CARDIAC INVOLVEMENT IN MRI IN YOUNG POPULATION AFTER COVID-19: A SINGLE TERTIARY CENTER EXPERIENCE

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Abstract

**Background:** Coronavirus 2019 (COVID-19) causes morbidity and mortality in an increasing number of people worldwide. Although it mainly affects the respiratory system, it influences all organs, including the heart. It is associated with a broad spectrum of widespread cardiovascular problems ranging from mild myocardial injury to fulminant myocarditis. We aimed to evaluate the presence and prevalence of cardiac involvement in asymptomatic or symptomatic patients after they recovered from COVID-19 infection.

**Methods:** A total of 100 consecutive patients with COVID-19 proven by reverse transcription polymerase chain reaction (RT-PCR), under 40 years of age and without any known additional chronic diseases were analyzed retrospectively for cardiac magnetic resonance (CMR) results and symptoms.

**Results:** Cardiac involvement was detected in 49 out of 100 patients on CMR imaging. In the cardiac involvement group, the number of patients with chest pain and/or dyspnea was 41 (84%), which was statistically significant ($p = 0.001$). Twenty-four patients (47%) in the without cardiac involvement group were asymptomatic and this was also statistically significant ($p = 0.001$). LV ejection fraction was statistically significantly lower in the group with cardiac involvement (61% vs 66%, $p = 0.001$). LV stroke volume and tricuspid annular plane systolic excursion (TAPSE) were statistically significantly lower in patients with cardiac involvement ($p = 0.028$ and $p = 0.019$, respectively).

**Conclusion:** Based on single center experience, myocardial involvement is common in symptomatic patients after COVID-19. More studies are needed for long-term side effects and clinical results in these patients.

**KEYWORDS**
cardiac involvement, cardiac MR, chest pain, COVID-19, dyspnea, myocarditis

1 INTRODUCTION

The pandemic of SARS-CoV-2, caused by coronavirus disease COVID-19, is nowadays a global public health problem leading to significant mortality and morbidity worldwide. In Turkey, from January 3, 2020 to May 20, 2021, there were 5 151 038 confirmed COVID-19 cases and 45 419 patients died. Since the beginning of the outbreak, complications of COVID-19 that affected multiple organ systems have been reported. Although lung injury and acute respiratory distress syndrome (ARDS) are frequently observed in patients hospitalized for COVID-19, severe cardiovascular injury, including myocarditis, has been reported as well. The proposed various mechanisms of
myocardial injury in COVID-19 are direct viral injury leading to myocarditis via ACE-2 receptors on target host cells, inflammatory plaque rupture unmasking the underlying subtle atherosclerotic disease, cardiac stress secondary to high cardiac output and respiratory failure, stress-induced cardiomyopathy, systemic inflammatory response due to massive cytokine release and combination of all these factors.5–9

Cardiac magnetic resonance (CMR) imaging is the preferred imaging modality for non-invasive identification and exclusion of myocardial involvement in myocarditis due to its unique ability to detect cardiac edema, fibrosis, and scar.10,11 This imaging modality also allows physicians to evaluate heart volume and functions quantitatively.11,12 Huang et al. who studied cardiac symptoms in an MR study, reported cardiac involvement in 58% of patients who had recovered from COVID-19.13 In another study by Puntmann et al., cardiac involvement was reported in 78% of patients with no cardiac symptoms.14 In the present study, we had the goal to assess the presence and prevalence of cardiac involvement in patients with no symptoms or mild symptoms recovering from COVID-19.

2 | METHODS

2.1 | Study design and participants

In this single-center study, a total of 100 consecutive patients diagnosed as COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) were analyzed retrospectively. The patients were under 40 years of age and did not have any known additional chronic diseases such as diabetes mellitus (DM), hypertension (HTN), coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease, dyslipidemia, chronic obstructive pulmonary diseases (COPD), chronic renal, or liver failure. Patients with suspected post-COVID-19 myocarditis were evaluated by CMR imaging examination. Patients with hemodynamic instability, claustrophobia, and other general contraindications to MRI were excluded from the study.

