IJC Heart & Vasculature 54 (2024) 101499

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Cardiac remodeling and inflammation detected by magnetic resonance imaging in COVID-19 survivors

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ARTICLE INFO

Keywords:
Myocardial edema
T2
Extracellular volume
Late gadolinium enhancement
Native T1
Long COVID-19

ABSTRACT

Background: Concerns have been raised about cardiac inflammation in patients with long COVID-19, particularly those with myocardial injury during the acute phase of the disease. This study was conducted to examine myopericardial involvement, detected by cardiac magnetic resonance (CMR) imaging in patients hospitalized for COVID-19.

Methods: Adult patients hospitalized with COVID-19 who presented myocardial injury or increased D-dimers were enrolled in this prospective study. All patients were invited to undergo CMR imaging examination after discharge. During follow-up, patients with nonischemic myocardial or pericardial involvement detected on the first CMR imaging examination underwent second examinations. CMR imaging findings were compared with those of a control group of healthy patients with no comorbidity.

Results: Of 180 included patients, 53 underwent CMR imaging examination. The mean age was 58.4 ± 18.3 years, and 73.6 % were male. Myocardial and pericardial LGE was reported in 43.4 % and 35.8 % of patients, respectively. Nonischemic myocardial or pericardial involvement was reported in 26 (49.1 %) patients. The prevalence of pericardial LGE was associated inversely with the interval between hospital discharge and CMR. COVID-19 survivors had higher end-systolic volume indices (ESVis) and lower left-ventricular ejection fractions than did healthy controls. Seventeen patients underwent follow-up CMR imaging; the end-diastolic volume index, ESVi, and prevalence of pericardial LGE, but not that of nonischemic LGE, were reduced.

Conclusion: Among COVID-19 survivors with myocardial injury during the acute phase of the disease, the incidences of nonischemic myocardial and pericardial LGE and CMR imaging–detected signs of cardiac remodeling, partially reversed during follow-up, were high.

1. Introduction

The 2019 coronavirus disease (COVID-19) pandemic has increased morbidity and mortality outcomes worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can present in different clinical forms, most commonly as typical respiratory symptoms and pneumonia, but also with cardiac complications, including thrombotic complications, acute cardiovascular injury, and myopericarditis [1]. The cardiac involvement of COVID-19 has been associated with worse outcomes [2].

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https://doi.org/10.1016/j.ijcha.2024.101499
Received 29 June 2024; Received in revised form 20 August 2024; Accepted 22 August 2024

