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Cardiac Involvement is the Reason for Persistent Dyspnea in Post COVID-19 Patients without Pulmonary Sequelae: A Retrospective Study

COVID-19 Geçiren Pulmoner Sekeli Olmayan Hastalarda Kalıcı Dispne Nedeni Kardiyak Tutulumdur: Retrospektif Çalışma

Tuğçe ÇÖLLÜOĞLU[a], Murat ACAT[b], Ömer ÖZSARAÇ[c], Yeşim AKIN[a], Orhan ÖNALAN[a]

[a]Department of Cardiology, Karabük University Faculty of Medicine, Karabük, Türkiye
[b]Department of Chest Disease, Karabük University Faculty of Medicine, Karabük, Türkiye
[c]Department of Nuclear Medicine, Karabük University Faculty of Medicine, Karabük, Türkiye

ABSTRACT Objective: Several forms of cardiovascular involvement have been described in acute coronavirus disease-2019 (COVID-19) infection and also it has been shown that acute infection is responsible for cardiac symptoms. However, the data on cardiac involvement and associated symptoms in chronic phase remains unclear. Recent evidence have shown that the reason for persistent dyspnea can be persistent cardiac dysfunction in post COVID-19 infection. The aim of our study was to investigate the relationship between persistent dyspnea and cardiac involvement in post COVID-19 patients without pulmonary sequelae. **Material and Methods:** In our study, we recruited 30 post COVID-19 patients with dyspnea between January 2021 and July 2021. In all patients, the absence of pulmonary sequelae was detected with PFT and chest- CT. 2D-TTE, 2D-STE and MPS were performed for each case. **Results:** Left ventricular dysfunction was detected in 63.3% of patients and also 93.3% of patients had extensive abnormal GLS at 3 month follow-up. Of the patients, 33.3% had myocardial perfusion defect (MPD) and all MPDs were observed to be reversible defects. MPD was obviously seen in anterior wall (60%) and mid (20%) to apical (70%) segments. As compared with patients without MPD, patients with MPD had higher CK-MB (p: 0.016) and troponin I (p: 0.011), lesser PW thickness (p:0.020) and lower peak systolic strain rate at A2C view (p:0.031). Patients with NYHA III had more impaired GLS than patients with NYHA II (p:0.035). **Conclusion:** Our study suggests ischemic or non-ischemic cardiac dysfunction may be associated with persistent dyspnea in post- COVID- 19 patients without lung sequelae.

Keywords: Dyspnea; post-acute COVID-19 syndrome; heart function tests

ÖZET Amaç: Akut koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] enfeksiyonunda çeşitli kardiyovasküler tutulum biçimleri tanımlanmıştır ve ayrıca akut enfeksiyonun kardiyak semptomlardan sorumlu olduğu gösterilmiştir. Bununla birlikte, kronik fazda kardiyak tutulum ve ilişkili semptomlar ile ilgili veriler belirsizliğini korumaktadır. Son kanıtlar, kalıcı dispne nedeninin COVID-19 enfeksiyonu sonrası kalıcı kardiyak işlev bozukluğu olabileceğini göstermektedir. Çalışmamızın amacı, COVID-19 sonrası pulmoner sekeli olmayan hastalarda persistan dispne ile kardiyak tutulum arasındaki ilişkiyi araştırmaktır. **Gereç ve Yöntemler:** Çalışmamıza Ocak 2021 ile Temmuz 2021 arasında COVID-19 enfeksiyonu geçiren ve nefes darlığı devam eden 30 hastayı dahil ettik. Tüm hastalarda pulmoner sekel olmadığı SFT ve toraks BT ile tespit edildi. Her hastaya 2D- TTE, 2D- STE ve MPS yapıldı. **Bulgular:** 3 aylık takipte hastaların %63.3'ünde sol ventrikül disfonksiyonu saptandı ve hastaların %93.3'ünde yaygın anormal GLS vardı. Hastaların %33.3'ünde miyokard perfüzyon defekti (MPD) vardı ve tüm MPD'lerin geri dönüşümlü defekt olduğu gözlendi. MPD en sık olarak ön duvarda (%60) ve orta (%20) ile apikal (%70) segmentlerde görüldü.MPD'i olmayan hastalarla karşılaştırıldığında, MPD'li hastalarda daha yüksek CK-MB (p: 0.016) ve troponin I (p: 0.011), apikal iki boşluk görüntüde daha düşük PW kalınlığı (p:0.020) ve daha düşük tepe sistolik gerilim oranı vardı (p:0.031). NYHA III hastalarda NYHA II hastalara göre daha fazla bozulmuş GLS vardı (p:0.035). **Sonuç:** Çalışmamız, COVID-19 geçiren akciğer sekeli olmayan hastalarda iskemik veya non-iskemik kökenli kardiyak disfonksiyonun kalıcı dispne ile ilişkili olabileceğini düşündürmektedir.

