ORIGINAL ARTICLE

Patterns of myocardial injury in patients recovered from COVID-19: findings on cardiac magnetic resonance imaging studies and their prognosis

Patrones de injuria miocárdica en pacientes recuperados de COVID-19: hallazgos en estudios de resonancia magnética cardíaca y su pronóstico

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ABSTRACT

Background: COVID-19 continues to cause significant mortality and morbidity worldwide. Cardiac involvement is associated with long-term and medium-term negative clinical outcomes. Cardiac magnetic resonance imaging (CMRI) is a useful technique to detect and characterize myocardial disorders, so it has been used to identify different post-COVID-19 complications.
Objective: This study was aimed to evaluate the presence, the type, and the 6-month prognosis of the CMRI findings in an unselected cohort of patients referred to our site.
Methods: Single-center, prospective, observational cohort study. We included consecutive patients referred to our site for a CMRI. They were classified into five groups: normal CMRI (Group A), nonspecific myocardial fibrosis (Group B), isolated myocardial inflammation (Group C), myocarditis (Group D) and ischemic myocardial fibrosis (Group E). A 6-month follow-up was performed.
Results: We enrolled 298 patients, 51% women. CMRI was performed at a median of 68 days following epidemiological discharge. Patients were assigned to the groups as follows: 64.5% to Group A, 21.8% to Group B, and 10.4% to Group C. CMRI was repeated in six patients, and it showed that altered basal levels returned to normal. Six patients in Group D (2%) were diagnosed with myocarditis, and four in Group E (1.3%) suffered from myocardial infarction. Two patients in Group E underwent a revascularization procedure during their follow-up. The remaining cohort did not suffer from any event.
Conclusion: No pathological findings were found on most patients' CMRI (86%). Given the scale of the pandemic, we do not consider advisable to assess post-COVID-19 cardiac complications in general population by means of CMRI. In contrast, CMRI should be performed on those patients suspected of myocardial injury.

Key words: SARS-CoV-2 – COVID-19 – Coronavirus – Magnetic Resonance Imaging – Myocarditis – Myocardial Infarction

RESUMEN

Introducción: La pandemia de COVID-19 sigue causando mortalidad y morbilidad significativas en todo el mundo. La afectación cardiovascular se asocia con malos resultados clínicos a corto y mediano plazo. La resonancia magnética cardíaca (RMC) es un método muy útil para detectar y caracterizar alteraciones del miocardio, por lo que se ha utilizado para identificar las diferentes complicaciones post COVID-19.
Objetivo: El objetivo de este estudio fue evaluar la presencia, el tipo y el pronóstico a 6 meses de los hallazgos de RMC en una cohorte no seleccionada de pacientes derivados a nuestro centro.
Material y métodos: Estudio observacional de cohorte, prospectivo, unicéntrico. Se incluyeron pacientes consecutivos derivados para realización de RMC. Se clasificó a los pacientes en cinco grupos: RMC normal (grupo A), fibrosis inespecífica (grupo B), inflamación miocárdica aislada (grupo C), miocarditis (grupo D) y fibrosis isquémica (grupo E). Se realizó seguimiento a 6 meses.
Resultados: Se incluyeron 298 pacientes, 51% mujeres. La RMC se realizó una mediana de 68 días posterior al alta epidemiológica. El 64,5% fue clasificado como grupo A, el 21,8% como grupo B, el 10,4% como grupo C. De estos, en 6 pacientes se repitió la RMC, que evidenció normalización de la alteración basal. Seis pacientes presentaron diagnóstico de miocarditis (2%, grupo D), y cuatro (1,3%), de infarto de miocardio (grupo E). Dos pacientes del grupo E fueron revascularizados en el seguimiento, el resto de la cohorte no presentó eventos.
Conclusiones: La mayoría de los pacientes (86%) no presentaron hallazgos patológicos en la RMC. Dada la magnitud de la pandemia, no creemos recomendable el tamizaje de complicaciones cardíacas post COVID-19 con RMC en la población general, sino que debería reservarse para aquellos individuos con sospecha de injuria miocárdica.