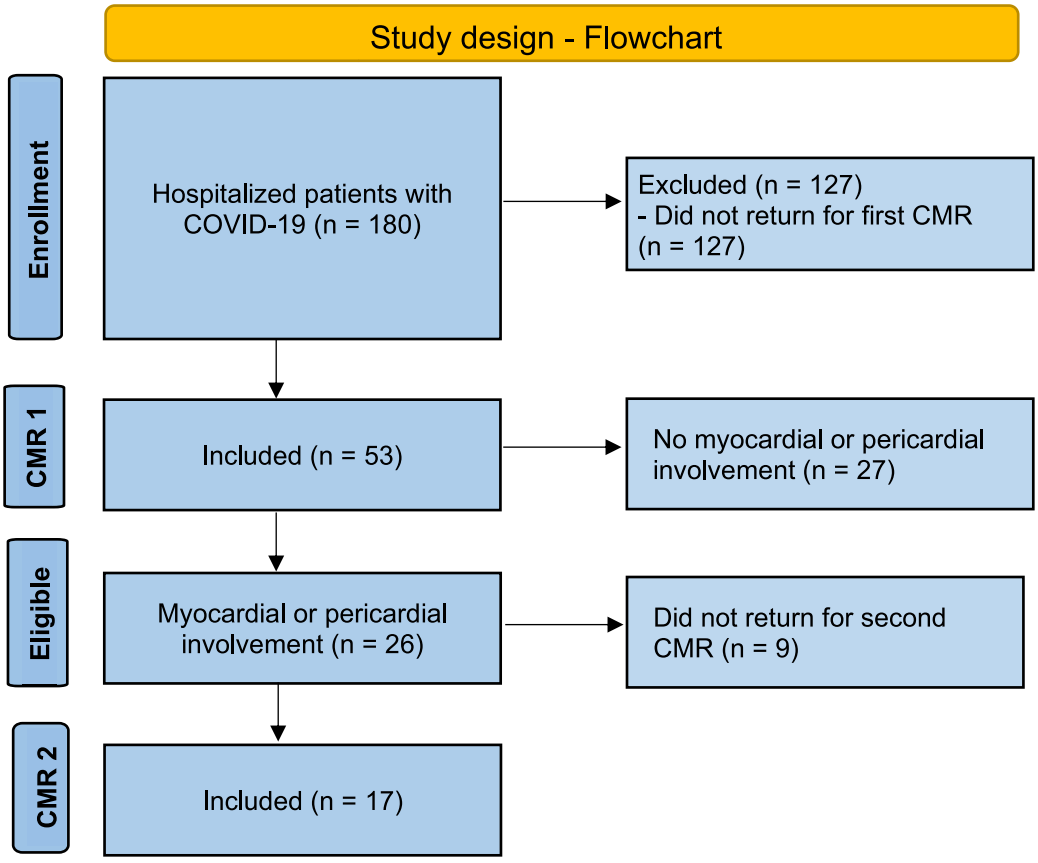

Fig. 1. Flowchart of the study design. CMR 1, first cardiac magnetic resonance; CMR 2, second cardiac magnetic resonance.

The pathophysiological mechanisms associated with cardiac symptoms in long COVID-19 remain poorly understood. A high prevalence of myocardial injury during hospitalization has been reported and associated with a higher in-hospital mortality rate [3,4], and one postulated mechanism of myocardial injury in COVID-19 is the dysregulation of the immune inflammatory response [5].

Cardiovascular magnetic resonance (CMR) imaging is the best noninvasive method for the assessment of myocardial and pericardial inflammation, enabling the detection of edema and fibrosis [6]. Different rates of CMR imaging–detected abnormalities in COVID-19 survivors have been reported, raising crucial questions about the long-term sequelae of the disease [7–9].

In this study, we further explored the presence and persistence of myocardial and pericardial involvement and tissue characterization parameters, including native T1 and T2 characteristics and extracellular volumes (ECVs) assessed by CMR imaging at two time points, in a population of COVID-19 survivors who presented cardiac injury and/or increased D-dimer levels during hospitalization.

2. Methods

2.1. Population and design

This prospective study was conducted with data from consecutive adult patients hospitalized with confirmed COVID-19 diagnoses and referred to the cardiology departments of five tertiary hospitals in Rio de Janeiro, Brazil, due to myocardial injury (defined by increased troponin levels) or coagulation abnormalities (defined by increased D-dimer levels) between November 2020 and September 2022. SARS-CoV-2 infection was confirmed by real-time reverse-transcription polymerase chain reaction of nasopharyngeal and/or oropharyngeal swab samples. All patients were followed prospectively after hospital discharge and were invited to undergo CMR imaging examination. Patients with non-ischemic myocardial or pericardial involvement were invited for a second CMR imaging examination (Fig. 1). A historical control group of healthy individuals with no cardiovascular comorbidity and no previous SARS-CoV-2 infection was also included. The study was approved by the Brazilian Ministry of Health's National Commission for Research Ethics and the institutional review boards or ethics committees of the participating sites (CAAE#29496920.8.0000.5262).

During patients' hospitalization, trained investigators collected demographic, clinical, and laboratory data using the standardized form from the International Severe Acute Respiratory and Emerging Infection Consortium/World Health Organization Clinical Characterization Protocol [10]. Data were collected from electronic medical records and entered into electronic case-report forms using the Research Electronic Data Capture platform (Vanderbilt University, Nashville, TN, USA). Clinical data included comorbidities, symptoms, and vital signs at the time of hospital admission, as well as complications and treatment. Laboratory tests were performed throughout patients' hospitalizations according to local clinical practice.

