IV. Fixed + Random, 95% CI 8 1.00 [0.63; 1.00] Montogomery et al 8 2.5% 13.0% 28.9% Troung et al. 2021 54 97 19.3% 0.56 [0.45; 0.66] Pfajfer et al. 2021 3 0 1.0% 8.6% 0.00 [0.00; 0.71] 1.00 [0.29; 1.00] Lyengar et al. 2022 3 3 1.0% 8.6% Viskin et al. 2021 1 7 2.2% 12.4% 0.14 [0.00; 0.58] Jain et al. 2021 50 18.6% 0.89 [0.78; 0.96] 56 16.7% Aggregated Individual Patient Data 131 160 47.6% 19.6% 0.82 [0.75; 0.88] Total (fixed effect, 95% CI) 334 100.0% 0.78 [0.73; 0.83] ---Total (random effects, 95% CI) 100.0% 0.72 [0.50; 0.90] Heterogeneity: $Tau^2 = 0.0525$; $Chi^2 = 52.81$, df = 6 (P < 0.01); $I^2 = 89\%$ 0 0.2 0.4 0.6 0.8 1



LVEF < 55 (%)

			Weight	Weight							
Study	Events	Total	(common)	(random)	IV, Fixed + Random, 95% CI		IV, Fix	ed + Ra	andom,	95% CI	
Pfajfer et al. 2021	0	3	1.5%	3.8%	0.00 [0.00; 0.71]	-				-	
Jain et al. 2021	13	56	23.8%	36.6%	0.23 [0.13; 0.36]						
Aggregated Individual Ppatient Data	58	177	74.7%	59.6%	0.33 [0.26; 0.40]		4	•			
Total (fixed effect, 95% CI)		236	100.0%		0.28 [0.22; 0.35]		-	•			
Total (random effects, 95% CI)				100.0%	0.26 [0.16; 0.37]	_					
Heterogeneity: Tau ² = 0.0034; Chi ² = 3	.24, df = 2	2 (P = 0	.20); I ² = 38%			1	1	1	1	1	1
						0	0.2	0.4	0.6	0.8	1

FIGURE 2: Forest plot showing percentage (95% confidence interval [CI]) of cardiac MRI abnormalities in patients with suspected myocarditis following COVID-19 vaccination.

Diagnosis of myocarditis is still challenging due to the heterogeneity of clinical presentations, multiple potenunderlying etiologies, and variable severity and tial

prognosis.^{108,109} The abilities of cardiac MRI make it the first choice for the noninvasive assessment of suspected cases.¹¹⁰

Based on available evidence, the patterns of myocardial injury in COVID-19 vaccine-associated myocarditis are similar to findings in acute myocarditis induced by other causes such as viral and idiopathic myocarditis. In a cardiac MRI study of patients meeting both clinical and imaging diagnostic criteria for acute myocarditis, Fronza et al found a similar pattern of cardiac injury in patients with COVID-19 vaccine-associated myocarditis compared to those with myocarditis induced by COVID-19 disease and other causes; the most frequent pattern of LGE in three groups was subepicardial with basal inferolateral wall distribution.⁹ However, septal involvement was less frequent in the vaccine-associated myocarditis group.⁹

In 2009, LLC was defined as diagnostic cardiac MRI criteria for patients with suspected myocarditis.¹¹¹ In this multiparametric approach, acute myocarditis diagnosis was established with at least two out of three of the following tissue-based cardiac MRI markers: T2-weighted ratio, early gadolinium enhancement (EGE), and LGE.¹¹¹ To improve the diagnostic performance of the recommended criteria, LLC was revised following the introduction of mapping techniques in 2018.⁸ In the revised LLC, the presence of at least one edema-sensitive cardiac MRI criteria (T2-weighted images or T2 mapping) combined with at least one additional T1-based tissue characterization technique (LGE, T1 mapping, or ECV) was considered as a positive case.⁸ In patients with clinically suspected myocarditis, the presence of only one T1-/T2-based marker may still support the diagnosis of myocardial inflammation. LV systolic dysfunction and presence of pericardial involvement are supportive parameters but not required for the diagnosis of myocarditis based on both the revised and original LLC.⁴ Based on our pooled analyses of available cardiac MRI studies, LLC-based diagnosis of myocarditis was established in over two-thirds of patients with suspected myocarditis following COVID-19 vaccination. However, included studies mainly failed to provide information on the version of utilized LLC.

Myocardial involvement seems to be less severe in COVID-19 vaccine-associated myocarditis than those induced by other causes. Based on our analyses, most patients with myocarditis following the COVID-19 vaccination had a preserved LVEF, and WMA was not common in these patients. In the study by Fronza et al, patients with vaccine-associated myocarditis had markedly less cardiac functional impairment, lower noncontrast T1, and less frequent involvement of the septum compared to patients with myocarditis induced by other causes.⁹

Based on our systematic review, all reported cases with abnormal cardiac MRI findings showed a favorable clinical course at the acute phase. Similarly, myocarditis induced by other causes was recognized to be self-resolving in patients presenting with mild symptoms, even with minimal ventricular dysfunction. However, progression to dilated cardiomyopathy can occur in up to 30% of patients with biopsy-proven myocarditis.¹¹² In a follow-up study by Chalala et al, three out of five patients reported mild intermittent self-resolving chest pain after discharge, leading to an emergency department visit in one patient.⁷ Two patients underwent a second cardiac MRI 3 months after discharge, showing a persistent but diminished LGE with a similar distribution as compared to the initial MRI.⁷ In 2019, Aquaro et al evaluated the clinical and prognostic role of 6-month repetition of cardiac MRI in patients with acute myocarditis and found that LGE persisted at 6 months in about 90% of cases.⁶ The presence of LGE without edema at a 6-month cardiac MRI was the predictor of a worse prognosis, particularly in those with a midwall septal pattern; the presence of edema shows a residual chance of recovery.⁶ Cardiac MRI can be useful in the follow-up examination of patients with myocarditis to detect the disease activity and progression.¹¹³

Limitations

As a review of published reports, one of our major limitations was that a core laboratory did not review the actual images. Our data sets were incomplete for several variables, mainly due to the retrospective design of the included studies. Furthermore, the majority of included studies were conducted in the United States and European countries, and thus caution should be taken in generalizing the findings of this review to other populations. However, we performed a comprehensive search strategy and included all relevant studies to present a synthesis of currently existing evidence.

Conclusion

Diagnosis of myocarditis may be detected in over two-thirds of patients with suspected myocarditis following COVID-19 vaccination using the LLC. Myocardial LGE with a nonsischemic pattern and elevated T2 might probably be the most common cardiac MRI findings in these patients.

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