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ORIGINAL ARTICLE

Association Among Levels of Troponin and Inflammatory Biomarkers at Admission with SARS-CoV-2 Disease Severity and Recent Cardiac Injury Detected Using Cardiac Magnetic Resonance Imaging

Mikail Yarlıoğlueş[1], Damla Yalçınkaya Öner[1], Hasan Yiğit[2], Uğur Bozkurt[1], Sani Namık Murat[1]

[1]Clinic of Cardiology, University of Health Sciences Türkiye, Ankara Training and Research Hospital, Ankara, Türkiye

[2]Clinic of Radiology, University of Health Sciences Türkiye, Ankara Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Background: Troponin and select inflammation biomarkers are associated with Coronavirus disease-2019 (COVID-19) severity and intensive care unit (ICU) admissions related to cardiac injury. However, cardiac magnetic resonance imaging (CMRI) remains the gold standard for detecting myocardial involvement.

Aim: This study aimed to determine whether troponin levels at admission are associated with clinical severity and CMRI-confirmed cardiac injury.

Study Design: A prospective, observational cohort study involving 51 recovered COVID-19 patients, categorized into ICU (n=16) and non-ICU (n=35) groups, and assessed 4-6 weeks postdischarge.

Methods: Blood samples were collected during hospital admission to ascertain the levels of high-sensitivity cardiac troponin T (hs-cTnT), C-reactive protein (CRP), procalcitonin, neutrophil-to-lymphocyte ratio (NLR), D-dimer, ferritin, and systemic immune-inflammation index (SII). Patients also underwent electrocardiography (ECG), transthoracic echocardiography (TTE), and CMRI. Group differences were analyzed statistically, and receiver operating characteristic (ROC) curve analysis assessed biomarker predictive performance for ICU admission and cardiac injury.

Results: ICU patients had considerably greater levels of inflammatory biomarkers and hs-cTnT ($p<0.05$). The ROC curve analysis revealed that hs-cTnT, NLR, D-dimer, ferritin, CRP, and SII levels predicted ICU admission ($p<0.05$). ECG and TTE findings were comparable between the groups. On CMRI, non-ischemic fibrosis was observed to be more prevalent in ICU patients ($p=0.03$). ROC curve revealed that hs-cTnT and SII levels predicted CMRI-detected cardiac injury ($p<0.05$).

Conclusion: The troponin and SII levels at admission were associated with disease severity and CMRI-confirmed cardiac injury, even in the presence of normal echocardiographic findings. Both markers may help predict ICU necessity and serious cardiac involvement.

Keywords: COVID-19, clinical severity, cardiac injury, biomarkers, MRI

INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), has continued to spread globally since its emergence in 2019. Despite primarily affecting the respiratory tract, cardiovascular (CV) manifestations have become increasingly significant in terms of mortality and morbidity.[1,2] A review article examining the relationship between COVID-19 and CV involvement found that myocardial injury occurred in over a quarter of critically ill patients, either during the acute phase or as the disease severity progressed.[3]

Multiple biomarkers have been associated with COVID-19 severity and intensive care unit (ICU) admissions.[4-6] Patients with elevated high-sensitivity cardiac troponin I (cTnI), cardiac troponin T (cTnT), creatine kinase-myocardial band (CK-MB), dimerized plasma fragment (D-dimer), C-reactive protein (CRP), and interleukin-6 (IL-6) have been linked to a higher risk of developing severe disease or requiring ICU admission due to cardiac injury.[7-9]

Although several biomarkers can predict cardiac injury, cardiac magnetic resonance imaging (CMRI) remains the gold standard for detecting myocardial involvement.[10] Recovered COVID-19 patients exhibited elevated rates of cardiac involvement on CMRI, with even

Address for Correspondence: Damla Yalçınkaya Öner MD, Clinic of Cardiology, University of Health Sciences Türkiye, Ankara Training and Research Hospital, Ankara, Türkiye

E-mail: damlaykaya@gmail.com **ORCID ID:** orcid.org/0000-0002-8047-389X

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higher prevalence observed in more severe cases.[11,12] This study aimed to investigate the association between admission troponin levels, clinical severity, and CMRI-confirmed cardiac injury.