After at least 14 days of the quarantine period, patients admitted to the cardiology clinic were included in the study. The cardiac symptom was described as the presence of at least one of the symptoms of dyspnea or chest pain that were not present prior to COVID-19 or were exacerbated by COVID-19. Patients having pain unrelated to effort and pleuritic type were defined as chest pain. Patients without the symptoms mentioned above were noted as asymptomatic. Our hospital is a designated, large-volume hospital capable of receiving severe COVID-19 patients. The study was approved by the Ethics Committee of the hospital and the requirement for written informed consent was waived by the Ethics Commission.

2.2 | Data collection and analysis

Information on demographic characteristics (gender and age), and presence of COPD, HTN, DM, CAD, cerebrovascular disease, peripheral vascular disease, dyslipidemia, renal and liver failure, smoking, clinical manifestations, laboratory findings, treatment, outcomes (duration of hospitalization), and COVID-19 RT-PCR positivity of the patients were extracted from electronic medical records using a standardized data collection form. Coronary artery disease was defined as a history of either myocardial infarction or primary percutaneous intervention, or a stenosis of more than 50% in any coronary vessel. HTN was defined as receiving antihypertensive treatment and/or arterial blood pressure > 140/90 mm Hg in more than one measurement. A history of DM and/or antidiabetic therapy or postprandial blood glucose > 200 mg/dl was accepted for the diagnosis of DM. Hyperlipidemia was defined as having a total cholesterol > 200 mg/dl, low density lipoprotein (LDL) > 130 mg/dl, history of dyslipidemia, and/or being under antilipidemic treatment. The routine blood examinations collected at admission included complete blood count (CBC), coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), myocardial enzymes (troponin I, CK-MB, creatine kinase, LDH), C-reactive protein (CRP), procalcitonin (PCT), serum ferritin, interleukin-6 (IL-6), and D-dimer. Peripheral venous blood samples were obtained from a large antecubital vein upon admission as well. Total CBC test (Symex K-1000, Kobe, Japan) and blood chemistry parameters (Roche Diagnostic Modular Systems, Tokyo, Japan) were carried out at our hospital’s biochemistry laboratory. Blood samples were taken into standardized EDTA containing tubes for total CBC test and measurements were performed immediately after the blood sampling. Serum CRP levels were measured by the immune nephelometric method (NBL BN-II; Dade Behring, Siemens). PCT was determined by Biomerieux Mini VIDAS automatic fluorescence immuno-analyzer. Serum ferritin levels were detected by the electrochemiluminescence method (Cobas E601, Roche). IL-6 was measured by Roche Cobas E601 electrochemical luminescence immuno detector, using the corresponding reagent. D-dimer was quantitatively determined using Sysmax CS-5100 hemagglutinin analyzer.

2.3 | Transthoracic echocardiography

Two-dimensional (2D) and Doppler echocardiographic examinations performed by experienced research echocardiographer blinded to the clinical status and laboratory data of the patients. Measurements were performed by using a commercially available echocardiograph equipped with a 2.5- and 3.5-MHz transducer with Philips IE33 xMatrix (Philips Healthcare, Inc., Andover, MA, USA) in a dedicated echocardiography laboratory for the examination of COVID-19 patients during the pandemic. All examinations were performed at left lateral decubitus position, adhering to a focused, time-efficient protocol with use of protective equipment provided both for the patient and echocardiographer. Left ventricular end diastolic diameter (LVEDd) was calculated from parasternal long axis image and left ventricular ejection fraction (LVEF) was measured through the modified two-dimensional biplane method of disks summation technique. Left atrium anterior-posterior diameter was calculated from parasternal long axis view at the end of systole. Right atrium (RA) and right ventricle (RV) diameters
were assessed from apical four-chamber view and RV focused apical four-chamber view. Mitral inflow E and A waves were measured through left ventricular spectral doppler analysis. Afterwards, E/A ratio was calculated. Similarly, tissue Doppler imaging derived E’ was measured from the septal annulus and E/E’ was calculated. Systolic pulmonary artery pressure (sPAP) was assessed through the modified Bernoulli equation.

