■ ORIGINAL ARTICLE

A distinct septal pattern of late gadolinium enhancement specific for COVID-19-induced myocarditis: A multicenter cardiovascular magnetic resonance study

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Editorial
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ABSTRACT

Background: COVID-19 is a great medical challenge as it provokes acute respiratory distress and has pulmonary manifestations and cardiovascular (CV) consequences.

Aims: This study compared cardiac injury in COVID-19 myocarditis patients with non-COVID-19 myocarditis patients.

Methods: Patients who recovered from COVID-19 were scheduled for cardiovascular magnetic resonance (CMR) owing to clinical myocarditis suspicion. The retrospective non-COVID-19 myocarditis (2018–2019) group was enrolled (n = 221 patients). All patients underwent contrast-enhanced CMR, the conventional myocarditis protocol, and late gadolinium enhancement (LGE). The COVID study group included 552 patients at a mean (standard deviation [SD]) age of 45.9 (12.6) years.

Results: CMR assessment confirmed myocarditis-like LGE in 46% of the cases (68.5% of the segments with LGE <25% transmural extent), left ventricular (LV) dilatation in 10%, and systolic dysfunction in 16% of cases. The COVID-19 myocarditis group showed a smaller median (interquartile range [IQR]) LV LGE (4.4% [2.9%–8.1%] vs. 5.9% [4.4%–11.8%]; *P* <0.001), lower LV end-diastolic volume (144.6 [125.5–178] ml vs. 162.8 [136.6–194] ml; *P* <0.001), limited functional consequence (left ventricular ejection fraction, 59% [54.1%–65%] vs. 58% [52%–63%]; *P* = 0.01), and a higher rate of pericarditis (13.6% vs. 6%; *P* = 0.03) compared to non-COVID-19 myocarditis. The COVID-19-induced injury was more frequent in septal segments (2, 3, 14), and non-COVID-19 myocarditis showed higher affinity to lateral wall segments (*P* <0.01). Neither obesity nor age was associated with LV injury or remodeling in subjects with COVID-19 myocarditis.

Conclusions: COVID-19-induced myocarditis is associated with minor LV injury with a significantly more frequent septal pattern and a higher pericarditis rate than non-COVID-19 myocarditis.

Key words: CMR, COVID-19, myocarditis, myocardial injury, LGE

WHAT'S NEW?

To our knowledge, this large prospective multicenter study, which assessed consecutive patients with suspected COVID-19 myocarditis, is the only study comparing those findings with a retrospective non-COVID-19 myocarditis group. Myocardial injury related to COVID-19 was confirmed in half of the cases and was associated with preserved cardiac function in most cases. COVID-induced myocarditis showed a significantly smaller myocardial area with a lesser transmural extent, higher left ventricular ejection fraction, but more frequent pericarditis than non-COVID-19 myocarditis. Finally, COVID-induced myocarditis showed significantly higher affinity to left ventricular septal segments, and non-COVID-19 myocarditis was more prevalent in left ventricular lateral wall segments.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for the coronavirus disease-19 (COVID-19) global pandemic. According to the World Health Organization, over 280 million people globally were COVID-19-positive at the end of December 2021 [1]. Most cases were mild or moderate, and the respiratory system was the primary disease target for the virus [2]. However, primary studies suggest that myocardial injury is associated with COVID-19 and provided various data on the prevalence and severity of the symptoms [3, 4]. There is considerable heterogeneity among studies, which originated mainly from small study groups, various clinical characteristics, and different times between the infection and study evaluation, hindering the process of arriving at clear conclusions [5].

Moreover, obesity, immune system abnormalities, and older age were some of the important risk factors for COVID-19 [6]. However, whether there is a correlation between obesity and severity of COVID-19-related myocarditis is unknown.

Given the high prevalence of obesity and large numbers of infected patients, a considerable group of patients with mild cardiac injury would require cardiovascular screening. Cardiovascular magnetic resonance (CMR) is a comprehensive imaging tool that delivers accurate results and reproducibility in evaluating cardiac chambers, function, and myocardial injury [7]. CMR examination is a gold standard for patients recovering from COVID-19 and with clinical suspicion of myocardial injury.

This study aimed to evaluate cardiac injury in patients with suspected COVID-19 myocarditis compared to non-COVID-19 myocarditis. In addition, we verified the correlation between obesity and SARS-CoV-2 myocarditis.

METHODS

Study patients

All the study patients recovered from COVID-19, and they were scheduled for CMR (April 2020–October 2021) due to cardiac symptoms and suspected myocardial injury. The inclusion criteria were: (1) SARS-CoV-2 infection previously confirmed by a reverse transcription polymerase chain reaction (RT-PCR) swab test; (2) suspected myocarditis related to SARS-CoV-2 infection as the main indication for CMR.

The exclusion criteria were as follows: (1) SARS-CoV-2 infection diagnosed only on the basis of clinical symptoms or other means that RT-PCR swap test; (2) a history of myocardial infarction or previous myocarditis; (3) a history of significant valve diseases, congenital heart diseases, cardiomyopathy or previous cardiac surgery; (4) contraindication to gadolinium contrast; (5) suboptimal CMR image quality due to arrhythmia or patients' incompliance. The severity of COVID-19 was classified according to the guidelines [8].

Data on the control group of non-COVID-19 myocarditis were collected retrospectively using a CMR database in each of the CMR center. The search included all the consecutive patients scheduled for CMR due to myocarditis, which was performed between January 2018 and December 2019. Patients with the following chronic cardiovascular (CV) diseases were excluded: a history of myocardial infarction, significant valve diseases, congenital heart diseases, cardiomyopathy, or previous cardiac surgery.