2.2. CMR imaging protocol

2.2.1. Image acquisition

CMR imaging studies were performed using a 3.0-Tesla scanner (Magnetom Prisma; Siemens Healthcare, Erlangen, Germany). Steady-state free-precession cine images were obtained in long- and short-axis planes. Late gadolinium enhancement (LGE) images were acquired with an inversion recovery gradient echo sequence after the intravenous injection of gadolinium-DOTA contrast (Dotarem; Guerbet, Aulnay-sous-Bois, France). T1 mapping images were obtained in a mid-ventricular plane using a modified look-locker inversion recovery sequence before and 15 min after contrast infusion [11–14]. A blood

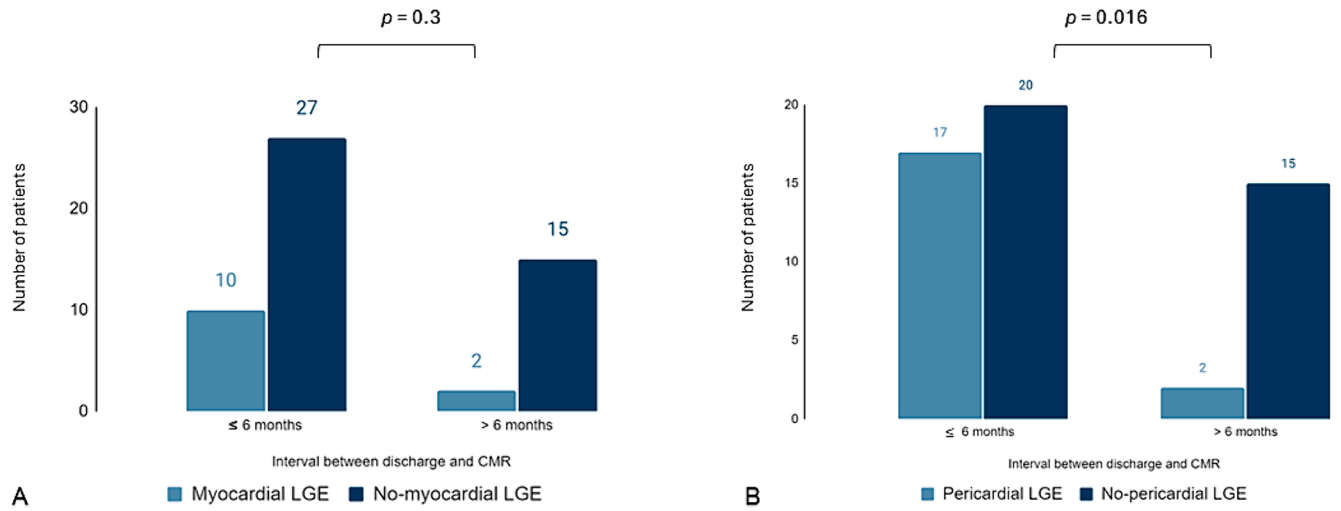

Fig. 2. Nonischemic myocardial **(A)** and pericardial **(B)** late gadolinium enhancement (LGE) according to the interval between hospital discharge and cardiac magnetic resonance (CMR) imaging examination.

sample was obtained from each participant, and the ECV was calculated with the incorporation of the hematocrit value to account for contrast distribution.

2.2.2. *CMR image analyses*

Image analyses were conducted in a blinded manner using OsiriX MD software (Pixmeo, Geneva, Switzerland). Cine images were evaluated to determine left-ventricular (LV) morphological and functional parameters [15]. Myocardial T2 and pre- and post-contrast T1 values were determined directly from T2 and T1 mapping images using manually drawn regions of interest (ROIs) based on signal intensity. Myocardial LGE masses across 17 segments were determined using a semi-quantitative five-point scoring system. Additionally, a circular ROI measuring 2 cm^2 was positioned at the center of the LV cavity on T1