Palabras clave: SARS-CoV-2 - COVID-19 – Coronavirus - Imágenes de resonancia magnética - Miocarditis - Infarto de miocardio

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INTRODUCTION

In December 2019, a new coronavirus was identified as the cause of an outbreak of severe pneumonia and acute respiratory distress syndrome (ARDS) in Wuhan, China. This new disease (COVID-19) spread to the rest of the world and was declared a pandemic by WHO on March 11, 2020. (1) Throughout 2022, COVID-19 continues to cause significant mortality and morbidity worldwide. (2) Although most cases are mild, a minority of patients suffer from ARDS, the most frequent cause of death. Besides, multiple organ involvement, including the heart, has been reported, (3) as well as the consequent concern for the increased risk of long-term sequelae. As regards myocardial injury, it is associated with a worse prognosis, (4) and has been reported especially in hospitalized patients, older patients, and those with comorbidities (obesity, diabetes mellitus, arterial hypertension, among others). (5-7) The increase in plasma troponin level, a diagnostic criterion of myocardial damage and a marker of poor prognosis in patients with COVID-19, could be a consequence of several mechanisms: acute coronary syndromes, myocarditis, arrhythmias, multiorgan failure syndrome, pulmonary thromboembolism, among others. (8)

Given the excellent spatial resolution and the multiplicity of tissue characterization sequences of cardiac magnetic resonance imaging (CMRI), it is a very useful technique to detect myocardial fibrosis secondary to various pathologies, to establish a diagnosis in patients with elevated troponin levels of unclear etiology (9-11) and is essential for the diagnosis of myocarditis. (12)

In this context, although the first studies that used CMRI in patients who survived COVID-19 have had limitations derived from studying a totally unknown pathology, they have shown different results, some of them very worrying, and have reported findings consistent with cardiac involvement in ambulatory patients with mild infection (including young, asymptomatic athletes). (13,14) This study was aimed to evaluate the presence, the type and the 6-month prognosis of the CMRI findings in an unselected cohort of patients referred to our site.

METHODS

Single-center, prospective, observational cohort study.

Study population

Between September 2020 and March 2022, we included 298 patients referred to our site for CMRI in order to study possible myocardial sequelae of SARS-CoV2 infection. Clinical and laboratory data were also recorded. Patients were classified into five groups according to the index CMRI findings: completely normal (Group A), nonspecific myocardial fibrosis without signs of active inflammatory process (Group B), signs of isolated myocardial inflammation without diagnostic criteria of myocarditis (Group C), definite myocarditis (Group D) and ischemic myocardial fibrosis (Group E). A 6-month follow-up was performed through the electronic medical record (or telephone call in case no data were available) to record hospitalizations and/or mortality.

The studies and therapeutic interventions were decided by each treating physician. The report of the CMRI studies of patients in Group C included an indication to perform a 4- to 6- month follow-up study to evaluate the resolution of the inflammatory findings.

CMRI study

All studies were strictly performed in accordance with national and institutional infection control protocols. We used a Philips Ingenia® V5 3.0T high-field magnetic resonator (Philips Healthcare, The Netherlands) equipped with advanced cardiac package including radiofrequency magnetic field shimming technology (MultiTransmit). Non-ferromagnetic carbon electrodes were placed to obtain electrocardiogram (ECG)-triggered images. A multi-detector surface antenna was placed on the thorax. Axial anatomical images were obtained with black blood sequence (T1-Single Shot TSE). For T1 and T2 Stir images, turbo spin-echo sequences were used. Cine imaging was performed with Balanced-FFE sequences. Post-contrast images were obtained after the infusion of gadopentetate dimeglumine (Gd-DTPA-Dimeglumine) 0.3 mmol/kg and the adjustment of TI, with PSIR TFE sequences. For T1 mapping imaging, a modified Look-Locker (MOLLI), balanced steady state precession sequence was used, which requires a short apnea (approximately 12 seconds); it was performed in three short-axis slices (basal, midventricular, apical) before administering the contrast agent. Approximately 10 minutes later, post-contrast T1-mapping images were acquired in the same short-axis slices. It was programmed with the following parameters: TE/TR/flip-angle (FA): 1.02 ns/2.2 ns, voxel size 2 × 2 × 10 mm, phase encoding steps n = 166, 11 images of three inversions (3 + 3 + 5) with pauses after three beats before the second and third inversion and an adiabatic pre-pulse. Figure 1 details the protocol used.