This was a multicenter, observational study with a prospective enrollment of the study group (COVID-19) and a retrospective enrollment of the control group performed in 5 CMR centers covering different regions in Poland. All the CMR centers have cardiac teams experienced in CMR and research leaders in the Board of the Polish Cardiac Society Section for Cardiac CMR and Computed Tomography. The study was conducted in accordance with the principles of the Declaration of Helsinki and the local ethics committee.

Clinical characteristics

Diabetes (DM) was reported in patients with prior diagnosis or abnormal fasting plasma glucose concentration ($\geq$126 mg/dl) or HbA1c ($\geq$6.5%) or 2-hour post-load plasma glucose ($\geq$200 mg/dl) in the case of discrepancies [9, 10]. Dyslipidemia was determined based on plasma lipid levels or prior diagnosis and current treatment [11]. The diagnosis of hypertension was confirmed by taking office blood pressure or prior diagnosis and current treatment [11]. Obesity was classified according to body mass index (BMI, body mass [kg]/height [m²]) as normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obesity ($\geq$30.0 kg/m²): class 1 (30.0–34.9 kg/m²), class 2 (35.0–39.9 kg/m²), and class 3 ($\geq$40.0 kg/m²). Chronic kidney disease was determined based on the estimated glomerular filtration rate (<60 ml/min/1.73 m²) or prior diagnosis and treatment.

Coronary artery disease (CAD) was included in the clinical characteristics in patients with prior diagnosis, which was based on either coronary angiography or computed tomography angiography. Chronic pulmonary disease was reported in individuals with prior diagnosis and/or specific pharmacotherapy.

Cardiovascular magnetic resonance imaging

All the CMR images were obtained on the 1.5T systems: GE Optima MR450w (GE Healthcare, Waukesha, WI, US), Magnetom Aera (Siemens, Erlangen, Germany), Magnetom Avanto (Siemens, Erlangen, Germany) with dedicated phased array cardiac coils or body matrix coil. The CMR studies were ECG-gated and based on routine clinical protocols according to the guidelines [12, 13]. The CMR protocol included: (1) conventional non-contrast multi-planar cine acquisitions (steady state free precession, SSFP) for functional sequences; (2) T2-weighted triple inversion recovery (short tau inversion recovery, STIR) for edema imaging; (3) late gadolinium enhancement (LGE) for viability imaging obtained 10–15 minutes after contrast injection (0.1 mmol/kg of body weight of Gadovist). Functional sequences consisted of a stack of short-axis views from base to apex and 3 long-axis views (2-chamber view, 4-chamber view, and left outflow track view). LGE acquisitions were based on the same planes as the short- and long-axis cines. The STIR images were based on the same imaging planes as the long-axis cines and the short-axis planes covering LV.

All the CMR images were assessed by experienced teams in each of the centers (5–20 years of experience in CMR). Cardiac volumes, mass, and function (left [LV] and right ventricular [RV] end-diastolic and end-systolic volumes [V]; ejection fraction [EF]; mass [M]) were analyzed using dedicated commercial software. All the volumes and mass were indexed to body surface area (BSA) [14]. Afterward, individual LV parameters indexed to BSA were interpreted according to the normal LV reference values adjusted for sex and age, which were presented in the European Association of Cardiovascular Imaging guidelines [15].

The LV myocardium was divided into 17 segments as recommended by the American Heart Association [16]. The contractility of each of the LV segments was assessed as normal (1 point), hypokinetic (2 points), akinetic (3 points), or dyskinetic (4 points). Afterward, the wall motion score index (WMSI) [17] was calculated as the sum of the points for all segments divided by 17.

Myocardial edema was defined as an abnormal ratio (>2.0) between myocardial to skeletal muscle signal intensity on STIR [12, 13]. The presence, location, distribution, and severity of LGE were assessed in all patients. Finally, the total percentage of LV LGE was manually calculated in a semi-quantitative manner using short-axis slices covering all 17 segments of the LV.

Myocarditis-like injury was reported according to the CMR expert recommendations [12, 13] (Lake Louise Criteria), and it also included typical non-ischemic mid-wall and/or subepicardial LGE. Pericarditis was reported based on gadolinium uptake within the pericardium (LGE) and any of the following: pericardial thickening, edema on STIR imaging, or the presence of pericardial effusion.

Statistical analysis

The distribution of variables was tested for normality with the Kolmogorov-Smironov test. Numerical variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), and categorical variables were presented as numbers and percentages. Baseline clinical parameters and the measures were compared between subgroups using t-tests for normally distributed continuous variables (unpaired Student's t-test) or the Mann-Whitney test if the distribution of the samples was not normal. The χ^2 test was used to test the differences between the proportions. Associations between numerical variables were assessed using Pearson or Spearman correlation. The cut-off values of the baseline clinical parameters for prediction of myocardial injury or dysfunction were determined in receiver operating characteristic (ROC) curve analysis. A P-value <0.05 was considered statistically significant. Statistical analysis was undertaken using Medcalc software (version 19.1, Osten, Belgium).

RESULTS

Study groups

COVID study group

A total of 552 patients who recovered from COVID-19 were enrolled in the COVID-19 study group. Median time between scheduled CMR and the disease onset was 12 (8–20) weeks. The clinical indication for CMR was a suspicion of COVID-19-related myocardial injury. The COVID-19 study group included mostly middle-aged patients (age 45.9 [12.6] years old; 52% females) with obesity (25%), hypertension (25%), and diabetes (6%). All the studies were performed within 10 months from the COVID-19 onset (88% within 7 months), and the infection was mostly moderate (Table 1). There were 3 cases of cardiogenic shock, 3 cases of acute pulmonary embolism, 2 cases of cerebral infarction, and 1 case of miscarriage related to the acute phase of COVID-19.