MATERIALS AND METHODS

Study Population and Design

This single-center, prospective, observational cohort study included patients diagnosed with COVID-19 on reverse transcription-polymerase chain reaction (RT-PCR). Patients over 18 years of age with a positive RT-PCR test who required in-hospital follow-up either in COVID-19 clinics or COVID-19 ICU were included. In COVID-19 clinics, patients with characteristic COVID-19-related symptoms and a respiratory rate (RR) >24 beats per minute or an oxygen saturation (SpO_2) <93% were monitored. ICU admission criteria included the following: dyspnea and respiratory distress, RR ≥30/min, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) 300, elevated oxygen requirement, SpO_2 <90% or PaO_2 <70 mmHg despite 5 L/min oxygen therapy, hypotension (systolic blood pressure <90 mmHg or a drop in systolic blood pressure of more than 40 mmHg and mean arterial pressure <65 mmHg), tachycardia (>100 beats/min), acute kidney damage, impaired liver function tests, development of acute organ dysfunction (confusion, acute bleeding diathesis, etc.), immunosuppression, troponin elevation, arrhythmia, lactate >2 mmol, and skin disorders such as capillary return disorder and cutis marmaratus existence. The study excluded those under the age of 18 years, those who did not need in-hospital follow-up (RR under 24/minute, SpO_2 above 93%, and absence of bilateral diffuse (>50%) involvement on lung imaging), those with contraindications for CMRI, and those who did not volunteer.

Between November 2020 and March 2021, we enrolled 70 patients with COVID-19 who required in-hospital follow-up. The study participants were examined in two separate groups. Group 1 (n=24) contained patients who needed COVID-19 ICU follow-up, and group 2 (n=46) included patients who did not require ICU and were monitored in the COVID-19 clinics. Of these patients, four died and eight declined to participate in the study. Following their discharge, 58 patients who recovered and survived COVID-19 were monitored. Patients were deemed to have recovered if their symptoms subsided and their inflammatory markers returned to normal while their swab test findings were negative. CMRI appointments were scheduled for all participants, typically 4-6 weeks following discharge. Finally, our study population consisted of 51 patients (group 1, n=16 and group 2, n=35) after excluding those lost to follow-up (n=4) and those unable to undergo CMRI for any reason (n=3). Transthoracic echocardiogram (TTE), CMRI, and electrocardiogram (ECG) were performed concurrently on all 51 participants. Figure 1 presents the study flow diagram.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethical Committee of the Ankara Training and Research Hospital, Ankara, Türkiye (approval number: 485/2020, date: 15.01.2021). Approval for the study was obtained from the Scientific Research Platform of the Ministry of Health in Türkiye. Written informed consent was obtained from each patient after providing detailed information regarding the

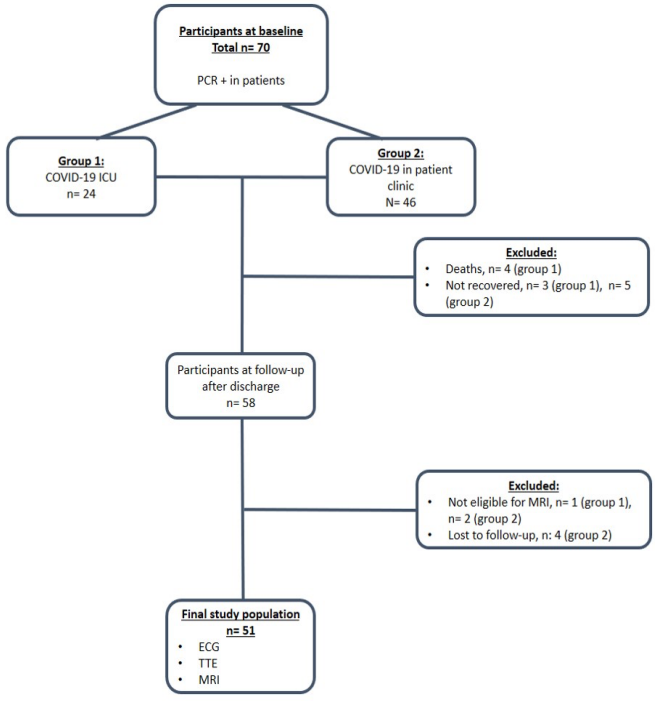

Figure 1. Flow diagram of the study population
PCR: Polymerase chain reaction, COVID-19: Coronavirus disease-2019, ICU: Intensive care unit, MRI: Magnetic resonance imaging, ECG: Electrocardiography, TTE: Transthoracic echocardiography

study. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

Data Collection and Analysis

Demographic data (sex, age, and body mass index) and clinical information, including the presence of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, heart failure, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, history of smoking, and COVID-19 RT-PCR results, were obtained from the electronic medical records and medical history forms. Initial symptoms, vital signs, and treatment administered were recorded during the in-hospital follow-up. ECG, TTE, and CMRI were performed concurrently after discharge and were evaluated by specialists in the relevant field.