### 2.4 Cardiac magnetic resonance image analysis and acquisition

The CMR was performed with a 16 channel 1.5 T MR scanner (Signa Explorer, General Electric, Milwaukee, USA) and a 16-channel body coil. All images were acquired with ECG triggering during repeated expiration breath-holds. For each subject, localizing scans were obtained to define the long (two-chamber) axis of the left ventricle. A midventricular short-axis view was prescribed and used to plan a four-chamber view. The short axis orientation was then defined accurately, perpendicular to both the two- and four-chamber views. The CMR protocol consisted of steady-state free precession cines at two-chamber and four-chamber views, with a stack of 9–15 slices covering both ventricles at the short-axis with the following parameters: time of repetition: 4 ms; time of echo: 1 ms; flip angle: 60°.

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After obtaining T2-weighted short-tau inversion-recovery (T2w) and T1-weighted spin-echo (T1w) in short axis, phase-sensitive inversion recovery (PSIR) imaging was obtained for early and late gadolinium enhancement assessment after giving IV of 0.2 mmol Gadobutrol (Gadovist) per kg of body weight. The optimal inversion time ranged from 200 to 480 ms which was chosen based on a T1-scout scan performed just before the LGE acquisition. PSIR sequence parameters were: repetition time: 6.1 ms, echo time: 1 ms, voxel size: 1.6 × 2.1 × 8 mm, flip angle: 25°. It was performed on 3rd, 7th and 15th minutes after the administration of Gadolinium. Images were acquired in two short-axis stacks covering the entire left ventricle and one four-chamber view. Through-plane 2D PC flow measurements of the mitral, aortic, and pulmonary valve were performed during end-expiratory breath-hold using ECG gating. The imaging planes were planned perpendicular to the great vessels. The parameters were: slice thickness: 7 mm, matrix size: 132 × 190, flip angle: 25°, echo time: 4.0 ms, repetition time: 6.2 ms. All the obtained cardiac MR results were transferred to GE workstation (AW 4.7, VX cardiac software, Milwaukee, USA).

First of all, the routine morphologic evaluation was performed. Left ventricular end-diastolic volume, end-systolic volume, stroke volume, ejection fraction, myocardial thickness, end-diastolic myocardial mass, and end-diastolic mass were assessed at the short-axis steady-state free precession images by applying Simpson’s method. RV functions were assessed using the same method with the left ventricle. On the cine short-axis stack, LV and RV endocardial contours were manually traced in end-diastole and end-systole according to the guidelines of Society for Cardiovascular Magnetic Resonance on CMR image post-processing. Atrial width, pericardial thickness, and effusion were evaluated as well. All of the measured parameters were indexed to body surface area when necessary. In T2-W images, the signal ratio was measured from the region of interest covering the left ventricular myocardium as well as within a skeletal muscle in the same slice. For PC velocity analysis, the aorta and pulmonary artery were manually delineated in at least one cardiac phase. Automatic border detection was used for the other cardiac phases. These contours were reviewed and adapted accordingly for each cardiac phase. Moreover, mitral valve flow was evaluated especially for the diastolic dysfunction. In perfusion images, we evaluated perfusion delay or defect visually in the subendocardial area. If there were any suspicious conditions, we drew endo-contour and epi-contour of the left myocardium, and obtained perfusion graphics for perfusion delay or defect. In T1-W early enhancement which reflecting hyperemia and capillary leak as a marker of inflammation, the early myocardial enhancement was measured from the region of interest covering the left ventricular myocardium as well as within a skeletal muscle in the same slice. For the LGE analysis, the reader first identified the presence or absence of scar based on visual assessment. To assess the contrast-enhanced images (LGE), all short-axis slices from base to apex were evaluated for areas of normal (completely nulled) myocardium (Figures 1 and 2). Scar distribution patterns were then evaluated according to the transmural, focal, and diffuse involvement. All image analyses were performed by one of the two radiologists. The study was considered as positive for myocarditis, according to Lake Louise criteria. In the end, the parenchymal area was evaluated for any kind of lung, mediastinal, or pleural pathologies.

### 2.5 Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, New York, USA). Kolmogorov-Smirnov test was used in order to examine the distribution of numerical variables. Chi-square or Fisher’s exact test were applied for categorical variables and presented as percentages. Student’s t-test was applied to the numerical data which conforms to the normal distribution and the results were entered as mean and standard deviation. Conversely, Mann Whitney-U test was performed for the anormal distributed variables and the results were given as median with inter-quartile range. A two-sided p value of less than 0.05 was determined to be statistically significant.