We found dilatation (10%) and moderate (11%) or severe (5%) systolic dysfunction of the LV with wall motion abnormalities (13.5%) in COVID-19 patients. We also found dilatation (4.7%) and dysfunction of the RV (EF <45%) in 37 cases (6.7%). Moreover, half of the CMR studies (n = 256 patients; 46%) revealed a myocarditis-like injury (LGE) in the LV myocardium, including 41 patients (7.5%) with myocardial edema (Table 2). Finally, 3 patients had only myocardial edema (no LGE), and one patient was found to have a subendocardial scar within the inferior wall (Figure 1).

Table 1. Clinical characteristics of the study groups

	COVID-19 group (n = 552)	Non-COVID-19 group (n = 221)	P-value
Age, years, mean (SD)	45.9 (12.6)	39.3 (14.6)	<0.001
Female/male sex, n (%)	285 (52) / 267 (48)	81 (36) / 140 (64)	0.01
Diabetes, n (%)	35 (6)	15 (7)	0.6
Dyslipidemia, n (%)	41 (7)	24 (11)	0.07
Hypertension, n (%)	140 (25)	45 (25)	1.0
Coronary artery disease, n (%)	21 (3.8)	15 (7)	0.08
Chronic pulmonary diseases, n (%)	41 (7.5)	12 (5.5)	0.32
Body mass index, kg/m^2, mean (SD)	27.2 (4.9)	26.3 (4.5)	0.3
Normal weight, n (%)	199 (36)	61 (27)	0.01
Overweight, n (%)	216 (39)	124 (56)	<0.001
Obesity, n (%)	137 (25)	36 (16)	<0.01
Chronic kidney disease, n (%)	2 (0.4)	2 (1)	0.3
Atrial fibrillation, n (%)	12 (2.2)	7 (3)	0.51
COVID-19			
Confirmed by PCR test, n (%)	552 (100)		
Disease onset and CMR, weeks, mean (SD)	15 (9)		
Moderate, n (%)	416 (75)		
Severe, n (%)	133 (24)		
Critical, n (%)	3 (0.5)		
Cardiovascular magnetic resonance			
Myocardial injury			
Myocarditis			
LV LGE, n (%)	256 (46)	200 (90)	<0.001
Pericardium			
Pericardial effusion, n (%)	73 (13.2)	48 (21)	0.01
Pericarditis, n (%)	40 (7)	12 (5.5)	0.44
Pleural effusion, n (%)	16 (2.8)	42 (19)	0.001

Abbreviations: BSA, body surface area; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; PCR, polymerase chain reaction; RV, right ventricle; SD, standard deviation

In the patients who recovered from COVID-19, myocardial LGE was found more often in males (69% vs. 56%; *P* <0.001), but it was not related to age (45.6 [11.8] years vs. 46.3 [13.5] years; *P* = 0.5) or BMI (26.9 [5] kg/m^2 vs. 27.1 [4.9] kg/m^2; *P* = 0.6).

The median number of injured LV segments was 3 (2–4), which was 4.4% (2.9%–8.1%) of the LV mass. The majority of injured segments (68%) showed only a mild degree of LGE (<25% transmural extent), and the most frequently diseased LV segments were: 2, 3, and 4 (Figure 2). Finally, every fifth patient showed a pericardial effusion, and co-existing pericarditis was found in 35 patients (13.6%) with predominantly mild manifestations.

The patients' age, obesity, body mass index (BMI), or time from the COVID-19 onset were not associated with total LGE mass (data not shown). Time of CMR from the onset of the disease was similar between males and females (12 [8–20] vs. 12 [8–20]; *P* = 0.1), and it showed only a weak association with LV end-diastolic volume (EDV)//BSA (r = −0.2; *P* = 0.01), LV mass/BSA (r = −0.3; *P* <0.001), RV EDV/BSA (r = −0.2; *P* <0.01), but not with any other CMR parameters, including LVEF or RVEF. As expected, patients with pericarditis confirmed on CMR showed larger LGE area compared to patients without pericarditis (7.35% [4.4%–23.5%] vs. 4.4% [2.9%–7.3%]; *P* <0.0001).

Among baseline parameters, LVEF ≤56% showed a statistical trend (area under the curve [AUC], 0.560; sensitivity, 37%; specificity, 80%; *P* = 0.07), and WMSI >1.0 (AUC, 0.589; sensitivity, 25%; specificity, 93%; *P* <0.01) was the predictor of myocardial injury (LGE).

Non-COVID control group

A total of 221 consecutive patients were included in the control group with non-COVID-19 myocarditis (age, 39.3 [14.6] years; 64% males). The clinical characteristics and main CMR parameters in comparison with the COVID study group are presented in Table 1. In brief, the non-COVID group included slightly younger patients, mostly males, more overweight individuals, but fewer with obesity; there were no other clinical differences. However, CMR confirmed myocarditis-like LGE at a significantly higher rate in the control group (90% vs. 46%; *P* <0.001), with a higher rate of pericardial (21% vs. 13%; *P* = 0.01) and pleural (19% vs. 2.8%; *P* = 0.001) effusions.