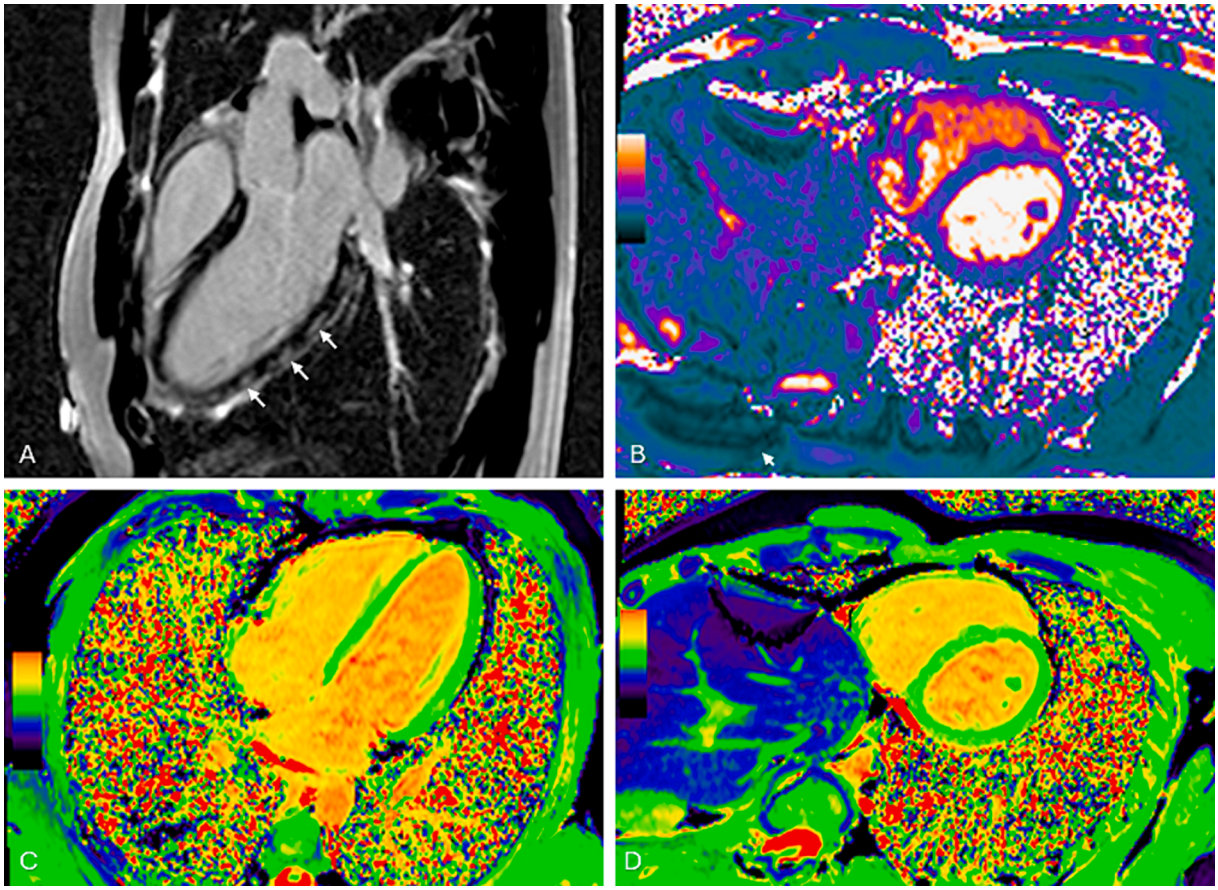

Fig. 3. CMR images from an 18-year-old male COVID-19 survivor who had myocardial injury during hospitalization for the disease and no hypertension. A steady-state free-precession three-chamber view **(A)** shows nonischemic myocardial LGE at the inferolateral wall (arrows), with an EF of 60 %, T2 value of 42.0 ms **(B),** and a native T1 value of 1190 ms **(C** and **D)**, resulting in an ECV of 23.5 %.

Table 1
Baseline characteristics of COVID-19 survivors ($n = 53$) according to the presence of nonischemic myocardial and/or pericardial LGE.