### 3 RESULTS

A total of 100 patients who were shown to be infected with COVID-19 by PCR were enrolled retrospectively. Baseline and clinical characteristics, and laboratory findings are shown in Table 1. While 49 patients had cardiac involvement on CMR, no cardiac involvement was observed in the remaining 51 patients. The mean age of the patients in the study was 35 (range: 19–39 years) and 52% were male. The median time from PCR test positivity to the time of cardiac imaging
TABLE 1  Clinical features and laboratory measurements of patients recovered from COVID-19

| Variables                        | All patients (n = 100) | Cardiac involvement+ (n = 49) | Cardiac involvement- (n = 51) | p value |
|----------------------------------|------------------------|-------------------------------|-------------------------------|---------|
| **Age (years)**                  | 35 (31–37)             | 35 (31–37)                    | 33 (31–37)                    | 0.151   |
| **Minimum/Maximum**              | 19/39                  | 19/39                         | 19/39                         |         |
| **Gender**                       |                        |                               |                               |         |
| Male                             | 52 (52%)               | 27 (55%)                      | 25 (49%)                      | 0.543   |
| Female                           | 48 (48%)               | 22 (45%)                      | 26 (51%)                      |         |
| **Smoking**                      | 36 (36%)               | 17 (35%)                      | 19 (37%)                      | 0.790   |
| **Comorbidities**                |                        |                               |                               |         |
| Diabetes mellitus                | 0                      | 0                             | 0                             | NA      |
| Hypertension                     | 0                      | 0                             | 0                             | NA      |
| Coronary artery disease          | 0                      | 0                             | 0                             | NA      |
| Cerebrovascular disease          | 0                      | 0                             | 0                             | NA      |
| Peripheral vascular disease      | 0                      | 0                             | 0                             | NA      |
| Dyslipidemia                     | 0                      | 0                             | 0                             | NA      |
| Chronic obstructive pulmonary diseases | 0                | 0                             | 0                             | NA      |
| Chronic renal failure            | 0                      | 0                             | 0                             | NA      |
| Chronic hepatic failure          | 0                      | 0                             | 0                             | NA      |
| **Cardiac symptoms**             |                        |                               |                               |         |
| Chest pain                       | 39 (39%)               | 21 (43%)                      | 18 (35%)                      | 0.438   |
| Dyspnea                          | 16 (16%)               | 11 (22%)                      | 5 (10%)                       | 0.085   |
| Chest pain and dyspnea           | 13 (13%)               | 9 (18%)                       | 4 (8%)                        | 0.118   |
| Chest pain or dyspnea            | 68 (68%)               | 41 (84%)                      | 27 (53%)                      | 0.001*  |
| Asymptomatic                     | 32 (32%)               | 8 (16%)                       | 24 (47%)                      | 0.001*  |
| **Duration between cardiac symptoms onset to CMRI examination (days)** | 54 (44–62)             | 54 (45–61)                    | 54 (40–65)                    | 0.822   |
| **Cardiac involvement types**    |                        |                               |                               |         |
| Isolated myocardial involvement  | 33 (33%)               | ...                           | ...                           | ...     |
| Isolated pericardial involvement | 6 (6%)                 | ...                           | ...                           | ...     |
| Both pericardial and myocardial involvement | 10 (10%)   | ...                           | ...                           | ...     |
| **2-D echocardiographic findings** |                      |                               |                               |         |
| Left atrial diameter (mm)        | 35 (32-37)             | 35 (32-37)                    | 35 (32-37)                    | 0.680   |
| Left ventricular diastolic diameter (mm) | 46 (44-47)             | 46 (43-48)                    | 46 (44-47)                    | 0.760   |
| Left ventricular ejection fraction, % | 60 (60-65)             | 60 (60-65)                    | 60 (60-65)                    | 0.352   |
| Interventricular septum diameter (mm) | 9 (9–10)               | 10 (9–10)                     | 9 (9–10)                      | 0.559   |
| Posterior wall diameter (mm)     | 9 (9–10)               | 9 (9–10)                      | 9 (9–10)                      | 0.657   |
| Right atrium diameter (mm)       | 36 (34–40)             | 36 (34–40)                    | 36 (34–40)                    | 0.747   |
| Right ventricular diastolic diameter (mm) | 36 (34–39)             | 36 (33–39)                    | 36 (34–38)                    | 0.824   |
| Pericardial effusion             | 3 (3%)                 | 3 (6%)                        | 0                             | 0.073   |
| Moderate or severe any valvular disease | 0                    | 0                             | 0                             | NA      |
| **Doppler echocardiographic findings** |                      |                               |                               |         |
| Mitrail inflow E/A ratio          | 1.2±.1                 | 1.2±.2                        | 1.2±.1                        | 0.478   |
| Mitrail septal E/E’ ratio        | 8.8 (8.5-8.9)          | 8.7 (8.4-8.8)                 | 8.6 (8.6-8.9)                 | 0.332   |
| Aortic velocity (m/sec)          | 1.3±.1                 | 1.3±.1                        | 1.3±.1                        | 0.288   |
| Pulmonary velocity (m/sec)       | 9.2±.1                 | 9.3±.1                        | 9.2±10                        | 0.455   |
| Systolic pulmonary artery pressure (mm Hg) | 24 (23-25)             | 25 (23-27)                    | 23 (22-24)                    | <0.001* |