Cardiac Magnetic Resonance Imaging

CMRI was performed using a 1.5 Tesla MR system (Magnetom Aera, Siemens Healthineers) with an 18-channel phased-array torso surface coil. To synchronize with the cardiac cycle, vectorcardiography was employed, and breath-hold imaging for image acquisition. Blood samples were collected while the patients were on the CMRI table, immediately before the scan, to determine hematocrit levels required for extracellular volume (ECV) calculation.

The CMRI protocol comprised static axial balanced steady-state free precession (b-SSFP) and half-Fourier acquisition single-shot turbo spin echo images beginning from the supra-aortic level and encompassing the entire heart and cine long-axis and short-axis images of both

ventricles and the left ventricular (LV) outflow tract obtained using the b-SSFP sequence. T2-weighted short-tau inversion recovery and late gadolinium enhancement (LGE) images were acquired in both long-axis and short-axis planes. For LGE imaging, a phase sensitive inversion-recovery sequence was performed ten minutes after administering gadolinium-based contrast material at a dose of 0.15 mmol/kg; TI scout software was used to determine the optimal inversion time. T2 mapping, native precontrast, and postcontrast T1 mapping sequences were added to the protocol and acquired at the same long-axis and short-axis image planes. An optimized modified look-locker inversion recovery sequence was employed for T1 mapping, acquired with a 5(3)3 scheme before contrast administration and a 4(1)3(1)2 scheme after contrast. For T2 mapping, a T2-prepared b-SSFP sequence was utilized.

Image analyses were performed on a remote diagnostic workstation (Leonardo Syngo MR E11, Siemens Healthineers) by a radiologist with 13 years of experience in CMRI. The radiologist was blinded to the participants' data when assessing the CMRI images. Cardiac analysis software (Argus; Siemens Healthineers) was used for routine cardiac measurements and functional assessment. T2-weighted short-tau inversion-recovery sequences and T2 maps were used to determine the presence of focal or global myocardial edema. Myocardial damage was assessed using both precontrast native T1 maps and postcontrast T1 maps. Pre- and post-contrast T1 and T2 times were measured using a region of interest (ROI) from focal myocardial lesions, and the ECV was calculated for these lesions. Furthermore, the mean native T1 and T2 times were ascertained with an ROI positioned in the lesion-free areas of the septal wall in all patients, and the mean myocardial ECV volume was calculated. The normal ranges of T1 and T2 times for our scanner were previously established in healthy volunteers, in accordance with the consensus statement of the Society for Cardiovascular Magnetic Resonance.

Transthoracic Echocardiography

Echocardiography was performed using a standard imaging system (Vivid S60N, GE Healthcare) equipped with a 1.5- to 4-MHz phased-array transducer. Quantitative measurements followed the American Society of Echocardiography guidelines.[13] All measurements for each participant were performed by the same specialist. The researchers were blinded to the participants' data when analyzing the TTE images. All assessments were performed with the participant in the left lateral decubitus position. LV volumes and LV ejection fraction (LVEF) were measured based on the modified two-dimensional biplane Simpson's method from apical 2 and 4-chamber views. LV end diastolic and LV end-systolic diameters were calculated using the Teichholz method from the parasternal long-axis view. Mitral inflow E and A wave velocities were assessed using pulsed wave (PW) Doppler from the apical four-chamber view, and the E/A ratio was calculated. The E' wave velocity was measured using PW tissue Doppler at the lateral mitral annulus, and the E/e' ratio was calculated. Right ventricular (RV) functioning was assessed using tricuspid annular plane systolic excursion (TAPSE) and tricuspid S' velocity. TAPSE and tricuspid S' velocity were measured through the apical four-chamber view using M-mode echocardiography and PW tissue Doppler at the lateral tricuspid annulus, respectively. The peak tricuspid regurgitation velocity was measured, while the systolic pulmonary artery pressure was evaluated using the modified Bernoulli equation.