The subgroups of COVID-19 and non-COVID-19 patients with myocarditis confirmed on CMR are presented in Table 2. The total LV LGE and the number of involved segments were significantly smaller, and the severity of segmental injury (transmural extent) was lesser in COVID-19-myocarditis compared to non-COVID-19 myocarditis, except for the

Table 2. Clinical characteristics of the studied patients with late gadolinium enhancement

	COVID-19 LGE(+) (n = 256)	Non-COVID-19 LGE (+) (n = 200)	*P*-value
Age, years, mean (SD)	46.3 (13.5)	38.8 (14.7)	<0.001
Female/male sex, n (%)	113 (44) / 143 (56)	64 (32) / 136 (68)	<0.01
Diabetes, n (%)	24 (9)	14 (6)	0.3
Dyslipidemia, n (%)	25 (10)	19 (9)	0.7
Hypertension, n (%)	59 (23)	58 (29)	0.15
Coronary artery disease, n (%)	10 (6.5)	13 (6)	0.8
Chronic pulmonary diseases, n (%)	13 (5)	10 (4.5)	0.8
Body mass index, kg/m², mean (SD)	27.2 (4.8)	26.1 (4.7)	0.01
Obesity, n (%)	60 (23.4)	36 (18)	0.12
Chronic kidney disease, n (%)	2 (0.8)	3 (1.3)	0.6
Atrial fibrillation, n (%)	6 (2.3)	7 (3.1)	0.6
Cardiovascular magnetic resonance			
Left and right ventricular remodeling			
LV EDV, median (IQR)	144.6 (125.5–178)	162.8 (136.6–194)	<0.001
LV EDV/BSA, ml/m², median (IQR)	75.8 (62–86.3)	84.2 (71.6–96)	<0.0001
Dilated LV, n (%)	25 (10)	39 (19.5)	0.08
LV mass, g, median (IQR)	117 (94–142)	133.1 (111–143.3)	<0.0001
LV mass/BSA, g/m², median (IQR)	54.4 (42–64)	66.8 (54.2–75.5)	<0.0001
LV hypertrophy, n (%)	9 (3.5)	13 (6.5)	0.25
LVEF, %, median (IQR)	59 (54.1–65)	58 (52–63)	0.01
LVEF ≥50%, n (%)	215 (84)	157 (78)	0.2
LVEF 40%–49%, n (%)	28 (11)	21 (10.5)	0.7
LVEF <40%, n (%)	13 (5)	22 (11)	<0.01
LV WMSI, median (IQR)	1 (1–1)	1 (1–1.2)	<0.001
Wall motion abnormalities, n (%)	59 (23)	74 (37)	<0.01
RV EDV, ml, median (IQR)	135.5 (116–165)	139 (122–168)	0.1
RV EDV/BSA, median (IQR)	68.4 (56.4–80)	70.1 (62.1–82)	0.1
Dilated RV, n (%)	12 (4.7)	18 (9)	0.3
RVEF, %, median (IQR)	55 (50–61)	54 (49–59.7)	0.25
Myocardial injury			
Myocarditis			
LV LGE, n (%)	256 (100)	200 (100)	
Nb of LV segments with LGE, median (IQR)	3 (2–4)	4 (2–5.5)	<0.01
Total LGE in LV mass, %, median (IQR)	4.4 (2.9–8.1)	5.9 (4.4–11.8)	<0.001
Patients with LGE in LV segment, n (%)			
51%–75%	20 (7.8)	20 (10)	0.02
26%–50%	61 (24)	67 (33.5)	<0.001
≤25%	174 (68)	109 (54.5)	<0.0001
LV edema, n (%)	42 (16.4)	75 (37.5)	0.05
Pericardium			
Pericardial effusion			
<10 mm, n (%)	40 (15.5)	38 (19)	0.32
≥10 mm, n (%)	4 (1.5)	6 (3)	0.56
Pericarditis, n (%)	35 (13.6)	12 (6)	0.03
Severity of LGE in the pericardium			
Mild, n (%)	29 (11.3)	7 (3.5)	<0.01
Moderate, n (%)	6 (2.3)	4 (2)	0.83
Severe, n (%)	0	0	

Abbreviations: BSA, body surface area; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; PCR, polymerase chain reaction; RV, right ventricle; SD, standard deviation

transmural injury (0.4 vs. 2 %; *P* = 0.09) (Table 2). There was a trend toward a less frequent LV edema reported in the COVID-19 subgroup (16.4% vs. 37.5%; *P* = 0.05). Moreover, patients with non-COVID-19 myocarditis demonstrated a significantly lower LVEF with a doubled rate of significant LV dysfunction (LVEF <40%), more frequent LV wall motion abnormalities, and LV remodeling compared to

