

Cardiac Magnetic Resonance Imaging Findings in 2954 COVID-19 Adult Survivors: A Comprehensive Systematic Review

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Background: Recent studies have utilized MRI to determine the extent to which COVID-19 survivors may experience cardiac sequels after recovery.

Purpose: To systematically review the main cardiac MRI findings in COVID-19 adult survivors.

Study type: Systematic review.

Subjects: A total of 2954 COVID-19 adult survivors from 16 studies.

Field Strength/sequence: Late gadolinium enhancement (LGE), parametric mapping (T1-native, T2, T1-post (extracellular volume fraction [ECV]), T2-weighted sequences (myocardium/pericardium), at 1.5 T and 3 T.

Assessment: A systematic search was performed on PubMed, Embase, and Google scholar databases using Boolean operators and the relevant key terms covering COVID-19, cardiac injury, CMR, and follow-up. MRI data, including (if available) T1, T2, extra cellular volume, presence of myocardial or pericardial late gadolinium enhancement (LGE) and left and right ventricular ejection fraction were extracted.

Statistical Tests: The main results of the included studies are summarized. No additional statistical analysis was performed.

Results: Of 1601 articles retrieved from the initial search, 12 cohorts and 10 case series met our eligibility criteria. The rate of raised T1 in COVID-19 adult survivors varied across studies from 0% to 73%. Raised T2 was detected in none of patients in 4 out of 15 studies, and in the remaining studies, its rate ranged from 2% to 60%. In most studies, LGE (myocardial or pericardial) was observed in COVID-19 survivors, the rate ranging from 4% to 100%. Myocardial LGE mainly had non-ischemic patterns. None of the cohort studies observed myocardial LGE in “healthy” controls. Most studies found that patients who recovered from COVID-19 had a significantly greater T1 and T2 compared to participants in the corresponding control group.

Data Conclusion: Findings of MRI studies suggest the presence of myocardial and pericardial involvement in a notable number of patients recovered from COVID-19.

Level of Evidence: 3

Technical Efficacy Stage: 3

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To date, coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected over 184 million people, of whom approximately 170 million have recovered.¹

Myocardial injury have been noted in a 17.85% (95% confidence interval (CI): 13.18–23.72) of hospitalized patients with SARS-CoV-2 infection in the acute phase.² Consistent with other viral diseases,^{3,4} there are increasing

concerns that some of these cardiac sequels may persist beyond the acute phase of the disease into several weeks and months of recovery in survivors. Also, it has been assumed that some survivors may develop cardiac complications due to persistent inflammation in the convalescent period.⁵ If untreated, sustained cardiac injury, especially myocarditis and fibrosis, could have severe consequences such as malignant arrhythmia, heart failure, and sudden cardiac death.^{6,7}

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Given the high prevalence of the infection and the potential poor prognosis of cardiac complications in the absence of timely management, it is important to identify the extent to which survivors may be affected. Hence, recent studies have assessed the presence of cardiac involvement using MRI, a noninvasive diagnostic tool, in patients infected by SARS-CoV-2 after recovery.^{8–29}

There is no published systematic review of MRI studies focusing on COVID-19 survivors. In the systematic review of Ojha et al,³⁰ all except five selected articles were case reports on patients in the acute phase of COVID-19. Hence, the aim of this systematic review was to summarize the main cardiac MRI findings in COVID-19 adult survivors reported in all available case series and cohort studies.

Materials and Methods

The study's methodology followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.³¹ No ethical approval was required because this study was a systematic review of published studies.

All eligible studies that assessed cardiac sequels in COVID-19 adult survivors through MRI were included in this systematic review.

Search

Electronic databases, including PubMed, Embase, and Google Scholar, were searched on March 6, 2020, and again on June 24, 2021.

The search was conducted using key terms for four domains: 1) "COVID-19," "sars-COV-2," "novel corona," or "2019-nCoV," 2) "cardiac complications," "cardiac involvement," "myocardial inflammation," "cardiac injury," "heart injury," or "myocarditis"; 3) "cardiac magnetic resonance," "cardiac MRI," or "CMR,"; and 4) follow-up, "follow up," "after recovery," "after discharged," or "post-acute." While tailoring for each database, terms were combined by "OR" in each domain, then domains were combined by "AND."

The reference list of each retrieved article was checked to identify any potentially eligible items that had not yet been retrieved. All retrieved articles were added to EndNote X8.2 reference management software, and duplicate studies were removed from the list.

Study Inclusion

Two independent researchers ([H.M. 3 years experience] and H.T. [5 years experience]) screened titles, abstracts, and full texts of retrieved articles hierarchically to identify the eligible items. Any disagreements were resolved by involving a third researcher (NSh [Ex.: 13 years] or HR [Ex. 11 years]).

Eligibility Criteria

We included observational studies that met all five of the following criteria:

1. Cardiac evaluation by MRI
2. Median/mean follow-up time to MRI: at least 2 weeks after discharge or diagnosis
3. Including COVID-19 out/inpatients who were at postacute phase
4. Having a case series ($n > 10$ cases) or a cohort design
5. Written in English

Data Extraction

Three independent researchers [N.Sh., H.R., and H.T.] extracted the data from the articles that fulfilled the inclusion criteria and recorded them in a "Data Extraction Form" generated using Microsoft Excel, as outlined in the following.

First author's name, country, study design, sample size, age, sex, study population, follow-up duration (time from diagnosis/discharge to MRI), and main findings on: myocardial or pericardial late gadolinium enhancement (LGE), T1, T2, extra cellular volume (ECV), left ventricle (LV) and right ventricle (RV), ejection fraction (EF), global longitudinal strain (GLS), pericardial effusion (PE), troponin level. All extracted data were organized and presented in Tables 1–4.

Quality Assessment

Two members of the research team (H.M. and H.K.) independently assessed the quality of the included articles using an appraisal tool adapted for use in observational studies, and any disagreement was resolved through discussion or a third researcher (H.R., N.Sh., or H.T.).

Quality appraisal was performed using the Newcastle–Ottawa scale (NOS)³² for the cohort studies and NIH Quality Assessment Tool for Case Series Studies.³³ Both appraisal tools contained nine items, and their total score ranged from 0 to 9; the scores were categorized into three groups: poor: met 0–3, fair: met 4–6 criteria, and good: met 7–9 criteria.