Anahtar Kelimeler: Dispne; postakut COVID-19 sendromu; kardiyak fonksiyon testleri

Correspondence: Tuğçe ÇÖLLÜOĞLU
Department of Cardiology, Karabük University Faculty of Medicine, Karabük, Türkiye
E-mail: tugcecolluoglu48@gmail.com

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The novel coronavirus disease-2019 (COVID-19) outbreak was first reported on 8 December 2019 in China as well as was designated as a pandemic by the World Heart Organization on 11 March 2020. Since then, it has evolved into a global pandemic that continues to cause significant morbidity and mortality.[1]

The clinical manifestations of COVID-19 range from none or mild symptoms to acute respiratory distress syndrome and death in acute phase.[2] Unfortunately, most patients who recovered from COVID-19 suffer from various persistent symptoms in post COVID-19.[2,3] Like many other infectious diseases, the term of "post COVID-19 syndrome" has been emerged with ongoing symptoms.[4] Several studies have also shown that the most common reported persistent symptoms are fatigue and dyspnea in post COVID-19 syndrome.[3,5,6] The most common reason for persistent fatigue and dyspnea is lung sequelae.[7,8] However, we are often confronted with patients without pulmonary sequeale who suffer from ongoing dyspnea and fatigue even months after acute infection. Little is known about the possible reason for these patients. Cardiac sequeale can be the reason for persistent symptoms in post COVID-19 patients.[9]

In acute phase, COVID-19 infection prominently affects lungs. Histopathological specimens show the damage of alveolar-capillary membrane. So, the diffusion capacity of lung for carbon monoxide (DL_{CO}) is often impaired in post COVID-19 syndrome.[7] Besides lung inflammation, myocardial injury occurs in 20-30% of hospitalized patients, contributing to 40% of deaths.[10,11] Three possible mechanisms of cardiac injury were reported in COVID-19 infection. Proposed mechanisms for acute myocardial injury include direct invasion of virus into myocardial tissue as well as indirect mechanisms involving cardiac stress and cardiac inflammation due to systemic inflammation.[10] However, there has been insufficient data on persistent cardiac dysfunction in convelascence phase of COVID-19 infection as well as the contribution of cardiac dysfunction to ongoing symptoms has not been obviously known yet.

So, we aim to investigate the association of cardiac dysfunction with persistent dyspnea in post COVID-19 patients without pulmonary sequelae.

MATERIAL AND METHODS

STUDY POPULATION

We retrospectively investigated the records of 61 consecutive patients with persistent dyspnea after 3 months of COVID-19 recovery admitted to our chest disease outpatient clinic between January 2021 and July 2021. All patients had the following criteria: aged over 18, normal respiratory function test and chest computed tomography (CT) results. In addition, all patients did not require hospitalization during acute COVID-19 infection. Major exclusion criteria were the occurrence of pulmonary sequelae associated with COVID-19 (n=6), history of parenchymal and obstructive pulmoary disease (n=8), history of coronary artery disease (n=3), moderate to severe valvular heart disease (n=3), atrial fibrillation (n=2), left ventricular ejection fraction (LVEF) <40% (n=1). In addition, 3 patients had low image quality for two-dimensional speckle tracking echocardiography (2D-STE) analysis and myocardial perfusion scintigraphy (MPS) results were not be able to reach in 5 patients. As a consequence, 30 patients who successfully performed MPS and 2D-echocardiography with good image quality were included in our study (Figure 1). The study was conducted in full accordance with the Declaration of Helsinki and permission was obtained from Karabük University Non-invasive Clinical Trials Ethics Committee on December 15, 2021 with the decision number of 2021/765.