Imaging analysis

Routine CMRI analyses were performed using a commercially available software (ViewForum®, Extended Workspace, Philips Healthcare, The Netherlands). Myocardial native T1 values were quantified by drawing a region of interest (ROI) conservatively at the septal level, taking care not to contaminate the measurement with signals from the ventricular cavity. The values recently published by our group were taken as the upper limit of normal to define T1-mapping elevation and were obtained with the same equipment and sequence. (15) To estimate the extracellular volume fraction, ROIs were drawn at the myocardial and blood pool levels in the native and post-contrast T1-mapping images, in accordance with guidelines recommendations. (16) In those patients with no recent laboratory tests (<30 days), this variable was not estimated.

Statistical analysis

Statistical analysis was performed using Stata 14.0 software (StataCorp LLC, College Station, Texas, United States). The normality of the distributions was analyzed by inspection of histograms and the normal probability plot, and with the Kolmogorov-Smirnov test. Categorical variables were expressed as percentages, and continuous variables as mean ± standard deviation or median (interquartile range, IQR), as appropriate. For comparison of two or more variables with normal distribution, Student's t-tests and one-way analysis of variance (ANOVA with Bonferroni post-hoc test) were used, as appropriate. Associations were explored by simple linear and multivariate regression.

Ethical considerations

The present work was performed in accordance with the current international ethical guidelines to conduct studies on human subjects, as delineated in the Declaration of Helsinki (World Medical Association, 1964, last updated 2013).

All study data were treated with maximum confidentiality, in an anonymous and coded manner, with access restricted and available only for personnel authorized for the study purposes, and in accordance with the Argentina's current regulations: the Personal Data Protection Act 25326 (Habeas Data Act).

As this was a non-interventional study containing data derived from routine practice, it was not necessary to sign an informed consent form.

RESULTS

Clinical characteristics

A total of 298 patients were enrolled. Regarding baseline CMRI studies, 295 were performed with intravenous contrast agent (gadolinium), and 293 (98%) had T1- and T2-mapping images suitable for analysis. In five cases (1.6%), the parametric mapping images showed marked respiratory motion artifacts which hampered a reliable evaluation.

The median age was 45 years (IQR 32-53) and both sexes were equally represented (51% female, 49% male). Regarding COVID-19, 17% of patients reported no symptoms consistent with the infection (most of them were swabbed as they were close contacts of confirmed cases), and 5.4% required hospitalization due to pneumonia. At the time of the study, 39% had persistent symptoms (mainly exertional dyspnea, cough and/or palpitations). CMRI was performed at a median of 68 days following the epidemiological discharge (IQR 38-108) (Table 1).

Based on the findings from the CMRI study, patients were classified into five subgroups (Figure 2). A completely normal CMRI was observed in 64.5% (n = 192) of the patients (Group A), late gadolinium enhancement (LGE) in a nonspecific intramyocardial pattern was observed in 21.8% of the cases (n = 65) (Group B). Among these patients, intramyocardial linear patterns at basal septal level or at right ventricular insertion points were predominant.