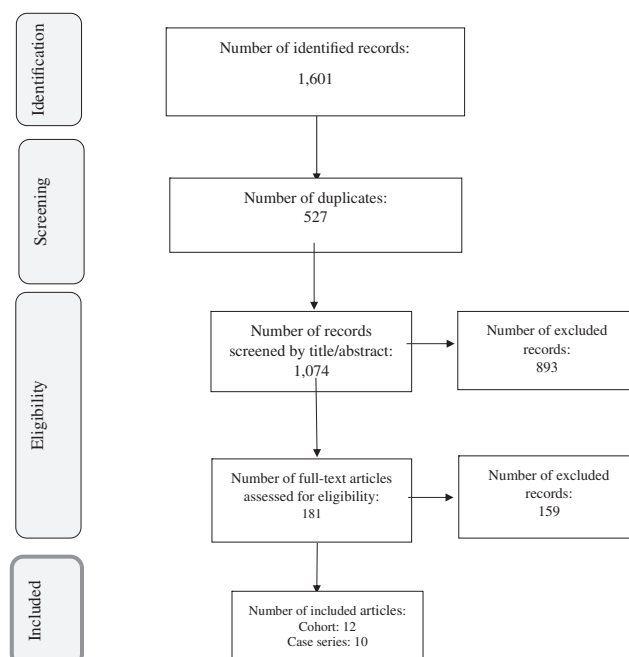


FIGURE 1: PRISMA flowchart of literature search and selection process

TABLE 1. Characteristics of the Included Studies

COVID-19 Group in the Acute Phase											Control Group(s)			
ID	Author	Country	Design	Follow-up Time (days)	Population	Disease Severity	Cardiac Symptom/Sign	N	% Male	Age (year) ^a	Control Group(s)			
											Population	N	% Male	Age (year) ^a
1	Puntmann et al ¹⁵	Germany	PC	71 (64–92) ^c	-General population ^d PMH: DM: 18% CAD: 13%, HTN: 22%	Asymptomatic: 18% Mild/moderate: 49% Severe: 33%/ventilated: 2% Hospitalized: 33%	El. hs. Tr: 15% Others: NR	100	53%	49 (45–53)	I) Age and sex- MHC	50	50%	48 (43–52)
											II) RF Matched	57	52%	49 (46–52)
2	Clark et al ²⁸	USA	RC	52 (NR) ^b	Athlete ^d PMH: Negative	Asymptomatic: 23% Mild: 77% Hospitalized: 0.0%	NR	22	41%	20 (19–21)	I) HC	22	64%	30 (27–32)
											II) Athletic	22	86%	31 (28–35)
3	Wang et. al ¹⁰	China	RC	102.5 (20.6) c	-General population ^d -PMH: Negative	Moderate: 72.7% Severe: 35%/critical: 2.3% Hospitalized:100%	NYHA III/IV: 8/2 Tr. I (ng/ml): 0.02 (0.01–0.02)	44	43%	47.5 ± 13.3	Normal ^d	31	61%	47.1 ± 11.0
4	Brito et al ²⁹	USA	RC	27 (22–33) ^c	-Athlete ^d -PMH: Negative	Asymptomatic: 30% Mild: 66% / Moderate: 4% Hospitalized: 0.0%	Cardiac Sym.: 20% ECG change: 3% El. Tr: 3%	54	85%	19 (19–21)	Athletic ^d	20	40%	20 (19–21)
5	Huang et al ²⁴	China	RC	47 (36–58) ^c	-Patients With cardiac sym. after discharge - PMH: HTN: 8%	Moderate: 85% Severe: 15% Hospitalized:100%	NR	26	38%	38 (32–45)	Healthy	20	35%	40 (29–50)
6	Ng et al ¹⁷	China	RC	56 (NR) ^d	-Patients with ECG changes or El. Tr at acute phase/-PMH: NR	Mild/moderate: 94% Not reported: 6% Hospitalized:100%	1_Cardiac sym.: NR ECG changes: 88% El. Tr: 44%	16	56%	68 (53–69)	Healthy	15	NR	NR
7	Eiros et al ²⁶	Spain	RC	73 (65–77) ^d	Health-care workers PMH: DM: 1%, HTN: 12%, CVD: 6%	Oxygen therapy 11% Hospitalized: 16%	Cardiac sym.: 62% Others: NR	139	28%	52 (41–57)	General Population (PMH: NR)	20	30%	53 (39–57)
8	Raman et al ¹³	UK	RC	70 (62–76) ^c	General population PMH: DM:: 15.5% HTN: 37.9%, CAD: 3.4%	Moderate:64% Severe: 36% Hospitalized:100%	El. hs. Tr: 8% Chest pain 27.6% Others: NR	58	59%	55.4 ± 13.2	Comorbidity/sex/ age- MC	30	60%	53.9 ± 12.3
9	Pan et al. ¹⁶	China	PC	46 (43–50) ^d	General population PMH: negative	Mild/moderate/severe/critical 19%/67%/14%/ 0% - Hospitalized:100%	NR	21	47.6%	36 (31–47)	Age /sex- MC	20	40%	50 (32–61)
10	Vago et al ¹¹	Hungary	RC	F:17 (17–19) M: 67/90 ^d	Athlete ^d -PMH: Negative	Asymptomatic: 17% Mild: 83% Hospitalized: 0.0%	Cardiac sym. 8% (1) El. Tr.: 0.0% (0) ECG change: NR	12	17%	23 (20–23)	Athlete	15	NR	NR
											HC	15	NR	NR
11	Kotecha et al ²¹	UK	RC	68 (39 103) ^d	General population PMH; DM: 34% HTN: 57%/CAD: 7%	Severe: 100% ventilated: 32% Hospitalized:100%	Elevated Tr.: 100% Tr level (median [IQR]): 26 (19– 70)	148	70%	64 (12)	Age/sex MHC	40	70%	64 (9)
											HC	40	57%	49 (6)
12	Joy et al ²³	UK	PC	180 ^c	Seropositive HCW HTN: 10%, DM: 2%, CAD: NR	Asymptomatic: 39% Mild: 61% Hospitalized: 3%	NR	74	38%	39 (30–48)	Seronegative HCW, age, sex, ethnicity	75	47%	37 (31–47)