	Myopericardial LGE[a] n = 26	No myopericardial LGE n = 27	*p*-value
Age, years	58.0 ± 19.8	58.7 ± 16.9	0.896
Gender (male)	21 (80.8)	18 (66.7)	0.352
Chronic Heart Disease[b]	2 (7.7)	8 (29.6)	0.076
Chronic Pulmonary Disease[c]	2 (7.7)	1 (3.7)	0.610
Asthma	3 (11.5)	1 (3.7)	0.351
Obesity	10 (38.5)	12 (44.4)	0.435
Diabetes	8 (30.7)	7 (25.9)	0.766
Hypertension	12 (46.2)	15 (55.6)	0.541
Coronary artery disease	1 (3.8)	4 (14.8)	0.351
Cardiac Arrhythmia	1 (3.8)	2 (7.4)	1.000
Orovalvar disease	1 (3.8)	0 (0)	0.491
Troponin (>10 × URL)[d]	18 (69.2)	20 (74.1)	0.766
D-dimer, ng/mL	1187 ± 1659	1359 ± 1810	0.726
NT-proBNP, pg/mL	842 ± 1211	1328 ± 1206	0.250

Categorical variables were described as frequency (%) and continuous variables as mean ± standard deviation.
[a]Nonischemic myocardial and/or pericardial LGE.
[b]Chronic heart disease, heart failure, coronary and valvular diseases.
[c]Chronic obstructive pulmonary disease.
[d]Normalized values to the 99th percentile upper reference limit of each assay.
COVID-19, 2019 coronavirus disease; LGE, late gadolinium enhancement; URL, upper reference limit.

maps, enabling the acquisition of pre- and post-contrast blood-pool T1 values for ECV calculation [16].

Patients were categorized according to the interval between hospital discharge and first CMR imaging examination (0–6 and 7–12 months, respectively). Myocardial involvement was diagnosed in the presence of pericardial or nonischemic myocardial LGE. Myocardial LGE was characterized as transmural, nonischemic, and subendocardial. Patients with myopericardial nonischemic LGE were invited to undergo a second CMR imaging examination for the assessment of inflammation persistence.

Controls CMR imaging examinations were performed in the same scanner and followed identical protocol for image acquisition and analysis to establish normal parameters for the local equipment and to allow the comparison of tissue characterization parameters.

2.3. Statistical analysis

Continuous variables are described by medians and interquartile ranges or means and standard deviations, as appropriate; categorical variables are described as percentages. The CMR imaging parameters were compared between cases and controls using the nonparametric Mann–Whitney *U* test for independent samples. The Wilcoxon signed-ranks test was used for paired comparison. Categorical values were analyzed using the chi-squared or Fisher test. The significance level was set at $p < 0.05$. All analyses were performed using SPSS software (version 29.0; IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Population and baseline characteristics

Of the 180 consecutive patients enrolled in the study, 53 consented to undergo CMR imaging examination. The mean age of the patients was 58.4 ± 18.3 years; 39 (73.6 %) were male, 27 (50.9 %) were hypertensive, and 16 (28.3 %) had diabetes. Ten (18.8 %) patients had chronic heart disease, five (9.4 %) had coronary artery disease, three (5.6 %) had arrhythmia, and one (1.9 %) patient each had heart failure and valvular heart disease. Asthma was reported in four (7.5 %) patients and chronic obstructive pulmonary disease was reported in three (5.7 %) patients. Twenty-two (41.5 %) patients had obesity. Troponin elevation was detected in 49 (92.4 %) patients, and D-dimer elevation was detected in 47 (88.7 %) patients. The median interval between hospital discharge and CMR imaging examination was 111 days. The healthy control group comprised 15 individuals [8 (53.3 %) males] with a mean age of 55 ± 12.7 years.

Table 2
CMR imaging parameters for COVID-19 survivors ($n = 53$) and controls ($n = 15$).