**Laboratory findings**

(Continues)
| Variables                          | All patients (n = 100) | Cardiac involvement+ (n = 49) | Cardiac involvement- (n = 51) | p value |
|-----------------------------------|------------------------|-------------------------------|-------------------------------|---------|
| Fasting glucose (mg/dl)           | 92 (83-102)            | 91 (83-106)                   | 92 (85-99)                    | 0.934   |
| Urea (mg/dl)                      | 28 (24-32)             | 29 (25-34)                    | 26 (23-30)                    | 0.104   |
| Creatinine (mg/dl)                | .80±.18                | .82±.19                       | .79±.16                       | 0.352   |
| Aspartate amino transferase (U/L) | 21 (17-29)             | 21 (17-29)                    | 21 (17-29)                    | 0.722   |
| Alanine amino transferase (U/L)   | 24 (18-41)             | 23 (18-41)                    | 25 (18-38)                    | 0.978   |
| Total protein (mg/dl)             | 69.8±3.9               | 69.6±3.7                      | 70.0±4.1                      | 0.624   |
| Albumin (mg/dl)                   | 46.8±3.7               | 46.6±4.0                      | 46.9±3.5                      | 0.662   |
| Lactate dehydrogenase (U/L) [90/100] | 187 (168-214)       | 190 (170-227)                 | 180 (165-207)                 | 0.131   |
| Total cholesterol (mg/dl)         | 174 (147-189)          | 174 (145-189)                 | 175 (155-189)                 | 0.804   |
| High density lipoprotein (mg/dl)  | 46 (37-59)             | 46 (37-57)                    | 46 (40-60)                    | 0.267   |
| Low density lipoprotein (mg/dl)   | 98 (78-110)            | 95 (79-109)                   | 99 (77-110)                   | 0.539   |
| Triglycerides (mg/dl)             | 130 (84-181)           | 147 (74-199)                  | 129 (88-176)                  | 0.759   |
| Sodium (mEq/L)                    | 139 (138-141)          | 139 (138-141)                 | 139 (139-140)                 | 0.702   |
| Potassium (mEq/L)                 | 4.3±.3                 | 4.3±.3                        | 4.3±.3                        | 0.329   |
| GFR (ml/min/m²)                   | 106 (92-117)           | 105 (89-115)                  | 107 (95-118)                  | 0.222   |
| NT-proBNP, pg/ml                  | 35 (35-36)             | 35 (35-49)                    | 35 (35-35)                    | 0.542   |
| CK-MB (µg/L)                      | .5 (.2-1.1)            | .5 (.2-1.3)                   | .5 (.2-1.0)                   | 0.338   |
| Troponin I (ng/L)                 | 2.5 (2.5-3.0)          | 2.5 (2.5-3.7)                 | 2.5 (2.5-3.0)                 | 0.323   |
| Fibrinogen, g/L                   | 2.6 (2.2-3.0)          | 2.5 (2.2-3.0)                 | 2.7 (2.2-3.0)                 | 0.679   |
| D-dimer (µg/ml)                   | .2 (.2-5)              | .2 (.2-5)                     | .25 (.2-50)                   | 0.424   |
| Ferritin (µg/L)                   | 40 (13-131)            | 51 (16-135)                   | 33 (13-127)                   | 0.506   |
| Procalcitonin (µg/L)              | .03 (0.03-0.03)        | .03 (0.03-0.03)               | .03 (0.03-0.03)               | 0.901   |
| Interleukin-6 (µg/ml)             | 2.5 (1.7-3.4)          | 2.2 (1.6-3.3)                 | 2.6 (2.0-3.5)                 | 0.102   |
| C-reactive protein (mg/L)         | 10 (5-40)              | 7 (5-51)                      | 12 (5-30)                     | 0.994   |
| Thyroid stimulating hormone (µIU/ml) | 2.1 (1.6-2.4)       | 2.1 (1.6-2.4)                 | 2.2 (1.4-2.4)                 | 0.479   |
| White blood cells (x10⁹/L)        | 6.87±1.65              | 6.96±1.80                     | 6.78±1.49                     | 0.575   |
| Neutrophils (x10⁹/L)              | 4.10±1.37              | 4.15±1.49                     | 4.05±1.25                     | 0.714   |
| Lymphocytes (x10⁹/L)              | 2.09±.62               | 2.13±.64                      | 2.05±.60                      | 0.518   |
| Monocyte (x10⁹/L)                 | .40 (.32-.45)          | .41 (.33-.46)                 | .4 (.3-.5)                    | 0.631   |
| Hemoglobin (g/dl)                 | 13.9±1.9               | 13.9±1.9                      | 13.9±1.8                      | 0.921   |
| Hematocrit, %                     | 42±5                   | 42±5                          | 42±5                          | 0.719   |
| Red cell distribution width (%)   | 14.3±1.6               | 14.3±1.4                      | 14.3±1.8                      | 0.890   |
| Platelets (x10⁹/L)                | 265±82                 | 277±92                        | 253±70                        | 0.150   |
| Mean platelet volume (fL)         | 8.3±.9                 | 8.3±.10                       | 8.2±.8                        | 0.528   |
| Hospitalization                   | 3 (3%)                 | 2 (4%)                        | 1 (2%)                        | 0.614   |