In addition, 31 patients (10.4%) presented alterations exclusively in the parametric maps (T1-mapping in 29 cases, T1- and T2-mapping in 2 cases), without other criteria supporting the diagnosis of myocarditis (clinical, ECG changes, subepicardial myocardial fibrosis, etc.). It was interpreted that this group had isolated inflammatory changes (Group C). Among these patients, six underwent a second CMRI, with a mean difference of 159 days (range 105-189 days). Normalization of T1-mapping signal was observed in all cases (Figure 3).

The baseline characteristics of groups A, B and C are presented in Table 2.

Six patients (2%) were diagnosed with myocarditis (Group D), and 4 (1.3%) with ischemic myocardial fibrosis (Group E). Two of the patients with ischemic pattern were revascularized. None of the remaining 296 patients had adverse clinical outcomes at 6 months.

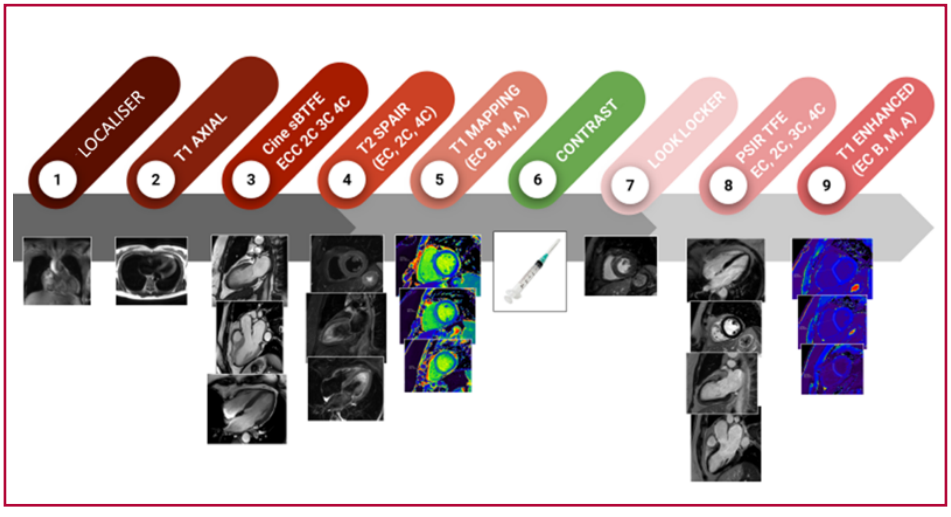


Fig. 1. Cardiac magnetic resonance imaging protocol used in the study

Female sex	51% (n = 153)	Asymptomatic presentation	17% (n = 51)
Age, years	45 (RIC 32-53)	Persistent symptoms	39% (n = 116)
High blood pressure	16% (n = 49)	Hospitalization	5,4% (n =16)
Dyslipidemia	13% (n = 40)	Days from discharge to CMRI	68 (IQR 38-108)
Smoking	6.7% (n = 20)		
Diabetes mellitus	5.4% (n = 16)		
Overweight/Obesity	4% (n = 12)		

Table 1. Table 1. (n = 298) Baseline characteristics of the studied population

With respect to the observed T1-mapping values, after excluding the 10 patients with a specific diagnosis (myocarditis or AMI), the only variable in the univariate analysis significantly associated with a higher value was the female sex (overall mean difference: 17 msec; $p<0.00001$) (Figure 4).