	COVID-19 survivors Median [IQR]	Controls Median [IQR]	*p*-value*
EDVi, mL/m^2	73.0 [59.0, 83.5]	71.0 [66.0, 76.0]	0.790
ESVi, mL/m^2	25.0 [20,5, 33,0]	20.0 [17.0, 25.0]	**0.013**
LVMi, mg/m^2	105.0 [88.0, 120.0]	100.0 [81.0, 112.0]	0.387
LAVi, mL	28.0 [25.0, 31.5]	28.0 [23.0, 32.0]	0.711
LV EF, %	62.0 [60.0, 66.0]	72.6 [68.0, 74.6]	**< 0.001**
T1, ms	1229 [1189, 1257]	1208 [1186, 1235]	0.379
T2, ms	41.0 [39.7, 43.0]	41.2 [38.6, 47.0]	0.707
ECV, %	23.6 [22.2, 25.6]	24.1 [23.4, 26.0]	0.249

*Mann–Whitney test. Bold values indicate $p \leq 0.05$.
CMR, cardiac magnetic resonance; COVID-19, 2019 coronavirus disease; ECV, extracellular volume; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; IQR, interquartile range; LAVi, left-atrial volume index; LV, left-ventricular; LVMi, left-ventricular mass index.

3.2. Baseline CMR imaging parameters

Myocardial LGE was observed in 23 (43.3 %) patients; it was subendocardial in 7 patients, nonischemic in 12 patients, and transmural in 4 patients. Among the 11 patients with transmural or subendocardial LGE, five were diagnosed with ischemic heart disease, two had hypertrophic myocardiopathy, and one patient had a right-ventricular muscular band. The percentage of patients with nonischemic LGE did not differ significantly according to the interval between hospital discharge and CMR imaging examination (≤ 6 and > 6 months, 27 % and 11.8 %, respectively; p = 0.3; Fig. 2A and 3).

Nineteen (35.8 %) patients had pericardial LGE, and this finding was more prevalent among patients who underwent CMR imaging examinations ≤ 6 months after discharge than among those who underwent examinations > 6 months after discharge (45.9 % vs. 11.8 %, p = 0.016; Fig. 2B and 4). Physiological pericardial liquid was detected in 18 (33.9 %) patients.

Of the 53 patients who underwent initial CMR imaging examinations, nonischemic myocardial or pericardial LGE was observed in 26 (49.1 %) patients. The baseline characteristics of patients with and without nonischemic myocardial LGE did not differ (Table 1).

COVID-19 survivors had higher end-systolic volume indices (ESVis; 25.0 vs. 20.0 ml/m^2, $p = 0.013$) and lower LV ejection fractions (EFs; 62 % vs. 72.6 %, $p < 0.001$) than did controls. The end-diastolic volume index (EDVi), left-ventricular mass index, left-atrial volume index, native T1 and T2 values, and ECV did not differ between patients and controls (Table 2). Controls had no myocardial or pericardial LGE.

3.3. Follow-Up of patients with myocardial or pericardial LGE

Of the 26 patients with myopericardial involvement, 17 underwent follow-up CMR imaging examinations within a median of 329 days. Nonischemic LGE was observed in six (35.3 %) patients, and this percentage did not differ from that obtained for the initial CMR imaging examinations. The percentage of patients with pericardial LGE declined from 70.6 % for the initial examination to 52.9 % for the follow-up examination ($p = 0.009$; Fig. 4). Between these examinations, the EDVi (77.0 vs. 70.0 ml/m^2, $p = 0.003$) and ESVi (28.0 vs. 27.0 ml/m^2, $p = 0.002$) decreased, with no difference in the T1 or T2 mapping values or ECV (Table 3).