TABLE 1. Continued

ID	Author	Country	Design	COVID-19 Group in the Acute Phase							Control Group(s)		
				Follow-up Time (days)	Population	Disease Severity	Cardiac Symptom/Sign	N	% Male	Age (year) ^a	Population	% N Male	Age (year) ^a
13	Daniels, et al ²⁷	USA	CS	22.5 (28.5) ^c	Athletes PMH: Negative	NR	NR	1597	NR	NR	-	- -	-
14	Moulson et al ¹⁸	USA	CS	33 (18–63) ^c	Athletes, clinically indicated CMR: 37.5% PMH: Negative	NR	NR	317	NR	-	-	- - -	-
15	Rajpal et al ¹⁴	USA	CS	23 (17–30) ^b	Athlete ^d PMH: Negative	Asymptomatic: 54% Mild: 46% Hospitalized: 0.0%	NR	26	58%	19.5 ± 1.5	-	- - -	-
16	Knight et al ²²	UK	CS	I) 46 ± 15 ^b II) 37 ± 10 ^c	Cases with an EL. Tr of unknown cause at the acute phase PMH: Negative	ICU ventilated: 34% Hospitalized: 100%	EL. Tr: 100% hsTr (ng/liter): 23.0 (19.0–32.8). Others: NR	29	83%	64 ± 9	-	- - -	-
17	Malek et al ²⁰	Poland	CS	32 (22–62) ^c	Athlete PMH: Negative	Asymptomatic: 23% Mild: 54% Moderate: 19% Severe/hospitalized: 4%	NR	26	19%	24 (21–27)	-	- - -	-
18	Fu et al ²⁵	China	CS	180	General population	Severe: 17% Hospitalized: 100%	EL. Tr: 21% EL. myocardial injury marker, abnormal echo, or ECG: 67.7%	34	NR	NR	-	- - -	-
19	Starekova et al ¹²	USA	CS	15 (11–194) ^c	Athlete PMH: Negative	Asymptomatic: 16.5% Mild: 49% Moderate: 27.5%	Chest Pain: 5% Other: NR	145	74%	19.6 ± 1.3	-	- - -	-
20	Wu et al ⁹	China	CS	180 ^c	General population PMH; DM: 18.5% HTN: 14.8%/CAD: 0.0%	Severe: 41% Hospitalized: 100%	At least one cTn concentration > 26 pg/mL: 50%	27	30%	63 [58, 70]	-	- - -	-
21	Martinez, et al ¹⁹	USA	CS	19 (3–156) ^c	Athletes with abnormal test results on cardiac screening at follow-up PMH: Negative	Asymptomatic/pauci-symptomatic: 41.7% Severe: 0.0% Hospitalized: 0.0%	NR	27	NR	NR	-	- -	-
22	Zhou et al ⁸	Hong Kong	CS	14–28 ^b	General population Abnormal ECG/elevated Tr	Hospitalized: 100%	NR	12	NR	NR	-	- -	-

CAD = coronary artery disease; CS = case series; DM = diabetes mellitus; EL. hs. Tr = elevated hs troponin; HTN = hypertension; IQR = interquartile range; MC = matched control; MHC = matched healthy control; NR = not reported; NYHA = New York Heart Function Classification; PMH = past medical history; PC = prospective cohort; RC = retrospective cohort; Sym. = symptoms; Tr = troponin.

^aMedian (IQR)/Mean ± SD.

^bMedian (IQR)/Mean ± SD time from discharge.

^cMedian (IQR)/Mean ± SD from diagnosis.

^dPatients were consecutively recruited regardless of having cardiac symptoms at the acute phase.

^eCardiac Sym./ECG change/EL. Tr, or Tr level (median [IQR]).

TABLE 2. Quality of the Included Cohort Studies

N.	Study	Selection				Comparability II (**)	Outcome			Total Of 9 scores	Class
		1	2	3	4		a	b	c		
1	Puntmann et al ¹⁵	*	*	*	-	**	*	*	*	8	Good
2	Clark et al ²⁸	*	*	*	-	**	*	*	*	8	Good
3	Wang et al ¹⁰	*	*	*	-	-	*	*	*	6	Fair
4	Brito et al ²⁹	*	*	*	-	**	*	*	*	8	Good
5	Huang et al ²⁴	-	*	*	-	-	*	*	*	5	Fair
6	Eiros et al ²⁶	*	*	*	-	-	*	*	*	6	Fair
7	Raman et al ¹³	*	*	*	-	**	*	*	*	8	Good
8	Pan et al ¹⁶	*	*	*	-	**	*	*	*	8	Good
9	Kotecha et al ²¹	*	*	*	-	**	*	*	*	8	Good
10	Ng et al ¹⁷	-	*	*	-	-	*	*	*	5	Fair
11	Vago et al ¹¹	*	*	-	-	-	*	*	*	5	Fair
12	Joy et al ²³	*	*	*	-	**	*	*	*	8	Good

1: Representativeness of exposed cohort (*).

2: Selection of nonexposed cohort (*).

3: Ascertainment of exposure (*).

4: The Outcome of Interest Was Not Present at Start of Study (*).

II: Comparability of Cohorts on the Basis of the Design or Analysis (**).

a: Assessment of outcome (*).

b: Enough follow-up time for outcomes to occur (*).

c: Adequacy of follow-up (*).

Results

Study Selection Process

A total of 1601 articles were identified through the initial search, of which 527 were duplicates and 1052 did not meet the inclusion criteria (by title/abstract: $n = 893$, full text: $n = 159$). Twenty-two articles, including 12 cohort studies and 10 case series studies, were eligible for inclusion in this review (Fig. 1).

Study Characteristics

Table 1 presents the characteristics of the studies included in this systematic review. These studies were carried out in China ($n = 6$), the United States ($n = 7$), the United Kingdom ($n = 4$), Poland ($n = 1$), Hungary ($n = 1$), Spain ($n = 1$), Germany ($n = 1$), and Hong Kong ($n = 1$). Overall, they involved 2954 COVID-19 adult survivors; the sample sizes ranged from 12 to 1597 COVID-19 survivors. Patients were consecutively recruited in 15 studies (six case series and nine cohort studies), regardless of cardiac symptoms at the acute phase or follow-up time.^{8,10,11,13–15,23,25–29,34} The mean/median age of participants ranged from 19 to 68 years, with a male predominance in most studies. Median/

mean time from diagnosis/discharge to the cardiac imaging assessment varied across the studies, with a minimum of 15 days and a maximum of 180 days.