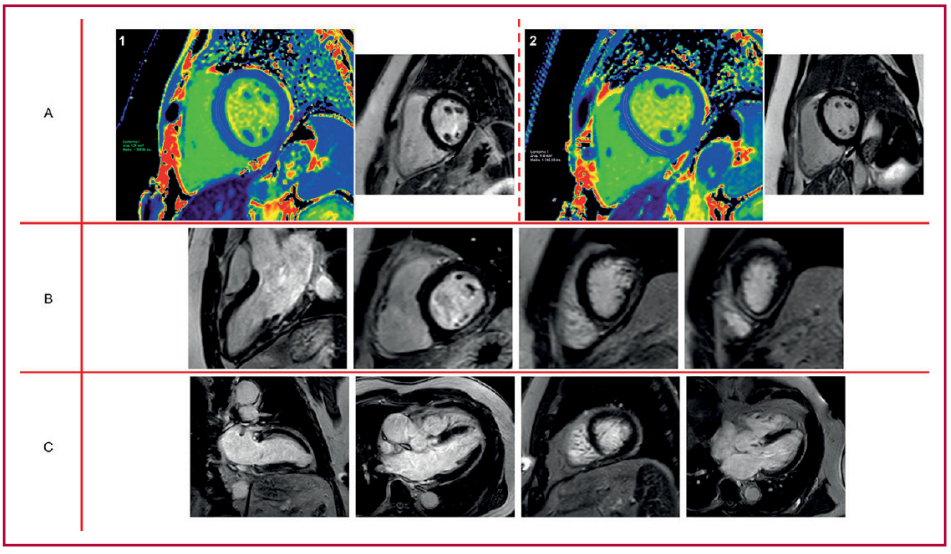
Myocardial injury patterns

In total, LGE was detected in 81 patients (27.2%). Most cases (88%) were foci of nonspecific intramyocardial enhancement (right ventricular insertion points, linear basal septal enhancement, etc.).

Four patients presented subendocardial/transmural injury and typical distribution of ischemic myocardial fibrosis. Of these, one patient had a history of coronary artery disease (apical myocardial infarction in 2009, not revascularized). The other three patients were referred to our center to study a possible post-COVID-19 myocarditis; two presented with palpitations and frequent ventricular ectopic beat, and the other one had a telehealth visit because of chest pain during the course of the infection and was evaluated following the epidemiological discharge. At that moment, the ECG showed T-wave inversion, therefore, a CMRI was indicated. All four patients presented regional wall motility abnormalities, without deterioration of the left ventricular ejection fraction (LVEF) (two apical sequelae, one in the basal inferior region and the other in the basal lateral region).

In addition, six patients were diagnosed with fibrosis consistent with myocarditis. Three of them had symptoms and signs of residual inflammation in T2- and T1-mapping sequences. As regards the other three patients, in two of them it was considered a finding (without signs of residual inflammation or clinical symptoms, so it cannot be certainly associated with the SARS-CoV2 infectious process) and in one patient the sequela had been previously known (under