Laboratory Findings

Blood samples were collected from patients upon hospital admission, within the first 24 hours after onset of their symptoms. Sample-giving time was defined as the interval between the onset of symptoms and the time of blood sampling. Routine blood tests included: complete blood count; serum biochemical tests [renal and liver function, creatinine kinase, glomerular filtration rate (mL/min/1.73 m^2), aspartate aminotransferase (units/L), alanine aminotransferase (units/L), and albumin levels (g/dL)]; inflammatory biomarkers [CRP, mg/dL, procalcitonin (PCT), ng/mL and ferritin, ng/mL]; coagulation biomarkers (D-dimer, ng/mL and fibrinogen, mg/dL); and cardiac biomarkers [high-sensitive cTnT (hs-cTnT, ng/L) and CK-MB, ng/mL]. Standardized test kits for hs-cTnT assay were used to process blood samples (Roche Diagnostics Cobas e411). The local laboratory cut-off value for detectable hs-cTnT was greater than 3 ng/L, with levels exceeding the 99th percentile (13.9 ng/L) considered significantly elevated. Hematological indices were measured using a SYSMEX XN-3000 automated hematology analyzer. Additionally, creatinine, serum electrolytes, and detailed liver function tests were performed utilizing a Roche Diagnostics Cobas 8000 modular analyzer. The neutrophil-to-lymphocyte ratio (NLR) represents the NLR, while the systemic immune-inflammation index (SII) is calculated as the ratio of platelet count to NLR.

Statistical Analysis

The post-hoc power analysis indicated that our study had a 91% power with an alpha value of 0.05, as calculated using a network software (https://clincalc.com/stats/Power.aspx). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) program (version 22.0; SPSS, Chicago, Illinois, USA). The Kolmogorov-Smirnov test was utilized to ascertain the distribution characteristics of the data. Normally distributed data are presented as mean±standard deviation, while the non-normally distributed data are presented as median (interquartile range). Categorical variables were compared using the chi-square test or Fisher's exact test. Results are presented as percentages. The independent sample t-test was used to evaluate the parametric scale variables, and the Mann-Whitney U test was used to analyze the non-parametric scale variables. Receiver operating characteristic (ROC) curve analysis was performed to establish the cut-off value of biomarkers for predicting the need for ICU and the presence of recent cardiac injury on CMRI. The optimal binning procedure was applied to these variables to reduce the cardinality of continuous and distinct data. A p value less than 0.05 was considered statistically significant.

RESULTS

Among the study population, 25 patients (49%) were infected with SARS-CoV-2 variants, including the alpha variant [n=16, (31%)], beta [n= 5, (10%)], and delta variants [n=4, (8%)]. Table 1 summarizes the baseline characteristics.

Table 1. Basal characteristics, clinical characteristics, and laboratory parameters of study group patients