In terms of the severity of COVID-19 disease, eight studies (five case series and three cohort studies) included nonhospitalized athletes with asymptomatic or mild infection.^{11,12,14,18,20,27–29} In others, study populations varied in terms of hospitalization rate and disease severity.

All cohort studies, but one,²³ included an external control group selected by different criteria.^{10,11,13,15–17,21,24,26,28,29} The exception was the cohort study conducted by Joy et al²³ that included SARS-CoV-2 seropositive and seronegative health care workers. In two studies, echocardiography was performed along with MRI for evaluating cardiac involvement.^{28,29}

The quality score was >5 in all cohort studies (Table 2) and >6 in the case series studies conducted by Rajpal et al¹⁴ (8 scores), Małek et al²⁰ (8 scores), Daniels et al²⁷ (8 scores), Starekova et al (8 scores),¹² Martinez et al¹⁹ (7 scores), Wu et al⁹ (7 scores), Moulson et al¹⁸ (7 scores), Knight et al²² (6 scores), Fu et al²⁵ (6 scores), and Zhou et al⁸ (6 scores).

Table 3 presents the cardiac MRI parameters of myocardial and pericardial involvement in recovered COVID-19 patients reported by different studies.

TABLE 3. Cardiac MRI Parameters of Myocardial and Pericardial Involvement in Recovered COVID-19 Patients

Author	Group	T1 (msec)		T2 (msec)		LGE % (N)				PE % (N) [cut point]	ECV ^a Mean (SD)	Abnormal Finding	Tesla
		Mean (SD)/ Median (IQR)	Abnormal % (N) [cut point]	Mean (SD)/ Median (IQR)	Abnormal % (N) [cut point]	Total	Myocardial		Pericardial				
							Ischemic	Nonischemic					
Puntmann et al ¹⁵	COVID-19	1130 (1119, 1150)	73% (73) [NR]	39 (37, 40)	60% (60)	74% (74)	32% (32)	20% (20)	22% (22)	20% (20) [>10 mm]	NR	T1 T2	3
	H C	1077 (1065, 1089)*	6% (3)*	35 (34, 36) *	4% (2)*	0.0 (0)*	0.0% (0)*	0.0 (0)*	0.0 (0)*	0.0 (0)*	NR	LGE PE	
	MC	1109 (1101,1119)*	40% (23)*	36 (35, 37)*	9% (5)*	39% (21)*	17% (9)*	7% (4)*	15% (8)	15% (8)*	NR		
Clark et al ²⁸	COVID-19	982 (973, 997) ^b	5% (1) [>1042 msec]	46.4 (45.2, 48.2) ^b	13.5% (3) [>53.9 msec]	9% (2)	4.5% (1)	4.5% (1)	4.5% (1)	NR	25.3 (2.6) ^b	T2 LGE ECV	1.5
	HC	978 (963, 998)	NR	44.6 (43.2, 45.4) *	0.0% (0)	0.0 (0)*	0.0% (0)	0.0 (0)	0.0% (0)	NR	24 (3)		
	Athletic C.	989 (963, 1008)	NR	NR	0.0% (0)	0.0 (0) *	0.0% (0)	0.0 (0)	0.0% (0)	NR	22.5 (2.6)*		
Wang et. al ¹⁰	COVID-19	NR	NR	NR	0.0% (0)	30% (13)	0.0% (0)	30% (13)	0.0% (0)	NR	NR	LGE	3
	Normal C	NR	NR	NR	0.0% (0)	0.0 (0)	0.0% (0)	0.0 (0)	0.0% (0)	NR	NR		
Huang et al ²⁴	COVID-19	1256.2 (27.66)	NR	40.8 (3.6)	57.6% (15) ^c	31% (8) ^c	0.0% (0)	31% (8)	0.0% (0)	27% (7) ^c [NR]	26.8 (4.7)	T1, T2 LGE, PE, ECV	3
	HC	1224 (10.5)*	NR	39.1 (3.1)*	0.0% (0)	0.0% (0)	0.0% (0)	0.0 (0)	0.0% (0)	0.0(0)	23.7 (1.5) *		
Brito et al ^{29d}	COVID-19	969 (950, 984)	19% (9) [>990 msec]	44.0 (42.0, 45.0)	0.0% (0) [>52 msec]	41.7% (20)	0.0% (0)	2.9% (1)	39.6% (19)	58% (28) [≥5 mm]	NR	T1, LGE PE	1.5
Rajpal et al ¹⁴	COVID-19	983 (961, 1002)	42% (11) [>990 msec]	52.5 (49.8, 53.0)	15.4% (4) [>54 msec]	46.2% (12)	0.0% (0)	46.2% (12)	0.0% (0)	8% (2)	24.7 (2.9)	T1, T2 LGE ECV	3
Ng et al ¹⁷	COVID-19	1209 (1164, 1219)	50% (8) [>1208 msec]	52 (50, 56)	31% (5) [>54.5 msec]	15% (4)	6.3% (1)	18.8% (3)	0.0% (0)	NR	NR	T1, T2 LGE	1.5
	HC	1158 (1109–1208) *	NR	48.0 (41.5, 54.8) *	NR	NR	NR	NR	NR	NR	NR		
Knight et al ²²	COVID-19	NR	NR	NR	0.0% (0)	100% (29)	31% (9)	51.7% (15)	0.0%(0)	7% (2) [NR]	NR	LGE	1.5
Eiros et al ²⁶	COVID-19	1020 (1005–1040)	42% (58) [NR]	50 (48–51)	4% (6) [NR]	7% (10)	NR	NR	NR	30% (42) [>3 mm]	NR	T1, T2, LGE, PE, ECV	1.5
	Controls	1004 (980–1034)*	0.0% (0)	54 (51–55)*	0.0% (0)	0.0% (0)	NR	NR	NR	0.0% (0)	NR		
Raman et al ¹³	COVID-19	1179-7 (34-4)	26-0% (13/50)	41-7 (2-2)	2% (1/50)	NR	1.9% (1/52)	11.5% (6)	NR	1.9% (1/52) [>10 mm]	30-4 (28-3–31-3)	T1 LGE	3
	MC	1149-3 (24-0)*	3-7% (1/28)	41-6 (2-2)	3.6%(1/28)	NR	7.4% (2/28)	0.0% (0)	NR	0.0% (0)	28-3 (26-8–31-5)		