Fig. 2. Examples of cardiac magnetic resonance imaging findings

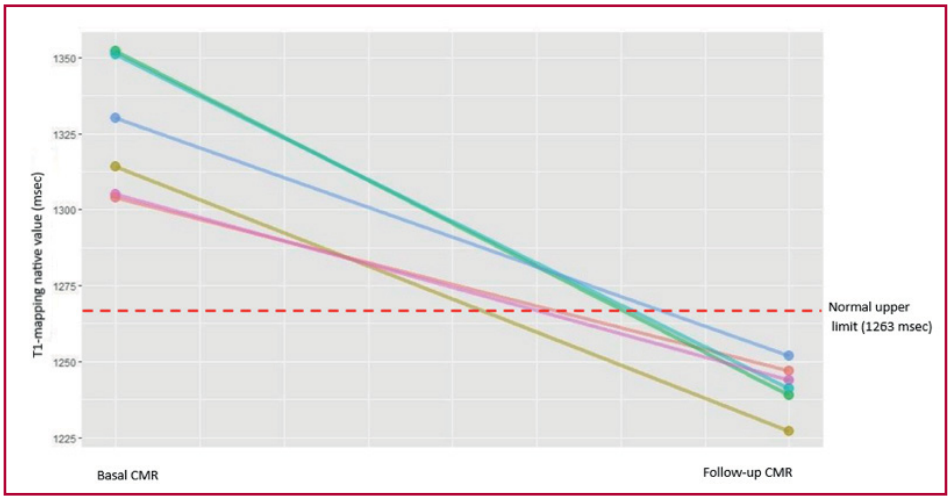


Panel A: 1. Patient with increased T1-mapping signal (1310 msec), without signs of focal fibrosis; 2. Same patient at 5-month follow-up with normal T1-mapping signal (1246 msec). Panel B: Subepicardial inferolateral and inferior subepicardial late enhancement in patient with diagnosis of myocarditis. Panel C: Strict inferior apical and apical subendocardial late enhancement consistent with sequelae of ischemic etiology.

Table 2. Baseline characteristics, Groups A, B and C

	A	B	C
Female sex	48%	54%	74%
Age	40 (31-70)	50 (35-55)	46 (38-55)
High blood pressure	12.5%	24.6%	19.4%
Dyslipidaemia	13%	15.4%	12.9%
Smoking	6.8%	4.6%	12.9%
Diabetes Mellitus	4.2%	9.2%	3.2%
Asymptomatic presentation	17.2%	12.3%	19.35%
Persistent symptoms	38.5%	40%	42%
Hospitalization	5.7%	7.7%	0%
Days from discharge to CMRI	67 (38-105)	68 (43-109)	50 (30-111)
Native T1_mapping (msec)	1224 ± 21	1231 ± 21	1284 ± 31.7
T2_mapping (msec)	45 ± 4	45 ± 3	46 ± 3

Group A: normal; Group B: inespecific fibrosis: Group C: isolated inflammation; CMRI: cardiac magnetic resonance imaging



CMRI: cardiac magnetic resonance imaging

Fig. 3. Change in T1-mapping values in six patients who had the study repeated (mean 159 days between studies). The dotted line indicates the upper limit of normal that has been considered.

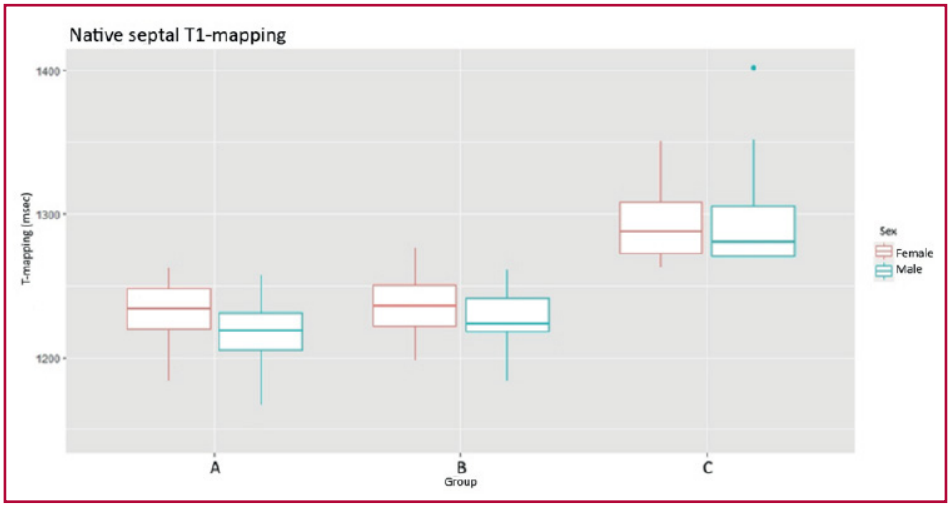


Fig. 4. Differences in the distribution of T1-mapping in women and men in the 3 largest groups of the study (A-C).

study in 2018). Only one patient presented regional wall motility abnormalities, and in all cases LVEF was preserved (mean 62.3%, range 58-68%). Regarding laboratory findings, elevated erythrocyte sedimentation rate was observed in two cases (both patients with signs of residual inflammation on imaging) and in no case was elevated cardiac troponin levels detected (probably due to the time elapsed between the discharge and the study, mean of 80 days).