Variables	All patients (n=51)	Group 1 (n=16)	Group 2 (n=35)	p value
Patient characteristics				
Age, years	53.1±12.7	56.8±11.6	51.3±10.6	0.077
Male, (n, %)	23 (45)	9 (56)	14 (40)	0.21
BMI	28 (24.8-32)	27.5 (24.8-29.2)	27.9 (24.8-30.3)	**0.022**
Hypertension, (n, %)	21 (41)	7 (44)	14 (40)	0.52
Diabetes mellitus, (n, %)	15 (29)	5 (31)	10 (28)	0.54
Hyperlipidemia, (n, %)	7 (14)	1 (6)	6 (17)	0.28
Current smoker, (n, %)	8 (16)	1 (6)	7 (20)	0.2
Prior history of CAD (n, %)	7 (14)	3 (19)	4 (11)	0.38
Prior history of stroke, (n, %)	1 (2)	0	1 (3)	0.68
Heart failure, (n, %)	1 (2)	1 (6)	0	0.31
CKD, (n, %)	5 (10)	1 (6)	4 (11)	0.5
COPD, (n, %)	5 (10)	3 (19)	2 (6)	0.17
Vital signs at rest				
SBP, mmHg	122.12±16.1	121.8±14.5	122.43±16.8	0.76
DBP, mmHg	74.1±.9.7	71.7±9.2	72.7±9.8	0.42
Heart rate (beats/minute)	80.29±13.6	81.1±20.2	78±12.2	0.19
Respiratory rate	19.82±4.7	23±6.7	19.8±2.5	**0.003**
Oxygen saturation level	88.18±11	76.21±14.7	90.2±1.9	**<0.001**
Temperature ≥38 °C, (n, %)	19 (33)	8	11	0.20
Initial symptoms				
Cough, (n, %)	29 (57)	8 (50)	21 (6)	0.35
Respiratory distress, (n, %)	27 (53)	12 (75)	15 (43)	**0.03**
Myalgia, (n, %)	24 (49)	8 (50)	17 (48)	0.58
Chest discomfort, (n, %)	10 (20)	1 (6)	9 (26)	0.10
Palpitation, (n, %)	7 (14)	2 (12)	5 (14)	0.62
Treatments				
Antivirals, (n, %)	50 (98)	16 (100)	34 (97)	0.68
Antibiotics, (n, %)	19 (37)	13 (81)	6 (17)	**<0.001**
IV steroids, (n, %)	32 (63)	15 (94)	17 (48)	**0.002**
Anticoagulants, (n, %)	50 (98)	16 (100)	34 (97)	0.68
Supplemental oxygen				
Nasal cannula, (n, %)	15 (29)	6 (37)	9 (26)	0.29
Reservoir mask, (n, %)	16 (31)	10 (62)	6 (17)	**0.002**
NIMV/high flow rate, (n, %)	10 (20)	10 (62)	0	**<0.001**
IMV, (n, %)	0	0	0	-
Initial laboratory measurements				
Sample collection time and hours	17 (7-23)	16 (6-23)	18 (8-23)	0.69
WBC, $\times 10^6$/L	6.43 (4.86-8.87)	8.2 (6.9-12.5)	5.31 (4-8.4)	**<0.001**
Neutrophil, $\times 10^9$/L	4.46 (3.16-7)	7 (4.82-10.63)	3.53 (2.97-7.13)	**<0.001**
Lymphocyte, $\times 10^9$/L	1.12 (0.73-1.37)	0.98 (0.69-1.4)	1.14 (0.71-1.37)	0.16
NLR	4.1 (2.5-9)	9.35 (3.87-15)	3.7 (2.97-7.13)	**0.001**
Creatine kinase, U/L	0.92±0.46	1.0±0.74	0.93±0.35	0.69
GFR (mL/min/1.73 m^2)	87.2±24.8	82.3±29.5	87.4±24.4	0.69
AST, U/L	25 (18-40)	26.5 (23.92-63.25)	30 (18.75-37.75)	**0.031**
ALT, U/L	23 (14-35)	27.4 (15.5-49.5)	25.5 (17.32-36.75)	**0.043**
Albumin, g/dL	4 (3.6-4.6)	3.2 (2.98-3.75)	4 (3.77-4.35)	**<0.001**
hs-cTnT, ng/L	5.24 (3-14.8)	23 (15.5-85.1)	4.67 (3-9.4)	**<0.001**
CK-MB, ng/mL	1.66 (0.92-2.6)	2 (1-6.2)	1.24 (0.82-2.51)	0.11
Procalcitonin, ng/mL	0.082 (0.05-0.12)	0.11 (0.09-0.33)	0.07 (0.039-0.13)	**<0.001**
D-dimer, ng/mL	490 (280-1330)	1315 (632-2832)	485 (352.5-1080)	**0.002**
Ferritin, ng/mL	387 (123-1000)	973 (403-1265)	337.5 (108-715)	**<0.001**
Fibrinogen, mg/dL	565±187.3	590.5±183.2	593.6±154.5	0.61
CRP, mg/dL	41.35 (12-114.6)	116.7 (41.1-202.1)	50.65 (17.2-98.8)	**0.011**
SII	684 (442.7-966.1)	874 (680.8-1191.9)	570 (387.2-936.2)	**0.024**

BMI: Body mass index, CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, NYHA: New York Heart Association, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanic ventilation, WBC: White blood cell count, NLR: Neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, hs-cTnT: High-sensitivity troponin T, CK-MB: Creatinine kinase myocardial bind, CRP: C-reactive protein, SII: Systemic immune-inflammation index

Group 1 patients experienced more respiratory distress as an initial symptom than group 2 patients. Group 1 patients exhibited higher RR, lower SpO_2 levels, and higher supplemental oxygen requirements than group 2 patients, consistent with the more pronounced respiratory distress. All patients received antiviral therapy. In the ICU arm, the requirement for antibiotics and intravenous steroids during hospitalization exceeded what would typically be anticipated given the disease severity.

Systemic inflammation markers, such as CRP and PCT levels, were significantly higher in group 1 patients. NLR, a crucial predictor of COVID-19 severity, was significantly higher in ICU patients. D-dimer and ferritin levels were also significantly higher in group 1. The SII, which has previously been proven to indicate COVID-19 severity, was significantly higher in group 1 patients. Hs-cTnT levels were significantly higher in group 1 compared to group 2 patients.