PULMONARY FUNCTION TEST

Every patient with dyspnea were performed pulmonary function test (PFT) by technicians in PFT laboratory. PFT and pulmonary diffusion capacity test were conducted with using spirometry (Spirolab-2), the procedure was followed by American Thoracic Society-European Respiratory Society guideline.[12] Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and FEV_1/FVC (%) were measured. Forced expiratory flow at 25-75% of forced vital capacity were taken from FVC manouevre with the highest sum of FEV_1 and FVC. Peak expiratory flow represents the maximum volume of air expired per minute or second during a single expiratory cycle. Results were expressed as absolute values and percentages of predictive values.

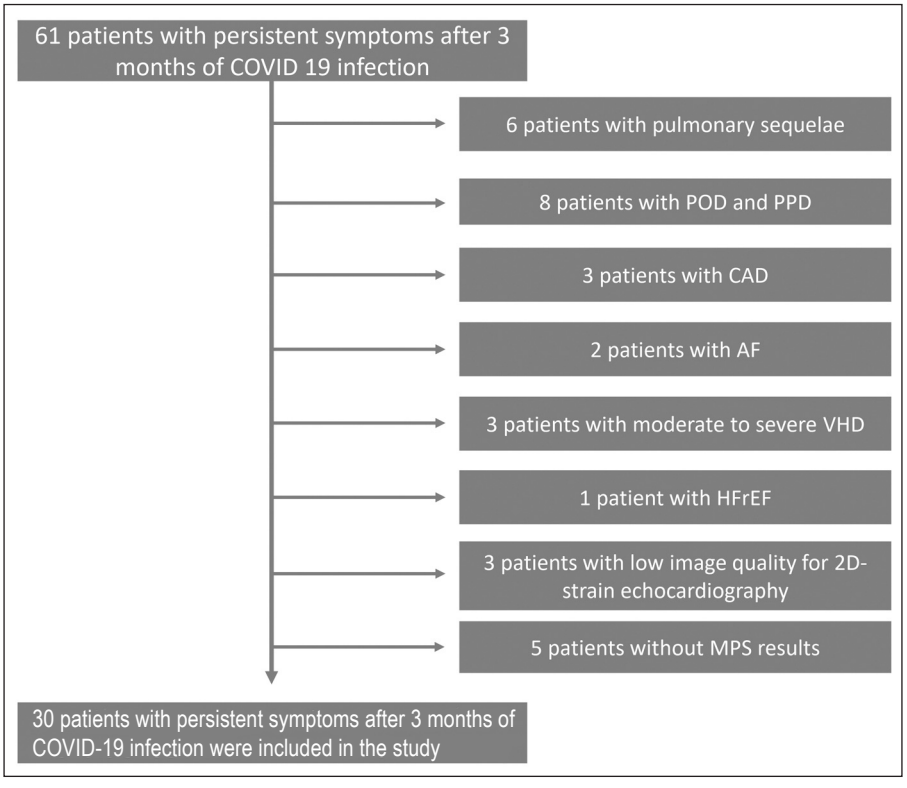

FIGURE 1: Flow chart of the study.
POD: Pulmonary obstructive disease; PPD: Pulmonary parenchymal disease; CAD: Coronary artery disease; AF: Atrial fibrillation; VHD: Valvular heart disease; HFrEF: Heart failure with reduced ejection fraction; MPS: Myocardial perfusion scintigraphy.

CHEST CT ACQUISITION

All scans were obtained using a 16-row multidetector scanner (Alexion 16 Multi-slice, Toshiba Medical System Corporation, Otawara, Japan) with the following parameters: 120 kVp, 200 mA, collimation 16*1, 1.0 pitch, reconstruction kernel (FC50-52), reconstruction matrix of 256×256, slice thickness of 1.0 mm, and high spatial resolution algorithm.