TABLE 3. Continued

Author	Group	T1 (msec)		T2 (msec)		LGE % (N)				PE % (N) [cut point]	ECV ^a Mean (SD)	Abnormal Finding	Tesla
		Mean (SD)/ Median (IQR)	Abnormal % (N) [cut point]	Mean (SD)/ Median (IQR)	Abnormal % (N) [cut point]	Total	Myocardial						
							Ischemic	Nonischemic	Pericardial				
Vago et al ¹¹	COVID-19	957 (943, 972)	NR	44 (44–45)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	NR	T1	1.5
	Athlete C.	957 (951, 976)	NR	44(44–45)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	NR		
	HC	981 (966, 990)*	NR	46(44–47)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	NR		
Pan et al ¹⁶	COVID-19	1208.4 (64.2)	23.8% (5/21) [1337.1]	49.2 (46.1–54.6)	47.6% (10/21) [>59.8]	NR	NR	NR	NR	NR	NR	T1, T2	3
	MC	1213.6 (61.7)	NR	48.3 (45.2–51.7)*	NR	NR	NR	NR	NR	NR	NR		
Kotecha et al ²¹	COVID-19	1033 (41)	13% (19) [>1076]	46 (3)	3% (4) [>52]	49% (70)	22% (32)	33% (47)	NR	5%(8)	NR	T1, LGE, PE	1.5
	MC	1028 (35)	13% (5)	47 (3)	3% (1)	45% (18)	15% (10)	20% (8)	NR	NR	NR		
	HC	1008 (35)*	NR	48 (2)	NR	0.0% (0)	0.0% (0)	0.0% (0)	NR	NR	NR		
Joy et al ²³	COVID-19	1020 (34)	7% (5) [>1072]	48.8 (2.5)	9% (7) [>52.4]	19% (14) ^c	NR	NR	NR	NR	22.3 (2.0)	T1, T2, LGE, ECV	1.5
	MC	1016 (28)	1% (1)	48.6 (1.9)	3% (2)	17% (13)	NR	NR	NR	NR	22.1 (2.2)		
Malek et al ²⁰	COVID-19	1010 (992–1028)	0.0% (0) [1054]	46 (45–48)	4% (1/26) [50]	4% (1)	0.0% (0)	4% (1)	0.0% (0)	8.0% (2) [NR]	26 (24–27)	LGE T2	1.5
Starekova, et al ¹²	COVID-19	978 (40) [3 T: 1129 (84)]	NR	48 (4) [3 T: 49 (5)]	NR	29% (42) ^c	NR	NR	NR	NR	NR	LGE	1.5 or 3
Wu et al ⁹	COVID-19	1211.7 [1185.2, 1247.1]	NR	NR	NR	30% (8)	NR	26% (7)	NR	NR	0.28 [0.26, 0.31]	LGE	3
Martinez, et al ¹⁹	COVID-19	NR	NR	NR	NR	18.5% (5)	NR	NR	7% (2)	NR	NR	LGE	NR
Zhou et al ⁸	COVID-19	NR	NR	NR	NR	0.0% (0)	NR	NR	NR	NR	NR	NR	NR

C = control; IQR = interquartile range; HC = healthy controls; MC = matched controls; NR = not reported; SD = standard deviation; PE = pericardial effusion.

**P* value < 0.05.

^aClark et al: ECV > 30.3% in 1 patient (4.5%); Rajpal: - ECV ≥27 in 6 (23%) and > 29% in 1 patient (4%).

^bOn mid septum slice.

^cOn conventional MRI.

^dMRI performed only for COVID-19 patients.

^eNon-RV insertion point: 8% in COVID-19 patients and 9% in controls.

TABLE 4. Cardiac Function Based on MRI Findings and Troponin Level in Patients Recovered From COVID-19

Author	Group	On CMR		Troponin (pg/mL)	Finding +	Other Important Findings
		LVEF	RVEF			
		Mean (SD)/ Med (IQR)	Mean (SD)/ Med (IQR)	Mean (SD)/ Med (IQR)		
Puntmann et al ¹⁵	COVID-19	56 (54–58)	56 (52–59)	5.6 (4.1–6.6)	-LV and RV dysfunction -Elevated Tr.	-Troponin was significantly correlated with native T1 and T2 mapping -Detectable hsTr.T (≥3 pg/mL) No. (%) in 71% (71) [COVID-19] > 11% (22) [HC] and 31% (57) [RF matched C.] - hsTr.T ≥ 13.9 pg/mL, No. (%) in 5% (5) of COVID-19 and 0.0% (0) of controls
	Healthy C.	60 (58–62)*	60 (56–63)*	3.2 (3.0–3.5)*		
	RF Matched C	61 (58–64)*	59 (56–62)*	3.9 (3.2–4.5)*		
Clark et al ²⁸	COVID-19	60 (59, 63)	52 (50, 54)	NR	-RV dysfunction	-Echocardiographic finding of COVID-19 cases (n = 16): LVEF, %: 59 (56, 63), GLS, %: −18.2 (−19.7, −15.6) -Increased RV volumes in COVID-19 cases rather than others on MRI -No one had abnormal Tr, ECG, or LVEF < 50% [on echocardiography]
	Healthy C.	60 (57, 64)	57 (55, 60)*	NR		
	Athletic C.	61 (57, 64)	56 (51, 59)*	NR		
Wang et al ¹⁰	COVID-19	62.8 (4.9)	57.4 (8.4)	NR	NR	-
	Normal C.	62.0 (6.7)	59.1 (6.5)	NR		
Brito et al ²⁹	COVID-19	59.91 (56.64, 62.88)	53.58 (48.33, 59.43)	NR	LV dysfunction	-LVEF < 50% in one symptomatic COVID-19 patient (echo and MRI) --None has elevated inflammatory biomarkers -On echocardiography, no significant differences between control and patients with and without symptoms regarding LVEF% and RVEF
	Athletic C.	NR	NR	NR		
Huang et al ²⁴	COVID-19	62.2 (6.3)	38.4 (7.5)	2.0 (1.9–2.2)	-RV dysfunction	-The hs-cTn I level was in the normal range for all recovered patients at the time of MRI - EF < 50% in one COVID-19 patient on MRI but not seen in controls
	Healthy C.	63.0 (8.9)	46.1 (12.0) *	NR		
Rajpal et al ¹⁴	COVID-19	57.73 (6.22)	56.88 (4.26)	NR	-LV dysfunction	- EF < 50% in one case, EF < 55 in 3 Cases on MRI - No athlete had elevated serum levels of Tr I or ECG changes