The ROC curve was used to determine the predictive value of hs-cTnT, NLR, D-dimer, ferritin, CRP, SII levels, and ICU admission (Supplementary Figure 1). The diagnostic accuracy of each of the significantly distinct biochemical markers was validated by the area under the curve (AUC). The hs-cTnT ROC curve for ICU admission prediction had an AUC of 0.91; the optimal cut-off value was 12.48 ng/L, with a 98% sensitivity and 87% specificity [95% confidence interval (CI): 0.83-0.98, p<0.001]. ICU admission was predicted by an NLR >3.2 with 81% sensitivity and 62% specificity [AUC=0.79 (95% CI: 0.64-0.93), p=0.001]. The optimal cut-off values for D-dimer, ferritin, and CRP to predict ICU admission were 660 ng/mL with a sensitivity of 75% and specificity of 75% [AUC=0.76 (95% CI: 0.62-0.91), p=0.002]; 294 ng/mL, with a 93% sensitivity and 52% specificity [AUC=0.81 (95% CI: 0.69-0.93), p=0.001]; 45.95 mg/dL with a 75% sensitivity and 68% specificity [AUC=0.72 (95% CI: 0.56-0.88), p=0.011], respectively. ICU admission was predicted by SII >683.2 with a 78% sensitivity and a 65% specificity [AUC=0.70 (95% CI: 544-852), p=0.02]. We also evaluated fibrinogen and CK-MB levels; however, no significant threshold values were identified for predicting ICU admission.

Table 2 details the TTE and CMRI features of the study groups. On TTE, LVEF and RV systolic functions were comparable between groups. CMRI data revealed that functional parameters were similar for both

Table 2. Electrocardiographic, transthoracic echocardiographic, and cardiac magnetic resonance imaging findings of study group patients

Variables	All patients	Group 1	Group 2	p value
Echocardiographic findings				
LVEF, %	59.1±7.8	60.3±6	56.9±9	0.77
LVED diameter = mm	49±7	51±7	50±10	0.42
RVED diameter = mm	30±3	33±9	30±4	0.64
PASP, mmHg	28.4±9	29.3±5.3	30.4±8.7	0.69
TAPSE, mm	17.7±5.2	19±5.2	17.1±5.3	0.29
RV S' velocity (mm/s)	12.48±3.2	13.9±2.8	11±2.8	0.12
Cardiac magnetic resonance imaging findings				
LVEF, %	62.23±10.26	60.44±10.84	64.42±9.9	0.46
LVEDV index (mL/m^2)	62±14.8	65.64±13.91	53±8.47	0.33
LVESV index (mL/m^2)	37.7±8.38	39.31±9.33	34±7.4	0.94
LV CO index (l/min/m^2)	2.82±0.53	3±0.58	2.57±0.5	0.28
LV mass index (g/m^2)	54.2±8.6	50.98±10.92	54.78±8	0.43
Native T1 (ms)	1091±81.6	1102±81.2	1102±78.5	0.89
Native T2 (ms)	50.14±3.9	50.5±3.9	48.93±4.8	0.76
EVF, %	34.92±11.34	34.26±9.8	36.38±14	0.59
RVEF, %	55.9±7.38	53.47±7.87	56.91±7.93	0.30
RVEDV index (mL/m^2)	67.12±13	71.6±13	60.43±10.88	0.25
RVESV index (mL/m^2)	37.42±8.52	38.21±9	34.33±7.77	0.73
RV CO index (L/min/m^2)	2.77±0.55	2.93±0.53	2.6±0.54	0.72
Late gadolinium enhancement findings				
Non-ischemic fibrosis, (n, %)	27 (44)	12 (75)	15 (43)	**0.03**
Ischemic fibrosis, (n, %)	8 (16)	3 (19)	5 (14)	0.48
Myocardial edema, (n, %)	7 (14)	3 (19)	4 (11)	0.38
Pericardial effusion, (n, %)	13 (25)	3 (19)	10 (28)	0.35
RV failure, (n, %)	12 (23)	4 (25)	8 (23)	0.56
Any injury, (n, %)	32 (63)	11 (69)	21 (60)	0.39

cQT: Corrected QT, LVEF: Left ventricular ejection fraction, LVED: Left ventricular end diastolic, LVES: Left ventricular end systolic, RVED: Right ventricular end diastolic, PASP: Pulmonary artery systolic pressure, TAPSE: Tricuspid annular plane systolic excursion, RV: Right ventricle, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end-systolic volume, LV CO: Left ventricle cardiac output, LV: Left ventricle, EVF: Extracellular volume fraction, RVEF: Right ventricular ejection fraction, RVEDV: Right ventricular end diastolic volume, RVESV: Right ventricular end-systolic volume, RV CO: Right ventricle cardiac output