the post-COVID-19 patients (Table 2). Nevertheless, COVID myocarditis resulted in a higher rate of pericarditis (13.6% vs. 6%; *P* = 0.03), which was mostly mild (11.3% vs. 3.5%; *P* <0.01), with a small pericardial effusion <10 mm in both groups. Finally, the distribution of LGE within LV showed significant differences between both groups (Figure 2). COVID-19-induced myocarditis was significantly more fre-
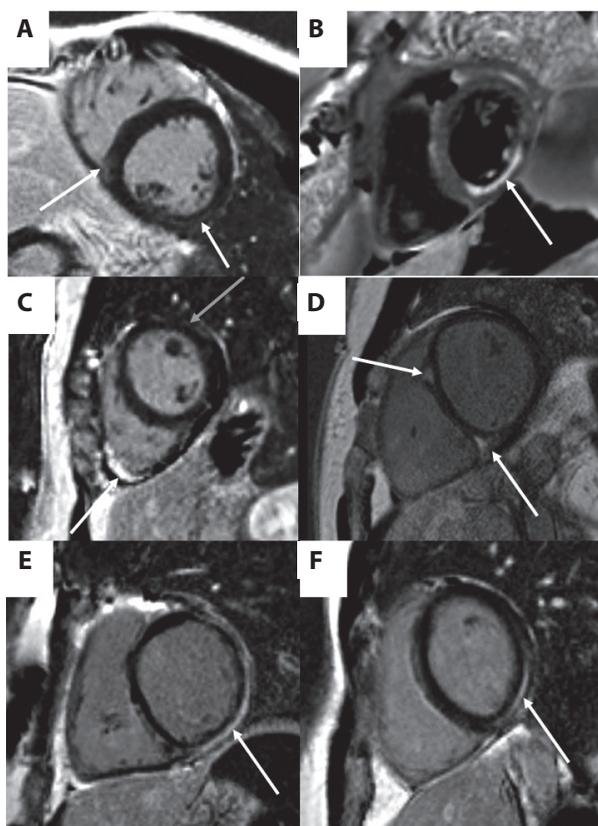
Figure 1. Myocardial injury (late gadolinium enhancement [LGE]) after COVID-19 (**A**–**D**) and after non-COVID-19 inflammation (**E**–**F**). **A.** Intramyocardial injury (arrows) on late gadolinium enhancement sequence in a 23-year-old male with documented myocarditis during COVID-19 (arrows). **B.** Subendocardial scar on dark blood late gadolinium enhancement sequence in a 64-year-old male (arrow). **C.** Pericarditis (white arrow) with pericardial effusion and myocardial injury (grey arrow) on late gadolinium enhancement sequence (arrows) in a 54-year-old female. **D.** Intramyocardial injury on late gadolinium enhancement sequence in a 40-year-old male (arrows). **E** and **F.** Subepicardial and intramyocardial injuries in late gadolinium enhancement sequence

quent in the 2nd (37% vs. 28%; $P = 0.04$), 3rd (44.1% vs. 30.5%; $P < 0.01$), and 14th (11.7% vs. 6%; $P = 0.03$) segments, and non-COVID-19 cases were more frequent in the lateral wall: 5th (36% vs. 57%; $P < 0.01$), 6th (18% vs. 32%; $P < 0.01$), 11th (19% vs. 41.5%; $P < 0.001$), and 12th (16.8% vs. 27%; $P < 0.01$). Moreover, post-COVID-19 patients with obesity showed a significantly more frequent injury within the 3rd LV segment compared to non-obese post-COVID-19 cases (53.5% vs. 39%; $P = 0.04$).

There was no difference in the LV LGE area between obese and non-obese patients in the COVID-19 group (4.4% [2.9%–10.3%] vs. 4.4% [3%–7.35%]; $P = 0.1$). There was also no difference in LV LGE between obese and non-obese individuals (8.1% [4.4%–14.7%] vs. 5.8% [2.9%–11.8%]; $P = 0.18$) in the non-COVID-19 group. Finally, there was a weak association between BMI and LV LGE in this subgroup ($r = 0.15$; $P = 0.04$)

In the non-COVID-19 subgroup, the patients' age showed a weak association with total LV LGE ($r = 0.25$; $P < 0.01$) and WMSI ($r = 0.35$; $P < 0.001$).

DISCUSSION

To the best of our knowledge, this is currently the largest prospective multicenter study assessing consecutive patients with suspected COVID-19-induced myocarditis and the only study comparing those findings with a retrospective non-COVID-19 myocarditis group. First, myocardial injury was confirmed in half of the patients despite their middle age and mostly a moderate infection. Second, COVID-19-induced myocarditis was in most cases associated with preserved LV and RV systolic function. Third, COVID-19-induced myocarditis revealed a significantly smaller myocardial injury (LGE) with a lesser transmural extent and higher LV EF but more frequent pericarditis
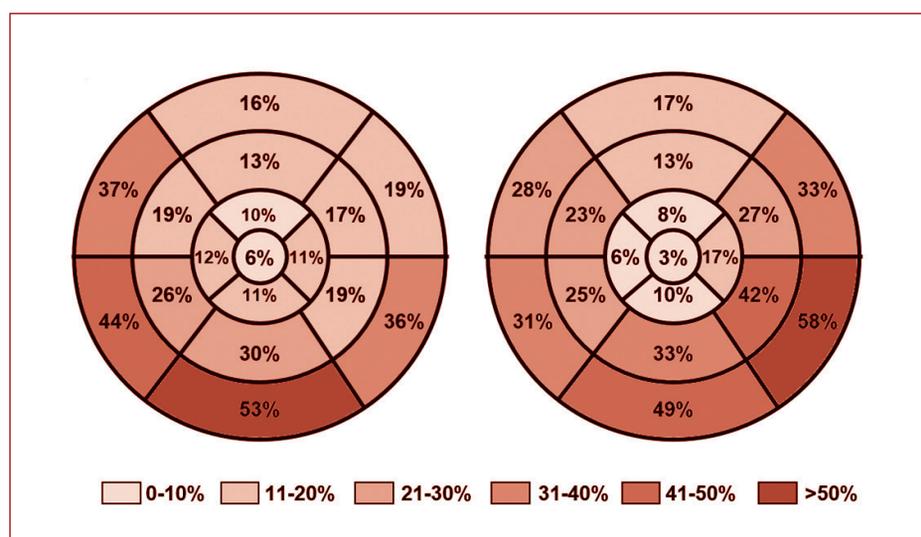

Figure 2. Bull's eye plots showing location and distribution of late gadolinium enhancement according to the 17-segment AHA (American Heart Association 17-segment model) rates of injured segments in patients with COVID-19-related myocarditis (**A**) and non-COVID-19 myocarditis (**B**)

than non-COVID-19 myocarditis. Finally, COVID-19-induced myocarditis showed higher affinity to LV septal segments, and non-COVID-19 myocarditis was more prevalent in LV lateral wall segments.