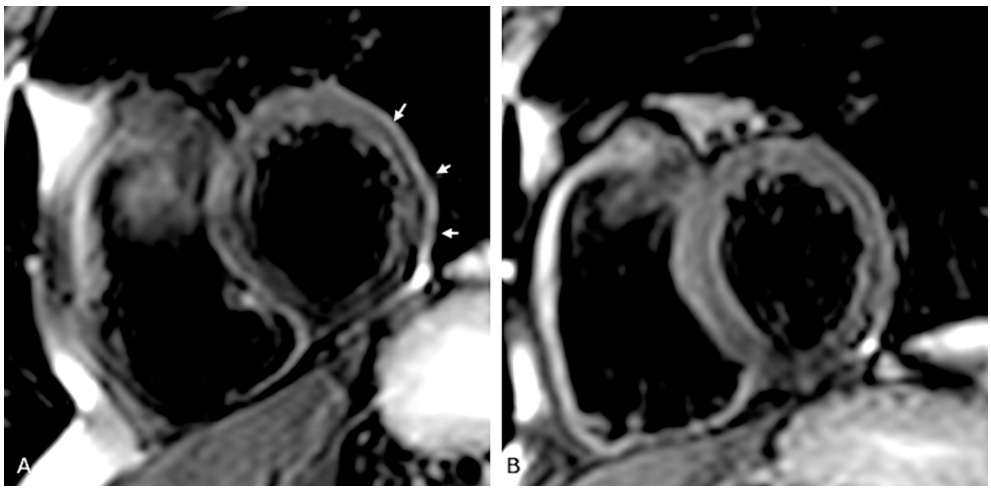

Fig. 4. CMR images from a 60-year-old male COVID-19 survivor with no hypertension. A steady-state free-precession short axis view **(A)** obtained 4 months after hospitalization for COVID-19 shows pericardial LGE at the inferolateral wall (arrows). Follow-up CMR image obtained 8 months later **(B)** shows improvement, with significant reduction of the pericardial LGE.

Table 3
Serial CMR imaging parameter values for patients with myopericardial involvement.

	CMR 1 Median [IQR]	**CMR 2** Median [IQR]	***p*-value***
EDVi, mL/m^2	77.0 [73.5, 92.0]	70.0 [63.0, 83.0]	**0.003**
ESVi, mL/m^2	28.0 [26.0, 37.5]	27.0 [22.5, 31.5]	**0.002**
LVMi, mg/m^2	104.0 [86.0, 124.0]	106.0 [85.5, 132.0]	0.589
LAVi, mL	27.0 [24.5, 30.5]	25.0 [23.0, 31.0]	0.491
LV EF, %	63.0 [60.0, 65.0]	61.0 [59.0, 67.0]	0.576
T1, ms	1237.0 [1209, 1251]	1220 [1205, 1246]	0.555
T2, ms	42.0 [40.0, 43.5]	42.0 [40.2, 44.0]	0.960
ECV, %	23.6 [22.1, 25.3]	23.6 [22.2, 26.6]	0.171

*Wilcoxon sign rank test. Bold values indicate $p \leq 0.05$.
CMR, cardiac magnetic resonance; ECV, extracellular volume; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; IQR, interquartile range; LAVi, left-atrial volume index; LV, left-ventricular; LVMi, left-ventricular mass index.

4. Discussion

The present study showed that CMR imaging–detected myocardial and pericardial involvement is prevalent in patients who had myocardial injury or increased D-dimers during hospitalization for COVID-19. Relative to controls, COVID-19 survivors had higher ESVi and lower LV EFs, but similar native T1 and T2 values and ECVs. Follow-up CMR imaging revealed reductions in the EDVi, ESVi, and pericardial LGE.

Nonischemic myocardial and pericardial LGE has been reported to be prevalent in COVID-19 survivors [17–19]; it may reflect the sequelae of an inflammatory process caused by immune dysregulation during the acute phase of the disease, which can be more exacerbated in patients with myocardial injury. Artico et al.[20], in a prospective multicenter cohort study, demonstrated a high prevalence (61 %) of heart abnormalities, including myocardial scarring and pericardial effusion, in patients with COVID-19 and myocardial injury. In addition, previous studies from our group and others have revealed a positive association between increased troponin levels and mortality [3,21–23] and stronger immune derangement, including increased circulating cytokine levels, lymphopenia, and the differential activation of CD8 + T cells [5], in patients with COVID-19 and myocardial injury.

The presence of nonischemic myocardial LGE did not differ significantly between patients who underwent CMR imaging examinations ≤ 6 and > 6 months after hospitalization in this study. This finding suggests that myocardial inflammation persists for months after acute SARS-CoV-2 infection and may explain some long-COVID symptoms. The persistence of cardiac sequelae has been reported in studies documenting not only CMR imaging–detected abnormalities [24,25], but also elevated sympathetic neural activity and signs of myocardial sympathetic denervation [26,27], in COVID-19 survivors.