### Treatments

|                           | All patients (n = 100) | Cardiac involvement+ (n = 49) | Cardiac involvement- (n = 51) | p value |
|---------------------------|------------------------|-------------------------------|-------------------------------|---------|
| Antiviral agents          | 100 (100%)             | 49 (49%)                      | 51 (51%)                      | NA      |
| Antibiotics               | 3 (3%)                 | 0                             | 3 (6%)                        | 0.243   |
| Hydroxychloroquine        | 96 (96%)               | 48 (98%)                      | 48 (94%)                      | 0.327   |
| Corticosteroids           | 5 (5%)                 | 5 (10%)                       | 0                             | 0.025   |
| Low molecular weight heparin | 10 (10%)            | 5 (10%)                       | 5 (10%)                       | 0.947   |
| Colchicine                | 2 (2%)                 | 2 (4%)                        | 0                             | 0.145   |

Data are mean ± SD, median (IQR) and n (%). p values were determined by student t-test, Mann-Whitney U test, Chi-square test, or Fisher’s exact test, as appropriate. *p value less than 0.05 was considered significant for statistical analyses.

Abbreviations: CK-MB, creatine kinase-myocardial band; CMRI, cardiac magnetic resonance imaging; GFR, glomerular filtration rate; IQR, interquartile range; NA, not applicable; NT-proBNP, amino-terminal pro-brain natriuretic peptide; SD, standard deviation.
was 54 days (range: 44–62 days). None of the patients included in the study had DM, HTN, CAD, vascular disease (cerebrovascular or peripheral), dyslipidemia, chronic obstructive pulmonary diseases, kidney or liver disease. In the group with cardiac involvement, 21 patients (43%) had chest pain, 11 patients (22%) had dyspnea, and nine patients had chest pain and dyspnea. Although there were numerically more patients in the group with cardiac involvement, these symptoms were not statistically significant. In the cardiac involvement group, the number of patients with chest pain and/or dyspnea was 41 (84%), which was statistically significant ($p = 0.001$). Twenty-four patients (47%) in the without cardiac involvement group were asymptomatic in a statistically significant way ($p = 0.001$). Thirty-three patients had isolated myocardial involvement, six patients had isolated pericardial involvement, and 10 patients had both pericardial and myocardial involvement (Figure 3). In the laboratory findings including NT-proBNP, Troponin I, CK-MB, D-dimer, and acute phase reactants (fibrinogen, CRP, PCT), there were no significant differences between both groups. There is no difference between the treatments initiated after COVID-19 in both groups.