COVID-19 and CMR

The ongoing pandemic and millions of confirmed cases provided a growing body of evidence on COVID-19-related cardiovascular injury. However, this is mainly based on small and heterogenous studies [5]. The rate of abnormal CMR results in post-COVID-19 patients found in our study was consistent with meta-analyses of smaller studies [5, 18]. Up to 60% of the study patients were found to have at least one or more abnormalities on CMR depending on the time from the onset and severity of the disease [5, 18–21]. Huang et al. [19] found that half of the patients assessed with CMR had abnormal myocardial edema and/or LGE. The myocardial injury did not affect LV volumes or systolic function compared to healthy controls. This study showed a decrease in RV functional parameters during an early post-COVID-19 period (first 2 months). Although Kotecha et al. [20] found that half of the study patients showed a myocardial injury, every fifth patient showed ischemic LGE. However, the exact time of coronary scar and its correlation with COVID-19 is unknown.

Moreover, one-third of the patients had a severe clinical manifestation of the ventilatory disorder. A limited functional consequence was observed despite myocardial injury. Another study by Puntmann et al. [21] reported a higher rate of myocarditis on CMR (60%), irrespective of the clinical manifestation or time from acute COVID-19. However, lower rates of post-COVID-19 myocardial injury were also reported in other studies [5, 18, 22]. For obvious reasons, no studies assessed acute myocardial injury in CMR patients with severe COVID-19.

Nevertheless, an autopsy study confirmed myocarditis as the cause of death only in 4% of patients with COVID-19, which is in line with our study showing a relatively high prevalence of any myocardial injury (LGE) and lower rates of LV systolic dysfunction. Moreover, LV wall motion abnormalities (WMA) were reported in only one in four [23%] patients with COVID-19-induced myocarditis. Therefore, despite using high-quality CMR images, the baseline WMA showed low sensitivity and predictive value for myocardial injury (LGE).

Our study also showed preserved RV systolic function and normal RV volume in most cases, consistent with previous studies [19–22]. The right heart is a passive conduit, dilated in an earlier phase of COVID-19.

Our non-COVID-19 group showed a higher rate of LV dilatation, systolic dysfunction, and wall motion abnormalities, resulting from more severe LV injury. We failed to show that obesity was associated with the presence, severity, and structural or functional abnormalities in COVID-19-induced myocarditis. This seems to be a feature of COVID-19 myocarditis important for clinical practice.

Finally, novel CMR techniques, including mapping and strain, showed a COVID-19-related myocardial injury, but the additional data were mostly consistent with LGE-based injury [20, 22, 23].

Septal LGE pattern specific for COVID-19

Based on the outcomes of our study, COVID-19-induced myocarditis was located mainly in LV septal segments, especially in patients with obesity. Most previous studies confirmed only a non-ischemic pattern of LGE as the main finding [5], and small studies provided divergent findings suggesting the most frequent locations of COVID-19-related injury [18, 19, 22]. This was the first study providing novel data regarding the most frequent COVID-related injury compared to non-COVID-19 myocarditis. We found that COVID-19-induced myocarditis is more specific to inferospetal and anterospetal segments than non-COVID myocarditis, and it is usually found in basal or mid-cavity lateral segments [24]. Higher affinity of SARS-CoV-2 to septal segments increases the risk of injury within the conduction system. QT prolongation and atrioventricular or ventricular block were reported in 12% and 13% of COVID-19 patients [25]. Moreover, an LGE septal location was more frequent in myocarditis (unrelated to COVID-19), which may result in heart failure and arrhythmias in the following months or years [24]. It was significantly associated with malignant ventricular arrhythmias [26] and left bundle branch block (LBBB) [25]. Finally, a new onset LBBB results in LV dyssynchrony and may lead to LV systolic dysfunction [27]. Myocardial LGE is clinically equal to myocardial injury in several cardiac conditions, which include myocarditis [28]. LGE is a well-evidenced independent predictor of cardiac and all-cause mortality [29, 30]. In addition, LGE plays a role in the pathophysiology of dilated cardiomyopathy [31, 32]. Future studies should assess the long-term consequence of LGE on LV dilatation and/or dysfunction in COVID-19-induced myocarditis. Given the mean age of study patients, even a mild residual myocardial injury plays a role in progression to cardiomyopathy, heart failure, ventricular arrhythmias, or even sudden cardiac death.

COVID-19 and myocardial injury

The main mechanisms of COVID-19 myocardial injury include a direct viral myocardial inflammation through angiotensin-converting enzyme 2 receptors or an indirect injury induced by a high inflammatory burden and an overexpressed immune response [33, 34]. Endomyocardial biopsy in patients with severe active myocarditis showed active lymphocytic inflammation with no evidence of viral genome [21]. An autopsy study confirmed myocardial infiltration and mononuclear inflammatory cells in patients who died from COVID-19 [35]. SARS-CoV-2 is the cause of endothelial dysfunction and thrombotic complications, which is another potential pathomechanism of myocardial

injury [36, 37]. However, we barely found any subendocardial scars in the COVID-19 study group.