2D-TRANSTHORACIC ECHOCARDIOGRAPHIC IMAGE ACQUISITION

The patients with normal PFT and chest CT imaging were directed to our cardiology clinic and were routinely processed with 2D-transthoracic echocardiography, tissue Doppler imaging and following 2D-STE by the same cardiologist with experience using Philips EPIQ-7C Ultrasound System for Cardiology (Andover, USA) with X5-1 probe in accordance with the guidelines of American Society of Echocardiography 2015 guideline of "Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults" and "American Society of Echocardiography and the European Association of Cardiovascular Imaging".[13,14] All acquisitions were recorded digitally over 5 consecutive cycles and were stored for offline analysis. Global longitudinal strain (GLS) was divided into three groups: normal GLS was >-18%, borderline GLS was-16% to-18% and abnormal GLS was <-16% and extensive abnormal longitudinal strain was defined as abnormal GLS exceeds >4 segments.[15,16] The result of automated function imaging presented as a bull's eye plot showing color-coded and numerical values for peak systolic LS of all LV segments (Figure 2).

MPS

Patients whose dyspnea was evaluated as angina equivalent were referred to MPS. Patients underwent a 2-day protocol using Technetium 99-m methoxyisobutyronitrile for each study. Stress and rest images were recorded as a single-photon emission CT (SPECT) acquisition. Gated SPECT was performed with a dual-head camera (Anyscan S, Mediso Medi-

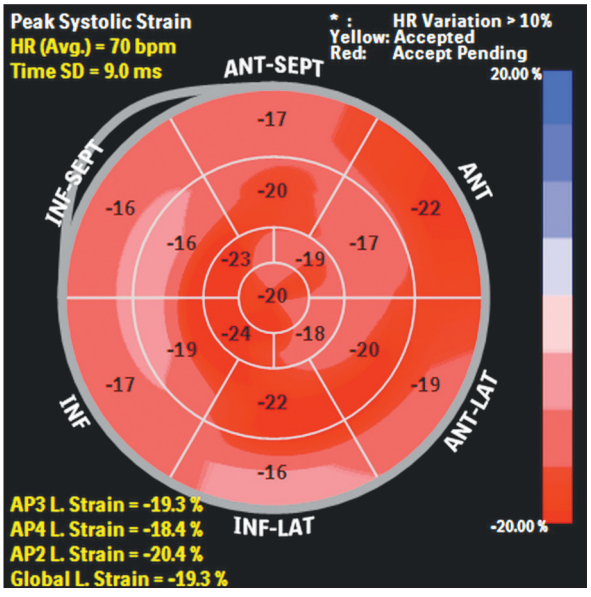

FIGURE 2: 2D-strain echocardiography displays longitudinal strain of each left ventricular segment on bull's eye map.

cal Imaging Systems, Budapest, Hungary) equipped with high resolution collimators, with the following parameters for supine acquisition: 180° angle orbit from right anterior oblique to left posterior oblique, 64 projections, 25 s/projection, 8 frames/heart cycle and 64x64 matrix.

Images were reconstructed in multiple color scales with Cedars-Sinai QGS/QPS (Los Angeles, California) software. MPS scans were viewed on a dedicated workstation (Interview XP, Mediso Medical Imaging Systems, Hungary) by using default reconstruction parameters in the standard format for display of tomographic cardiac studies.

After processing the raw data obtained from the patients with the aid of a computer, it was then evaluated both quantitatively and visually (Figure 3).

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS 25.0 Statistical Package Program for Windows (SPSS Inc., Armonk, NY: IBM Corp.). Categorical variables were expressed as absolute number or percentage and were compared using χ^2 test or Fisher's exact test, as appropriate. Normality was tested using the Shapiro-Wilk test. Continuous variables were expressed as mean± standard deviation for normally distributed variables and as median (interquartile range) for non-normally distributed variables. Comparison between two groups with continuous variables were performed by the student's t-test (two-sided) or Mann-Whitney U test, as appropriate. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF THE ENTIRE STUDY POPULATION

The baseline characteristics of the whole study population were depicted in Table 1. Our study population mainly consisted of New York Heart Association (NYHA) II class (93.33%), overweight (body mass