In contrast to myocardial LGE, pericardial inflammation was more prevalent in patients who underwent CMR imaging examinations ≤ 6 months after hospitalization than in those who underwent examinations later. In addition, the presence of pericardial LGE was reduced on follow-up CMR imaging examination, suggesting that this inflammatory process is of shorter duration than myocardial involvement. The reported prevalence of pericardial LGE ranges from 4.5 % to 39 % [28,29], but the duration and reversibility of this finding is not well established.

The finding in the present study of increased ESVis and lower EFs in COVID-19 survivors, together with the reduction of EDVis and ESVis on follow-up CMR imaging examination, suggests that the cardiac remodeling process is reversible. Previous studies have shown that most patients who have recovered from COVID-19 have normal EFs, and that myocardial tissue remodeling may precede the functional remodeling of the left ventricle [30]. The lack of increase in native T1 and T2 values and ECVs in the present study may be attributable to the transitory nature of the myocardial injury and partial recovery from the inflammatory process. The use of T1 and T2 values as dynamic markers of cardiac involvement in COVID-19 survivors has been discussed in a *meta*-analysis, and the authors concluded that LGE and, to a lesser extent, the ECV are more static biomarkers linked to preexisting risk factors [25]. Considering the median interval of 111 days between hospital discharge and CMR imaging examination in the present study, we may be able to detect biomarkers that are more likely to persist for months after the acute phase of COVID-19.

4.1. Limitations

One limitation of this study is the lack of previous CMR imaging data for the participants, which precluded the assessment of the preexistence of findings potentially reflecting existing comorbidities, such as nonischemic myocardial LGE and cardiac remodeling. Nevertheless, the reduction of the EDVi, ESVi, and percentage of patients with pericardial LGE on follow-up CMR imaging examination suggests that these findings were transitory and partially reversed during the follow-up period.

5. Conclusions

Myocardial injury in the acute phase of COVID-19 is associated with a high prevalence CMR imaging–detected cardiac sequelae. The persistence and clinical impact of these findings are variable, consequently we recommend monitoring cardiac and tissue remodeling with CMR to stratify the risk, to define the prognosis and to assess the response to treatment in symptomatic patients.

6. Fundings

This work was supported by intramural grants from the D'Or Institute for Research and Education, FAPERJ (nos. E-26/210.155/2020, E-26/010.000149/2020, E-26/210.191/2020, and E-26/210.253/2020, E-26/210.825/2021, SEI-260003/002709/2020 and SEI-260003/002718/2020, SEI-260003/011968/2021), CAPES, FINEP, and the Serrapilheira Institute.

CRediT authorship contribution statement

Eduardo B. Schaustz: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **José Carlos P. Secco:** Writing – original draft, Methodology, Investigation. **Julia M. Barroso:** Writing – review & editing, Methodology, Investigation. **Juliana R. Ferreira:** Writing – review & editing, Methodology, Investigation. **Mariana B. Tortelly:** Writing – review & editing, Methodology, Investigation. **Adriana L. Pimentel:** Writing – review & editing, Methodology, Investigation. **Ana Cristina B.S. Figueiredo:** . **Denilson C. Albuquerque:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Allan R. Kluser Sales:** . **Paulo H. Rosado de-Castro:** Writing – review & editing, Resources, Funding acquisition. **Martha V.T. Pinheiro:** Writing – review & editing, Validation, Investigation. **Olga F. Souza:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **Emiliano Medei:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Ronir R. Luiz:** Writing – review & editing, Software, Formal analysis. **Andréa Silvestre-Sousa:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Gabriel C. Camargo:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Conceptualization. **Renata Moll-Bernardes:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are very grateful to the staff and research assistants at the D'Or Institute for Research and Education and Rede D'Or hospitals who dedicated their time to support this study.

Ethics approval statement

The institutional review boards and ethics committees of the participating institutions approved the study protocol (CAAE#29496920.8.0000.5262). All patients provided written informed consent before enrollment.

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