COVID-19 and pericarditis

Seven patients in our study group who recovered from COVID-19 with myocarditis demonstrated mild pericarditis. We found that it was related to a larger area of myocardial injury, which seems understandable. Similar data were found in other studies, with differences most likely depending on clinical disease severity [19–22]. However, an unexpectedly high pericardial (27%) and low myocardial involvement (16%) were reported in young athletes with asymptomatic or mild COVID-19 [38], suggesting that young convalescents may be more prone to pericarditis. Our study patients were older, and we found a higher rate of pericarditis in patients with COVID-19-induced myocarditis than in non-COVID-19 myocarditis. The pathomechanism, which includes either a direct viral infection or generalized COVID-19 multisystemic inflammatory syndrome, remains unclear. However, we observed no pleural effusions in those individuals. Future research is required to explain the clinical effects of angiogenesis and an increased activity of the angiotensin converting enzyme receptor in pericardial mesothelial cells related to SARS-CoV-2 infection [39, 40].

Limitations

We collected data from middle-aged patients with mostly moderate clinical presentations of COVID-19. Our study participants do not reflect a complete spectrum of the disease. However, the study group was recruited from consecutive patients referred for CMR, and a postmortem study showed a small number of descendants who died from COVID-19-related myocarditis [26]. Second, we did not have lab markers of cardiac injury or natriuretic peptides for our study patients as they were mostly not hospitalized during the SARS-CoV-2 infection. We also did not have baseline CMR to verify the exact time of myocardial injury, which is similar to the outcomes of other studies. In addition, we did not have data to evaluate the clinical severity of non-COVID-19 myocarditis in the control group.

Moreover, we do not present CMR mapping as it was unavailable at all CMR centers. Still, T1/T2/ECV CMR mapping and LV strain were mostly consistent with conventional CMR sequences [20, 22, 23, 41]. Finally, all the study patients had clinical indications for CMR, which constitutes a potential selection bias.

CONCLUSIONS

Our large prospective multicenter study confirmed COVID-19-induced myocarditis in nearly half of the patients who recovered from COVID-19. COVID-19-related myocardial injury and functional sequelae were smaller than in the non-COVID-19 myocarditis cases.

This is the first study to show that septal LGE is more specific for COVID-19-induced injury, which may result in LV dyssynchrony and systolic dysfunction or arrhythmia. A regular follow-up of post-COVID-19 patients should verify the impact of a residual injury on clinical outcomes.

Article information

REFERENCES

1. WHO coronavirus disease (COVID-19) dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/. [Access: January 2, 2023].
2. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020; 20(4): 425–434, doi: 10.1016/S1473-3099(20)30086-4, indexed in Pubmed: 32105637.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497–506, doi: 10.1016/S0140-6736(20)30183-5, indexed in Pubmed: 31986264.
4. Wang D, Hu Bo, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061–1069, doi: 10.1001/jama.2020.1585, indexed in Pubmed: 32031570.
5. Kim JY, Han K, Suh YJ. Prevalence of abnormal cardiovascular magnetic resonance findings in recovered patients from COVID-19: a systematic review and meta-analysis. J Cardiovasc Magn Reson. 2021; 23(1): 100, doi: 10.1186/s12968-021-00792-7, indexed in Pubmed: 34479603.
6. Petrakis D, Margină D, Tsarouhas K, et al. Obesity a risk factor for increased COVID19 prevalence, severity and lethality (Review). Mol Med Rep. 2020; 22(1): 9–19, doi: 10.3892/mmr.2020.11127, indexed in Pubmed: 32377709.
7. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update : Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. J Cardiovasc Magn Reson. 2020; 22(1): 19, doi: 10.1186/s12968-020-00610-6, indexed in Pubmed: 32160925.
8. National Institutes of Health. COVID-19 treatment guidelines. Available online: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum. [Access: January 1, 2023].
9. World Health Organization (WHO) Consultation. Definition and diagnosis of diabetes and intermediate hyperglycaemia. 2006. Available online: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. [Access: January 2023].
10. World Health Organization (WHO), Abbreviated report of aWHO consultation. Use of glycated hemoglobin (HbA1c) in the diagnosis if diabetes mellitus. 2011. Available online: http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/. Access: January 2023].
11. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37(29): 2315–2381, doi: 10.1093/eurheartj/ehw106, indexed in Pubmed: 27222591.
12. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recom-

mendations. J Am Coll Cardiol. 2018; 72(24): 3158–3176, doi: 10.1016/j.jacc.2018.09.072, indexed in Pubmed: 30545455.

13. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson. 2020; 22(1): 17, doi: 10.1186/s12968-020-00607-1, indexed in Pubmed: 32089132.

14. Du Bois D, Du Bois EF. A to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916; 17: 863–871.

15. Maceira AM, Prasad SK, Khan M, et al. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2006; 8(3): 417–426, doi: 10.1080/10976640600572889, indexed in Pubmed: 16755827.

16. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002; 105(4): 539–542, doi: 10.1161/hc0402.102975, indexed in Pubmed: 11815441.

17. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989; 2(5): 358–367, doi: 10.1016/s0894-7317(89)80014-8, indexed in Pubmed: 2698218.

18. Petersen SE, Friedrich MG, Leiner T, et al. Cardiovascular Magnetic Resonance for Patients With COVID-19. JACC Cardiovasc Imaging. 2022; 15(4): 685–699, doi: 10.1016/j.jcmg.2021.08.021, indexed in Pubmed: 34656482.

19. Huang L, Zhao P, Tang D, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020; 13(11): 2330–2339, doi: 10.1016/j.jcmg.2020.05.004, indexed in Pubmed: 32763118.

20. Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J. 2021; 42(19): 1866–1878, doi: 10.1093/eurheartj/ehab075, indexed in Pubmed: 33596594.

21. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265–1273, doi: 10.1001/jamacardio.2020.3557, indexed in Pubmed: 32730619.

22. Wang H, Li R, Zhou Z, et al. Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2021; 23(1): 14, doi: 10.1186/s12968-021-00710-x, indexed in Pubmed: 33627143.

23. Urmeneta Ulloa J, Martínez de Vega V, Salvador Montañés O, et al. Cardiac magnetic resonance in recovering COVID-19 patients. Feature tracking and mapping analysis to detect persistent myocardial involvement. Int J Cardiol Heart Vasc. 2021; 36: 100854, doi: 10.1016/j.ijcha.2021.100854, indexed in Pubmed: 34368419.

24. Di Bella G, Camastra G, Monti L, et al. Left and right ventricular morphology, function and late gadolinium enhancement extent and localization change with different clinical presentation of acute myocarditis Data from the ITAlian multicenter study on MYocarditis (ITAMY). J Cardiovasc Med (Hagerstown). 2017; 18(11): 881–887, doi: 10.2459/JCM.0000000000000574, indexed in Pubmed: 28915139.

25. Deluigi CC, Ong P, Hill S, et al. ECG findings in comparison to cardiovascular MR imaging in viral myocarditis. Int J Cardiol. 2013; 165(1): 100–106, doi: 10.1016/j.ijcard.2011.07.090, indexed in Pubmed: 21885134.

26. Hooper JE, Padera RF, Dolhnikoff M, et al. A Postmortem Portrait of the Coronavirus Disease 2019 (COVID-19) Pandemic: A Large Multi-institutional Autopsy Survey Study. Arch Pathol Lab Med. 2021; 145(5): 529–535, doi: 10.5858/arpa.2020-0786-SA, indexed in Pubmed: 33449998.

27. Sharma S, Barot HV, Schwartzman AD, et al. Risk and predictors of dyssynchrony cardiomyopathy in left bundle branch block with preserved left ventricular ejection fraction. Clin Cardiol. 2020; 43(12): 1494–1500, doi: 10.1002/clc.23467, indexed in Pubmed: 32940385.

28. Schumm J, Greulich S, Wagner A, et al. Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis. J Cardiovasc Magn Reson. 2014; 16(1): 14, doi: 10.1186/1532-429X-16-14, indexed in Pubmed: 24461053.

29. Grün S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. J Am Coll Cardiol. 2012; 59(18): 1604–1615, doi: 10.1016/j.jacc.2012.01.007, indexed in Pubmed: 22365425.

30. Barone-Rochette G, Augier C, Rodière M, et al. Potentially simple score of late gadolinium enhancement cardiac MR in acute myocarditis outcome. J Magn Reson Imaging. 2014; 40(6): 1347–1354, doi: 10.1002/jmri.24504, indexed in Pubmed: 24293405.

31. Verdonschot JAJ, Merlo M, Dominguez F, et al. Phenotypic clustering of dilated cardiomyopathy patients highlights important pathophysiological differences. Eur Heart J. 2021; 42(2): 162–174, doi: 10.1093/eurheartj/ehaa841, indexed in Pubmed: 33156912.

32. Becker MAJ, Cornel JH, van de Ven PM, et al. The Prognostic Value of Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging in Nonischemic Dilated Cardiomyopathy: A Review and Meta-Analysis. JACC Cardiovasc Imaging. 2018; 11(9): 1274–1284, doi: 10.1016/j.jcmg.2018.03.006, indexed in Pubmed: 29680351.

33. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020; 17(5): 259–260, doi: 10.1038/s41569-020-0360-5, indexed in Pubmed: 32139904.

34. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009; 39(7): 618–625, doi: 10.1111/j.1365-2362.2009.02153.x, indexed in Pubmed: 19453650.

35. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8(4): 420–422, doi: 10.1016/S2213-2600(20)30076-X, indexed in Pubmed: 32085846.

36. Maiese A, Manetti AC, La Russa R, et al. Autopsy findings in COVID-19-related deaths: a literature review. Forensic Sci Med Pathol. 2021; 17(2): 279–296, doi: 10.1007/s12024-020-00310-8, indexed in Pubmed: 33026628.

37. Violi F, Pignatelli P, Cammisotto V, et al. COVID-19 and thrombosis: Clinical features, mechanism of disease, and therapeutic implications. Kardiol Pol. 2021; 79(11): 1197–1205, doi: 10.33963/KP.a2021.0154, indexed in Pubmed: 34847237.

38. Brito D, Meester S, Yanamala N, et al. High Prevalence of Pericardial Involvement in College Student Athletes Recovering From COVID-19. JACC Cardiovasc Imaging. 2021; 14(3): 541–555, doi: 10.1016/j.jcmg.2020.10.023, indexed in Pubmed: 33223496.

39. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020; 383(2): 120–128, doi: 10.1056/NEJMoa2015432, indexed in Pubmed: 32437596.

40. Sousa IR, Pereira IC, Morais LJ, et al. Pericardial Parietal Mesothelial Cells: Source of the Angiotensin-Converting-Enzyme of the Bovine Pericardial Fluid. Arq Bras Cardiol. 2017; 109(5): 425–431, doi: 10.5935/abc.20170155, indexed in Pubmed: 29267626.

41. Fijałkowska J, Sobolewski J, Glińska A, et al. Cardiac abnormalities detected by echocardiography and cardiac magnetic resonance in healthcare professionals recovered from non-severe COVID-19. Kardiol Pol. 2021; 79(11): 1256–1258, doi: 10.33963/KP.a2021.0114, indexed in Pubmed: 34599499.