TABLE 4. Continued

Author	Group	On CMR		Troponin (pg/mL)	Finding +	Other Important Findings
		LVEF	RVEF			
		Mean (SD)/ Med (IQR)	Mean (SD)/ Med (IQR)	Mean (SD)/ Med (IQR)		
Ng et al ¹⁷	COVID-19	59 (56–65)	53 (48–57)	NR	NR	- Six out of nine patients who had abnormal MRI finding (s) had elevated blood biomarkers of inflammation
Knight et al ²²	COVID-19	67.7 ± 11.4	63.7 ± 9.5	All	LV and RV dysfunction	- One patient had mild LV dysfunction, and one had severe biventricular dysfunction.
Pan et al ¹⁶	COVID-19	61.6 (6.5)	54.7 (7.1)	NR	RV dysfunction	-Severity of disease, elevated level of Hs-CRP and D-Dimer, and lymphopenia during hospitalization was significantly associated with higher T2 value. -Elevated Hs-CRP level was significantly associated with higher T1 value.
	Matched Controls	64.8 (9.5)	60.3 (6.9) *	NR		
Starekova, et al ¹²	COVID-19	58 (5)	54 (6)	NR	-	-
Wu et al ⁹	COVID-19	56 [54, 59]	NR	2.9 [2.0, 4.4]	NR	Patients with cardiac injury during hospitalization showed significantly higher levels of hs-cTnI (pg/mL) (4.3 [2.0, 6.7] vs. 2.5 [1.8, 2.9]; <i>P</i> value: 0.041) and d NT-pro BNP (99 [78, 138] vs. 47 [36, 61]; <i>P</i> value: 0.004)
Eiros et al ²⁶	COVID-19	64 (60–67)	63 (59–68)	NR	Elevated Tr.	-hs.Tr > 14 pg/mL in one patients
	Controls	68 (62–71)	66 (61–69)	NR		
Raman et al ¹³	COVID-19	63.0 (7.72)	57.9 (7.8)	2.0 (2.0–3.0)	NR	-
	Matched Controls	63.6 (6.32)	57.6 (6.0)	2.0 (2.0–3.0)		
Vago et al ¹¹	COVID-19	58 (55–61)	NR	NR	NR	-
	Athlete	57 (54–60)	NR	NR		
	Healthy Controls	60 (58–63)	NR	NR		

TABLE 4. Continued

Author	Group	On CMR		Troponin (pg/mL)	Finding +	Other Important Findings
		LVEF	RVEF			
		Mean (SD)/ Med (IQR)	Mean (SD)/ Med (IQR)	Mean (SD)/ Med (IQR)		
Malek et al ²⁰	COVID-19	61 (60–62)	59 (57–60)	4.0 (4.0–5.0)	LV dysfunction	Detectable Tr (>4 pg/mL): 15% (4), Abnormal Tr (>13.90 pg/mL): 0.0% Abnormal LVEF: 8% (2) / Abnormal RVEF: 0.0% (0)
Kotecha et al ²¹	COVID-19	67 (11)	61(9)	NR	NR	-
	Matched Controls	67 (9)	64(7)	NR		
	Healthy Controls	66(5)	61(5)	NR		
Joy et al ²³	COVID-19	67.5 (64.4–70.2)	NR	4 (3–7)	-	-
	Matched Controls	66.8 (62.8–70.1)	NR	4 (3–7)	-	-
Fu et al ²⁵	COVID-19	NR	NR	NR	LV dysfunction	LVEF<50: 47% (16), RVEF: 15% (5)
IMartinez, et al ¹⁹	COVID-19	NR	NR	NR	Elevated Tr. LV dysfunction	-Five patients had a hs- Tr level greater than the 99th percentile of the reference laboratory value -LVEF <50 reported in two patients on CMR -Abnormal ECG: 33% (9) 18 abnormal ECHO

C = control; IQR = interquartile range; GLS = global longitudinal strain; EF = ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; NR = not reported; RV = right ventricular; RVPLS = right ventricle peak longitudinal strain; SD = standard deviation; Tr = troponin.

*P value < 0.05.

MYOCARDIAL INVOLVEMENT. Of the 15 studies that evaluated both T2 and LGE, Vago et al found raised T2 or LGE in none of 12 patients.¹¹ Wang et al,¹⁰ Brito et al,²⁹ and Knight et al²² detected LGE in 30%, 41.7%, and 100% of their patients, respectively, but did not find a raised T2 in any of them. Starekova et al¹² found LGE in 14 of 74 (19%) patients but they failed to provide information on rate of raised T2. The remaining studies reported rates of increased T2 ranging from 2% to 60% and LGE ranging from 4% to 74%.

Four out of 22 studies that evaluated LGE ($n = 3$) or T2 ($n = 1$) of which, Pan et al reported raised T2 in 10 of 21 patients (47.6%)¹⁶ and remaining studies conducted by Wu et al,⁹ Martinez et al,¹⁹ and Zhou et al.⁸ found LGE in 30%, 18.5%, and 0.0% of participants, respectively.

The rate of nonischemic myocardial enhancement in COVID-19 patients varied from 2% in the Brito et al²⁹ study to 51.7% in the Knight et al²² study, more frequently detected in the studies that included a higher percentage of patients with severe form of the disease at the acute phase.^{9,13,15,21,22} None of the cohort studies observed myocardial LGE in healthy controls. However, Puntmann et al¹⁵ and Kotecha et al²¹ detected nonischemic myocardial enhancement in their risk-matched control groups, but with a lower frequency (Puntmann et al¹⁵: 7% vs. 20%; Kotecha et al²¹: 20% vs 33%).