groups. However, 32 patients demonstrated evidence of cardiac injury on CMRI, including at least one of the following findings: myocardial edema (n=7), pericardial effusion (n=13), RV failure (n=12), ischemic (n=8) or non-ischemic fibrosis (n=27) on LGE imaging. CMRI images of various myocardial injury patterns are presented in Supplementary Figure 2. There was a significant difference between patients monitored in group 1 and group 2 for non-ischemic fibrosis [n=12 (75%) vs. n=15 (43%); p=0.03].

The ROC curve demonstrated the predictive value of hs-cTnT for detecting any injury identified on CMRI. The ROC curve for hs-cTnT to predict cardiac injury had an AUC of 0.75; for the optimal cut-off value of 47 ng/L with a sensitivity of 70% and specificity of 70% (95% CI: 0.62-0.88, p=0.003). SII also predicted cardiac injury at a threshold above 936.4, with a sensitivity of 72% and specificity of 69% [AUC=0.72 (95% CI: 592-865), p=0.01]. We did not find a significant association between CMRI-detected cardiac injury and the following biomarkers: NLR [AUC=0.55 (95% CI: 0.37-0.71), p=0.54], D-dimer [AUC=0.60 (95% CI: 0.44-0.76), p=0.22], ferritin [AUC=0.50 (95% CI: 0.33-0.67), p=0.69], CRP [AUC=0.57 (95% CI: 0.40-0.73), p=0.40], fibrinogen [AUC=0.46 (95% CI: 0.29-0.64), p=0.69], or CK-MB [AUC=0.58 (95% CI: 0.41-0.74), p=0.36] (Supplementary Figure 3).

DISCUSSION

Our findings indicate that patients with COVID-19 who required ICU admission exhibited more pronounced inflammatory and immune responses compared to those who did not. Although no significant abnormalities were detected on ECG and TTE, CMRI revealed frequent evidence of cardiac involvement. Hs-cTnT and SII levels at admission were substantially correlated with the need for ICU and recent cardiac injury detected by CMRI in patients with COVID-19.

The inflammatory response is of significant relevance in COVID-19 progression. In a meta-analysis of inflammatory markers and COVID-19 severity, CRP, PCT, IL-6, and the erythrocyte sedimentation rate indicated a significant correlation with disease severity.[14] In COVID-19 patients, the NLR, an inflammatory marker, is linked to a poorer outcome. Consistent with previous studies, our findings showed that CRP, PCT, and NLR were associated with disease severity and ICU admission. In addition to COVID-19, NLR plays a critical role in the prediction of CV disorders. It is linked to increased mortality, particularly in acute coronary syndrome patients, and is a strong predictor of myocardial injury in severe COVID-19 patients.[15,16] Although previous studies have shown an association, our study could not find a statistically significant relationship between NLR and CMRI-detected cardiac damage. However, some studies have reported that these inflammatory markers may not always correlate with cardiac injury, suggesting a more complex relationship that warrants further investigation. For instance, a previous study reported a heterogeneous relationship between inflammatory markers and cardiac involvement, even among patients with elevated troponin levels, which may be attributed to multifactorial underlying mechanisms.[17] This discrepancy highlights the importance of interpreting inflammatory marker levels in a broader clinical context.

In a previous prospective study, CMRI was conducted to determine myocardial involvement in patients who had recently been diagnosed with COVID-19. CMRI was performed on 100 hospitalized or outpatient patients, and cardiac involvement was detected in 78% of cases.[11] Most cases were due to myocardial inflammation, ischemia, and pericardial involvement. Other studies have shown that 26% to 60% of COVID-19 patients exhibit cardiac involvement on CMRI, and these patients experienced worse prognoses and higher mortality rates.[18,19] Our study cohort only included in-hospital patients, and 32 of 51 patients (63%) showed cardiac involvement on CMRI, which is concordant with the findings of previous studies. Therefore, considering COVID-19 as a respiratory system disease may lead to an underestimation of the true extent of patient involvement. Particularly for hospitalized patients, a thorough CV evaluation is necessary.