All patients underwent transthoracic echocardiography (TTE). Two dimensional (2-D) and doppler echocardiographic findings were shown in Table 2. Except for systolic pulmonary artery pressure (SPAP), there was no significant difference between the two groups in terms of 2-D echocardiographic findings and doppler echocardiographic findings. SPAP is statistically significantly higher in the group with cardiac involvement ($p < 0.001$).

The CMR imaging parameters of patients with or without cardiac involvement are shown in Table 2. LV ejection fraction was statistically significantly lower in the group with cardiac involvement (61% vs 66%, $p = 0.001$). LV stroke volume and tricuspid annular plane systolic excursion (TAPSE) were statistically significantly lower in patients with cardiac involvement ($p = 0.028$ and $p = 0.019$, respectively). LV diastolic dysfunction was detected in 19 patients with cardiac involvement and in nine patients without cardiac involvement ($p = 0.019$). There was no statistically significant difference between the two groups in terms of LV end-diastolic and systolic volumes, LV wall thicknesses and atrial diameters. There was no significant difference between the groups through right ventricular ejection fraction (RVEF), RV end diastolic volumes, RV end systolic volumes, and RV stroke volumes ($p = 0.183$, $p = 0.853$, $p = 0.46$, and $p = 0.44$, respectively).

4 | DISCUSSION

This study which was carried out in a single-center, documents that 49 patients (49%) who recovered from COVID-19 had cardiac involvement identified by CMR imaging. This finding was consistent with the prevalence reported by other authors. Despite the fact that LVEF and RV functions assessed via TAPSE were in the normal range in patients with cardiac involvement as per ASE guidelines, patients with cardiac involvement had lower LVEF and TAPSE than patients without cardiac involvement. Our findings also demonstrate that even asymptomatic patients or patients with mild disease who recovered from COVID-19, had frequent cardiac involvement in the disease’s early phase. This observation is also consistent with other studies.
FIGURE 2  (A) Late gadolinium enhancement in the posterolateral wall and minimal pericardial effusion indicated by yellow arrowhead, (B) Myocardial edema in the anteroseptal wall on T2-STIR-weighted imaging, (C) Yellow arrowhead shows late gadolinium enhancement in the posteroseptal wall

FIGURE 3  Cardiac involvement types

In a systematic echocardiographic study, the most common pathology was detected as RV dilation and dysfunction followed by LV diastolic and systolic dysfunction. This is probably due to disease in the pulmonary vascular bed and parenchyma. In the current study, patients with cardiac involvement had lower LVEF and TAPSE, and more LV diastolic dysfunction concordant with the results of this study. The most severe presentation of COVID-19 spectrum, which is ARDS, has been associated with RV dilation and dysfunction, increased RV afterload, and systolic pulmonary arterial pressure. Although Hui et al. reported decreased RV function in patients with cardiac involvement, RV functions returned to normal values except RV strain, probably due to improved lung injury. In our study, although there was a numerical difference in the group with cardiac involvement in the parameters of RV functions (RVEF, RV end diastolic volumes, RV end systolic volumes, and RV stroke volumes) it did not reach statistical significance. One of these reasons may be that the median time from positive PCR test to time of cardiac imaging was 54 days. Thus, impaired RV functions during this period may have improved, but sPAB and TAPSE values may have remained high. In addition, the absence of critically ill patients in the study may explain the limited impact on RV functions. TAPSE is a parameter that demonstrates systolic functions such as RVEF and RV stroke volume. However, TAPSE is associated with longitudinal systolic functions, and RVEF and RV stroke volume are associated with global systolic functions. In our study, although RVEF and RV stroke volume values were found to be numerically low in the group with cardiac involvement, this difference did not reach statistical significance.