Fourteen out of 22 studies, including 4 case series and 10 cohort studies, performed T1 mapping; the rate of raised T1 varied from 0% in the Malek et al²⁰ study to 73% in the Puntmann et al¹⁵ study. Six out of 10 cohort studies reported that patients who recovered from COVID-19 had a significantly greater mean T1 (also T2) compared to participants in the corresponding control group.^{13,15,17,21,24,26} Based on Lake Louise criteria (LLC), Moulson et al¹⁸ identified cardiac involvement in 21 of 317 (7%) athletes, which was more frequent in those who underwent clinically indicated MRI (15/119, 12.6%) than in those undergoing a primary screening MRI (6/198 (3.0%)) and concluded that cardiac MRI will be optimized by confining its use to athletes presenting with cardiopulmonary symptoms and/or abnormalities on triad testing (ECG, elevated troponin, and echocardiography).

However, Daniels et al²⁷ identified myocarditis in 2.3% of athletes (37/1597) based on a modified version of LLC; they also found that a strategy using cardiac MRI in all athletes, regardless of cardiac symptoms or triad testing results, increases the prevalence of diagnosis to a 7.4-fold compared to the symptom-driven (2.3% vs. 0.31%) and to 2.8-fold to cardiac testing strategies (2.3% vs. 0.81%). In addition, cardiac MRI follow-up of 27 of these 37 athletes (follow-up duration [weeks] mean [SD]: 9.4 [3.1] from COVID-19 diagnosis) showed two patterns of resolution: 1) resolution of both T2 mapping abnormalities and LGE in 11 of 27 athletes and 2) resolution of T2 mapping abnormalities but

persistence of LGE in 16 of 27 athletes. Clinical myocarditis cases were less likely to experience resolution of LGE than subclinical cases.

Myocardial involvement defined by this criteria was also reported in other studies: Eiros et al²⁶ (26% [$n = 36$]), Ng et al¹⁷ (18.8% [$n = 3$]), Rajpal et al¹⁴ (15% [$n = 4$]), Clark et al,²⁸ (4.5% [$n = 1$]), Starekova et al¹² (1.3% [$n = 2$]), and Malek et al²⁰ (0.0% [$n = 0$]).

Among cohort studies that measured ECV (%), while Clark et al²⁸ and Huang et al^{24,30} both found a greater mean ECV (%) in COVID-19 patients than in control subjects, Raman et al¹³ and Joy et al²³ did not detect any significant difference. Increased ECV rates (%) were reported by Eiros et al²⁶ (36% [$n = 52$], cut point: not reported [NR]), Rajpal et al¹⁴ (23% [$n = 6$], cut point: $\geq 27\%$), Clark et al²⁸ (4.5% [$n = 1$], cut point: $>30.3\%$), Joy et al²³ (3.0%, cut point: NR), and Malek et al²⁰ (0.0% [$n = 0$], cut point: 31.9%).

Fu et al²⁵ reported the presence of edema in 10 (29.41%) and fibrosis in 2 (5.80%) patients, mainly in the subgroup of patients with cardiac abnormalities (having elevated myocardial injury marker, abnormal echocardiographic, and/or electrocardiographic results) at admission. However, they provided no information on how edema and fibrosis were defined on MRI.

Wu et al⁹ observed that patients with cardiac injury compared to those without cardiac injury (having at least one cTn concentration > 26 pg/mL during hospitalization) had a higher rate of LGE [7/13 (53.8%) vs. 1/14 (7.1%), $P = 0.013$]. They detected no significant differences between two groups regarding T1 and ECV measurements.

PERICARDIAL INVOLVEMENT. Pericardial enhancement in patients recovered from COVID-19 was observed in the studies conducted by Brito et al²⁹ (39.6%), Puntmann et al¹⁵ (22%), Martinez et al¹⁹ (7%), and Clark et al²⁸ (4.5%). Seven studies observed Pericardial LGE in none of their study population.^{10,11,14,17,20,22,24}

The rate of pericardial effusion in COVID-19 patients varied from 0%¹¹ to 58%²⁹ in 10 studies that evaluated its presence (Table 3).

Cardiac Function

As presented in Table 4, right ventricle ejection fraction (RVEF) mean in the COVID-19 group was significantly lower than that in the control group in four out of eight cohort studies.^{15,16,24,28} Mean/median left ventricle ejection fraction (LVEF) fell in the normal range in all studies; six studies also reported the number of cases with LVEF $<50\%$ ^{19,20,24,25,28,29}; while Fu et al²⁵ reported abnormal LVEF ($<50\%$) in 16 of 34 cases; the remained studies detected it in a maximum of two cases.

The study of Wang et al¹⁰ found that right ventricle (RV) and left ventricle (LV) strains significantly decreased in

COVID-19 with LGE compared to those without LGE and normal controls. Furthermore, Brito et al²⁹ found global longitudinal strain (GLS) < 16% (on echocardiography) only in COVID-19 patients with pericardial LGE.

However, Puntmann et al¹⁵ found that T1 and T2 had higher discriminatory values for COVID-19 related involvement than parameters of volume and EF.

Six out of nine studies measuring troponin level at the time of MRI found elevated level of this biomarker of cardiac injury in none of the participants.^{13,14,20,24,28,29} (Table 4).

Discussion

Included studies have reported different rates of cardiac MRI abnormalities in COVID-19 adult survivors; however, most of them, including those involving asymptomatic patients, found a notable number of patients with raised T1, T2, and/or myocardial LGE.

In the previous systematic review, Ojha et al³⁰ pooled data from 34 MRI studies (29 case reports, 3 case series, and 2 cohort studies) comprising 199 COVID-19 patients at different phases of the disease. Myocarditis was diagnosed in nearly 40% (80/199) of patients on cardiac MRI; and the common imaging findings, in order by frequency, were mapping abnormalities, edema, and LGE. However, their main findings' validity is questionable mainly due to the unreasonable pooling of the data from studies with different designs and population.³⁰

Varied rates of MRI abnormalities among studies may be explained by differences in the study populations in terms of past medical history (PMH) status, disease severity, follow-up duration, and presence of cardiac symptoms.