What we have known so far is that myocarditis is the most prevalent diagnosis in COVID-19 patients, as shown on CMRI.[20] Although most patients demonstrated normal ventricular functions in previous studies, T1-T2 mapping abnormalities, myocardial edema, late gadolinium uptake, pleural effusion, and perfusion deficits provided evidence of cardiac injury in these patients. In a multi-center prospective study of 1.216 hospitalized COVID-19 patients, 3% of the study population was diagnosed with acute myocarditis.[21] However, in a meta-analysis examining CMRI findings of COVID-19 patients, the prevalence of myocarditis was 14%, while that of LGE was 20%.[22] Thus, echocardiography has limited diagnostic utility, whereas CMRI is more valuable in detecting the underlying pathology. In our study, although 32 patients (63%) had fibrosis (either ischemic or non-ischemic) on CMRI, only five exhibited LV dysfunction on echocardiography. This study once again demonstrated that CMRI was superior to echocardiography in identifying cardiac involvement and myocardial damage patterns. We anticipated that ICU patients would have higher levels of cardiac involvement on CMRI; nevertheless, the only significant difference between the two groups was non-ischemic fibrosis. We ascribed this to the typical non-ischemic pattern of LGE in myocarditis. Cardiac involvement and the frequency of non-ischemic fibrosis on CMRI rose in our study cohort as the disease worsened.

The SII has been frequently investigated for its prognostic value in cancer patients. Because it represents the immune response and systemic inflammation, it is a promising marker for understanding the course of disease in COVID-19 patients. Our results are consistent with a recently published study demonstrating the utility of the SII in predicting the in-hospital prognosis and mortality of COVID-19 patients.[23] Our findings indicate that SII is associated with both ICU admission and CMR-detected cardiac injury, supporting its potential broader use as a sensitive and specific biomarker in these contexts.

Studies have demonstrated that myocardial injury is defined by elevated cardiac troponin value, and it is linked to an adverse prognosis. It is known that hospitalized COVID-19 patients with cardiac injury demonstrate elevated high-sensitivity cTnI (hs-cTnI) levels and experience higher hospital mortality than those without injury.[24] A retrospective study confirmed that non-survivors of COVID-19 demonstrated a higher peak level of hs-cTnI.[25] Blood samples were

obtained for our study during the first 24 hours after patients' complaints and at the time of hospital admission. A mildly elevated hs-cTnT below the 99th percentile upper reference limit (>12.48 ng/L) on admission may indicate poor prognosis and be predictive of ICU admission. Our results may provide relevant insights regarding the prognostic utility of admission troponin levels for in-hospital outcomes. Therefore, during the initial admission to the hospital, these patients should be evaluated more carefully and prepared for possible clinical deterioration.

Our data were consistent with the previous studies demonstrating the relationship between higher cTnT release and positive LGE on CMRI.[26] CMRI appointments were scheduled for patients considered to be recovered, typically 4-6 weeks after discharge. A significant elevation of hs-cTnT (>47 ng/L) on admission predicted CMRI-detected cardiac injury shown even after the acute phase of the disease.

Study Limitations

Our study has certain limitations. First, our sample size was small due to the limited availability of CMRI. The small number of patients in the study and the possible unbalanced distribution of comorbidities may have impacted the results. Second, we utilized admission troponin levels because they were part of the criteria for ICU admission; however, peak troponin levels would have provided greater value in demonstrating the relationship with cardiac injury. Third, since the COVID-19 virus and its alpha, beta, and delta variants emerged at the time of the study, we could not evaluate current variant infections, such as omicron. Fourth, opportunistic infections in addition to COVID-19 in the ICU group may have influenced our results. Finally, we could not evaluate the acute effect of COVID-19 using CMRI because of ethical considerations aimed at minimizing exposure risk to healthcare personnel.

CONCLUSION

In summary, COVID-19 induces pronounced inflammatory and immune responses that lead to cardiac injury detectable on CMRI, even in the presence of normal echocardiographic findings. A comprehensive CV examination, including CMRI in selected patients, is necessary, especially in hospitalized patients. Hs-cTnT and SII levels are useful and easily accessible markers that may aid in predicting both ICU admission and cardiac injury.

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethical Committee of the Ankara Training and Research Hospital, Ankara, Türkiye (approval number: 485/2020, date: 15.01.2021).

Informed Consent: Written informed consent was obtained from each patient after providing detailed information regarding the study.

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Supplementary Figures 1-3: https://d2v96fxpocvxx.cloudfront.net/4458d962-0fb2-48a3-a23a-e35265f70f9b/content-images/4bb03e64-8671-42e9-bd62-6fd89f346833.pdf