A significant portion of patients with myocardial injury due to COVID-19 may be missed and undiagnosed if only traditional workups such as ECG, cardiac markers, and TTE for myocardial injury are
TABLE 2 Cardiac magnetic resonance imaging (CMRI) of patients recovered from COVID-19

| CMRI parameters                  | All patients (n = 100) | Cardiac involvement- (n = 49) | Cardiac involvement- (n = 51) | p value |
|----------------------------------|------------------------|-------------------------------|-------------------------------|---------|
| LV ejection fraction (%)         | 64 (59–68)             | 61 (57–66)                    | 66 (61–71)                    | 0.001*  |
| LV end-diastolic volume (ml)     | 110 (98–127)           | 108 (89–128)                  | 111 (103–127)                 | 0.345   |
| LV end-systolic volume (ml)      | 37 (31–46)             | 41 (32–50)                    | 36 (31–42)                    | 0.050   |
| LV stroke volume (ml)            | 69 ± 17                | 65 ± 18                       | 73 ± 15                       | 0.028*  |
| RV ejection fraction (%) [n = 91] | 55 ± 7                 | 54 ± 7                        | 56 ± 7                        | 0.183   |
| RV end-diastolic volume (ml) [n = 91] | 134 ± 29             | 135 ± 31                      | 134 ± 28                      | 0.853   |
| RV end-systolic volume (ml) [n = 91] | 59 (47–70)            | 62 (48–69)                    | 56 (46–72)                    | 0.460   |
| RV stroke volume (ml) [n = 91]   | 73 ± 16                | 71 ± 15                       | 74 ± 17                       | 0.440   |
| TAPSE (mm)                       | 21.4 ± 2.6             | 20.8 ± 2.9                    | 22.0 ± 2.1                    | 0.029*  |
| LV diastolic dysfunction         | 28 (28%)               | 19 (39%)                      | 9 (18%)                       | 0.019*  |
| Interventricular septum diameter (mm) | 10 (9–11)      | 10 (9–11)                     | 10 (8–11)                     | 0.492   |
| Posterior wall thickness (mm)    | 10 (8–10)              | 9 (9–10)                      | 10 (8–10)                     | 0.730   |
| Left atrium diameter (mm)        | 34 (32–38)             | 34 (31–39)                    | 34 (32–37)                    | 0.827   |
| Right atrium diameter (mm)       | 37 (33–41)             | 39 (33–43)                    | 36 (33–41)                    | 0.188   |

Data are mean ± SD, median (IQR) and n (%). p values were determined by student t-test, Mann-Whitney U test, Chi-square test, or Fisher’s exact test, as appropriate. *p value less than 0.05 was considered significant for statistical analyses.

Abbreviations: CMRI, cardiac magnetic resonance imaging; IQR, interquartile range; LV, left ventricle; RV, right ventricle; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

performed. Puntman et al. reported over 70% of cases having cardiac involvement in their study population. Those cases, mainly consisted of asymptomatic or mildly symptomatic patients without a troponin concentration rise. In addition to these, substantial cardiac involvement may eventuate independently of the first presentation and perseveres beyond the early phase of the disease.

CMR provides detailed information about tissue characterization and detects abnormalities in spite of normal range troponin values or systolic functions of LV and RV. Regardless of the symptoms, the presence of LGE in patients diagnosed with viral myocarditis is an independent predictor of all-cause mortality and cardiac mortality. Nonetheless, myocardial edema with no fibrosis or scar has not been proven to be an independent prognosticator in patients with suspected myocarditis. A study performed on competitive athletes indicated that LVEF was significantly lower in patients with cardiac involvement.

This is a cross-sectional cohort study without any long-term follow-up data. Long-term follow-up of asymptomatic and mild cases will reveal the clinical importance of CMR findings indicating myocarditis. With the growing number of COVID-19 cases, we will likely understand the impacts of cardiac involvement in asymptomatic or mildly symptomatic patients in the upcoming years. Finally, more CMR studies are warranted to detect if cardiac involvement in asymptomatic or mild cases is relevant to prognosis.
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