Isolated T1-mapping elevation

In 31 cases an elevated T1-mapping signal was observed, without other signs of significant myocardial fibrosis (6 had linear intramyocardial LGE in the basal septum, considered nonspecific). In these cases, the report suggested that a follow-up and, in some cases, the repetition of the study without intravenous contrast agent at 4-6 months should be performed. Six patients underwent CMRI during the follow-up, and in all cases the T1-mapping signal decreased to values within the normal range, which we interpreted as the resolution of an inflammatory process which did not leave sequelae. Excluding sex, we did not identify clinical variables predictive of elevated T1-mapping (age, symptoms at onset, hospitalization requirement, presence of persistent symptoms, days from discharge to study, laboratory findings, among others) (Figure 5).

As recently published, in our setting, female sex is associated with a slightly higher T1-mapping value. (15) In fact, three female patients with values slightly above the cutoff point (between 1263 and 1268 msec) but extracellular volume fraction lower than 0.25 were included in Group A. No patient in this group presented complications during the follow-up.

DISCUSSION

In this study we report findings from 298 consecutive patients referred to our site for CMRI evaluation, and their prognosis at 6 months. In contrast to what has been reported by Puntmann et al. (13) and Rajpal et al., (14) in an unselected cohort of patients with predominantly mild SARS-CoV2 infection, almost two

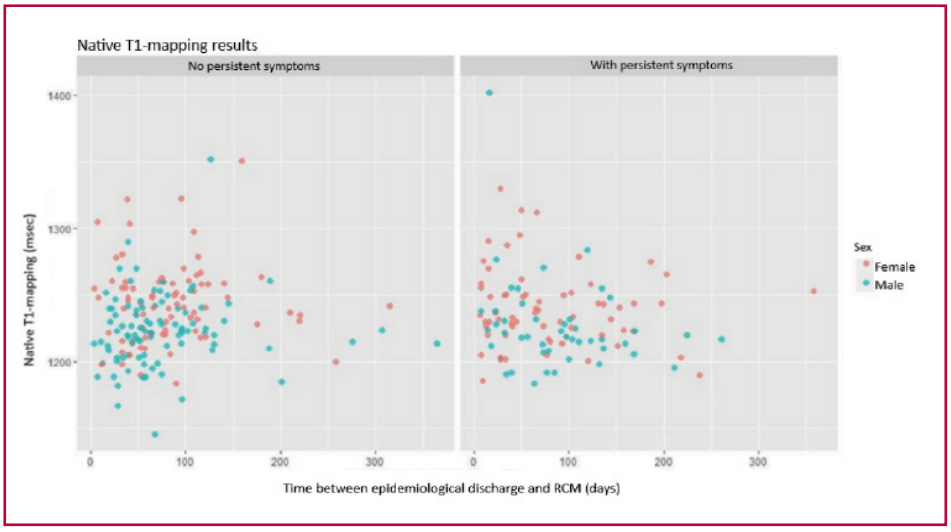


Fig. 5. Dot map with T1-mapping results from patients without persistent symptoms (left) vs. patients with persistent symptoms (right), according to sex, and based on the time elapsed between epidemiological discharge and CMRI.

CMRI: cardiac magnetic resonance imaging

thirds had a normal CMRI. We consider important to highlight this fact since those initial reports indicated very high risk of cardiac disorders (mainly "myocarditis") in patients who had suffered from mild infection and without previous heart disease, or even in young athletes. Obviously, many questions arose about the prognostic value of some findings (for example, alterations in T1 and T2 maps without evidence of fibrosis) and about the degree of certainty for individuals resuming regular physical activity after suffering from COVID-19. (17)

Subsequent studies, such as the one conducted in professional athletes in our country by Peidro et al. (18) did not show such a high prevalence of CMRI abnormalities, although they did not have advanced techniques, such as parametric maps in T1 or T2. In addition, Martinez et al. (19) demonstrated in more than 1500 athletes that CMRI could be reserved for those who presented abnormalities in preliminary studies (electrocardiogram, transthoracic echocardiogram, plasma troponin levels), without incurring in an excess of adverse events and with a 0.4% incidence of myocarditis.