Elevated T2 is specific for myocardial edema,^{34,35} and elevated T1 may detect diffuse myocardial fibrosis and/or edema.³⁶ While elevated T1 and T2 simultaneously represent an active inflammatory process, isolated raised T1 in the absence of a raised T2 suggests residual diffuse myocardial damage.³⁷

In addition to T1 and T2, LGE indicates the existence of myocardial damage and allows the differentiation of ischemic from nonischemic injury.³⁸ In the included studies, myocardial LGE mainly had nonischemic patterns. Some patterns of LGE distribution in nonischemic myocardial injury, such as sub-epicardial and mid wall patterns, are commonly attributed to myocarditis.^{39,40} Noteworthy, the studies that included a higher percentage of patients with severe form of the disease found a higher rate of nonischemic LGE compared to others.^{9,10,15,21,22}

Included studies also observed a notable prevalence of pericardial involvement, including effusion and/or positive LGE, either isolated or along with myocardial involvement in COVID-19 patients.

Some studies observed LGE in the absence of edema, suggesting that fibrosis and scar may be permanent.²² Also, studies found evidence of increased ECV

(%), a marker of myocardial fibrosis,⁴¹ in some patients. Myocardial fibrosis has been proven to be an independent predictor of cardiac mortality in patients with inflammatory myocarditis.^{42,43}

Prognostic value of abnormal CMR findings in recovered COVID-19 is unknown. However, previous long-term follow-up of patients with suspected myocarditis revealed that abnormal cardiac MRI findings are a prognostic factor for poor outcomes.^{44,45} Gräni et al⁴⁵ found that the presence of mid-wall LGE (hazard ratio, HR [95%] confidence interval [CI]: 2.39 [1.54–3.69]), abnormal T2-weighted ratio more than 2.0 (defined as signal intensity [SI] ratio of myocardium/skeletal muscle, HR [95% CI]: 2.14 [1.30–3.52]), and ECV mean greater than 35% (HR [95% CI]: 3.38 [1.43–7.97]) all were associated with a higher rate of major adverse cardiac events (MACE).

Also, evidence of isolated nonischemic myocardial LGE at MRI can be a substrate for malignant arrhythmia and severe complications, such as sudden cardiac death.^{6,7,46}

Based on Lake Louise Criteria, abnormalities in at least two out of three of T1, T2, and LGE suggest the presence of active myocarditis.⁴⁷ Eight studies reported myocarditis based on Lake Louise criteria, and its rate varied from 0%²⁰ to 36%.⁴⁷

The presence of myocardial inflammation could have severe consequences without timely diagnosis and appropriate treatment.^{6,7}

Acute viral myocarditis could progress to chronic smoldering myocarditis and subsequently lead to heart failure.^{48,49} Compared to patients with myocardial involvement, a majority of patients with isolated pericardial involvement are more likely to experience a benign course.⁵⁰ Noteworthy, about 15%–30% of these patients may develop recurrent pericarditis or constrictive pericarditis.⁵¹

Some studies found presence of cardiac MRI surrogates of myocarditis in COVID-19 patients without symptoms at postacute phase of disease. At present, given the unknown clinical significance of these findings in asymptomatic general population, cardiac MRI screening is recommended to be limited to the research settings.⁵²

All nine studies focused on athletes found abnormal MRI findings in some patients.^{11,14,18,21,28,29} However, there is uncertainty about clinical significance associated with these observed abnormal CMR findings, especially among athletes with asymptomatic to mild COVID-19.^{53,54}

Daniels et al²⁷ found that primary cardiac MRI screening strategy resulted in a higher diagnostic yield for myocarditis compared to both symptom-driven and cardiac testing strategies. At present, primary CMR screening prior to return to play after COVID-19 infection remains a subject of much debate due to high prevalence of cardiac damage and fibrosis with unknown prognostic significance in endurance athletes, the poor diagnostic yield of acute myocardial inflammation, in

combination with expertise required for advanced cardiac MRI interpretation, costs, and burden on health care system.⁵⁴

In addition, Daniels et al²⁷ observed that cardiac MRI abnormalities (LGE, T2) resolved for some cases at repeat MRI, more frequently in cases with subclinical myocarditis rather than those with clinical MRI.

At present, the American College of Cardiology's Sports and Exercise Council have recommended the selective use of cardiac MRI in the case of detected abnormalities by a tiered approach based on the presence of symptoms, followed by electrocardiography (ECG), injury biomarkers, and echocardiography.⁵³

Most included studies showed that the RV and LV traditional morphological and functional parameters fell in the normal range in the COVID-19 patients; however, RVEF mean in the COVID-19 group was statistically lower than that in controls in four studies although the observed differences were mainly clinically nonsignificant. The findings of two studies suggest that COVID-19 patients with LGE may have RV/LV dysfunction, which could be detected by strain analysis rather than other conventional parameters.^{10,29} Abnormal strain can be explained by the presence of LGE lesions in the middle myocardium and/or sub-epicardium.⁵⁵

Eight out of 13 studies measuring biomarkers of ongoing inflammation found MRI abnormality in the absence of an elevated level of these biomarkers^{13,14,20,24,28,29}; however, Puntmann et al¹⁵ found a significant direct correlation between high-sensitivity troponin with the results of T1 and T2 mapping.

The exact mechanisms in which SARS-CoV-2 can lead to myocardial injury have remained unclear. However, viral involvement of cardiomyocytes and systemic inflammation may be the possible mechanisms responsible for the virus's cardiac sequels.⁵⁶

Limitations

Our included studies involved different populations of COVID-19 survivors, used different cut points for detecting abnormal MRI findings, and had variable follow-up periods that all may result in different rate of abnormal findings, preventing meta-analysis. Overall, they each had some limitations, including small sample sizes and the bias in selecting controls. In addition, none of included studies performed baseline cardiac MRI examination; In this regard, Raisi-Estabragh et al showed that pre-existing cardiac MRI abnormalities is associated with greater odds of SARS-CoV-2 positivity, independent of cardiovascular risk factors.⁵⁷ They concluded that cardiovascular involvement after COVID-19 may reflect pre-existing cardiac status rather than COVID-19-related cardiac abnormalities. Also, available evidence failed to provide information on correlation of detected cardiac MRI abnormalities with clinical outcomes at long term.

Conclusion

There are evidence of cardiac involvement, including edema, pericarditis, cardiac fibrosis, myocarditis, and contractile function impairment in COVID-19 survivors with a diverse spectrum of disease severity at the acute phase. As most studies included healthy young patients with asymptomatic or mild SARS-CoV-2 infection, these findings are concerning as the presence of cardiac injury may be underestimated and, hence, undermanaged in this group of patients. Larger, well-designed cohort studies are needed to confirm these findings and to assess their long-term clinical consequences.

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