Moreover, in patients who recovered from more severe infections, such as those studied by Kotecha et al. (20) who included patients with troponin level elevation who were hospitalized, 46% had no pathological findings on the CMRI.

In addition to this, CMRI plays a central role in the diagnosis and stratification of myocarditis, given its ability to confirm the presence, the type, and the extent of myocardial injury, as well as to identify signs of persistent inflammation, even before regional wall motility abnormalities are evident. (21-22) The main CMRI findings associated with worse prognosis in patients with myocarditis are the presence and the extent of sequela (LGE), LVEF impairment (<40%), extracellular volume fraction >35% and T2 mapping elevation greater than 2 SD above p95. (23-25)

In the previously mentioned work of Kotecha et al. (20), as regards patients hospitalized due to COVID-19 and troponin level elevation, 27% had LGE with myocarditis pattern and one third showed evidence of ongoing active myocardial inflammation. The interval between the discharge and the CMRI was 68 days (IQR 39-103 days), and no signs of poor imaging prognosis were reported.

Considering all these reasons and the immense scale of the COVID-19 pandemic, we believe that screening and follow-up of all patients by means of CMRI does not seem practical or cost-effective. In a small subgroup of our patients with signs of inflammation according to CMRI and without signs of injury based on imaging or serological tests, we observed that these abnormalities remitted without sequelae. The case is different in patients with diagnostic criteria of myocarditis and imaging signs of active inflammation, in which the repetition of CMRI at 6 months was proved to be useful to establish the medium-term and long-term prognosis. (26)

In our study, four patients presented myocardial injury consistent with ischemic etiology. Two of them had clinical signs and images that indicated a recent onset of the condition which coincided with the infection. Although anecdotal, these cases explain the previously published findings which showed a 46.8% decrease in hospitalizations due to cardiovascular causes (27) and a decrease in visits and check-ups in cardiology clinics.

The present study has some limitations: first, it is a single-center study that incorporated consecutive patients referred to our site for a CMRI study, which could be associated with a selection bias (for example, patients with more severe infections, frail, renal failure, obesity, and/or claustrophobia were probably not referred). In any case, we consider this cohort to be

representative of real-life practice, with predominance of mild/moderate infections and significant prevalence of persistent symptoms. Second, we did not have a universal determination of plasma troponin levels, so we cannot rule out the presence of myocardial injury in the same way in all patients. Finally, as very few patients had previous CMRI, we cannot definitively establish a relation between the abnormalities detected in these studies and COVID-19. However, the clinical characteristics of the patients with myocarditis and myocardial infarction, and the performance of T1-mapping in patients who had the study repeated allow us to assume the relation based on a certain degree of confidence.

CONCLUSIONS

In summary, most of the patients referred to our site following SARS-CoV2 infection (86%) had no pathological findings on CMRI. A subgroup (~10%) presented findings consistent with myocardial inflammation without injury, that is, elevated T1-mapping without ECG abnormalities or increase in troponin levels. These patients did not present cardiovascular adverse events at 6 months, and in 6 subjects who had CMRI repeated, we observed abnormalities remission and no sequelae. Patients with acute myocardial injury consistent with COVID-19, both myocarditis and acute coronary syndrome, presented symptoms and disorders in other complementary studies that supported such diagnosis. Based on these results, although they come from a single-center study, the initial approach of post-COVID-19 cardiac complications by means of CMRI in the general population would not appear to be an appropriate strategy. In contrast, CMRI should be reserved for those patients with suspected myocardial injury detected by traditional methods (clinical presentation, electrocardiogram, biomarkers).

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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None.

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