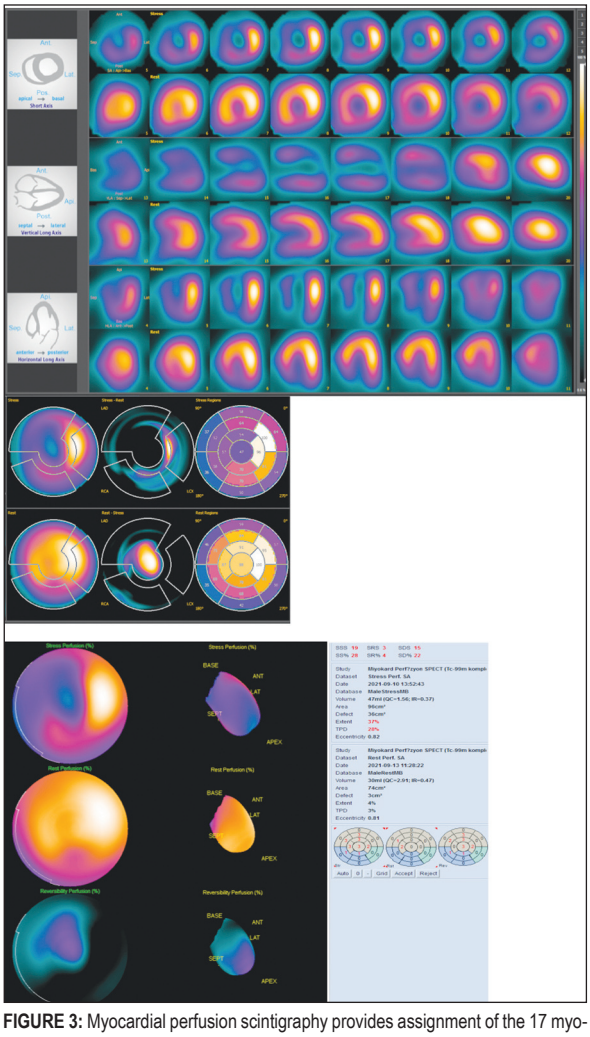

FIGURE 3: Myocardial perfusion scintigraphy provides assignment of the 17 myocardial segments to the territories of the left anterior descending artery, left circumflex artery and right coronary artery.
GLS: Global longitudinal strain.

index: 29.42±4.03 kg/m^2) and normotensive (systolic blood pressure: 130.50±15.41, diastolic blood pressure: 82.96±8.82) during 2D-echocardiographic procedure. Four patients had mild dry cough and 5 patients had exertional chest pain classified Canadian Cardiovascular Society 2 in addition to dyspnea. Troponin I, D-dimer, lymphocyte and ferritin levels were within normal range (Table 1).

BASELINE ECHOCARDIOGRAPHIC CHARACTERISTICS OF THE ENTIRE STUDY POPULATION

On echocardiography, all patients had normal to mildly reduced mean LVEF (55.65±5.75) and normal mean right ventricle (RV) lateral Sm (13.51±1.74). 2D-STE analysis revealed moderately reduced mean GLS (-17.45±2.32) and GLS at all apical chamber views (A4C: -16.69±2.80; A3C: -18.55±3.06; A2C: -17.07±2.80). Abnormal GLS was detected in 9 (30%) patients and 10 (33.3%) patients had borderline GLS (Figure 4A). Of patients, 93.3% showed extensive dysfunctional segment defined by decreased GLS (Figure 4B). The other results of echocardiographic examinations are summarized in Table 2.

MPS RESULTS

The mean time to MPS imaging was 94.76±5.98 days. Myocardial perfusion defect (MPD) was detected in 10 out of 30 patients. All these patients had reversible MPD. Mean MPD size was detected as a small defect size (6.68±2.11). The most affected segment of MPD was detected in the mid to apical segment of LV (70%), followed by the mid segment of LV (20%) and entire segment of LV (10%), respectively. In addition, 6 out of 10 patients had MPD at anterior wall. MPD was observed at inferior wall in 2 patients and at multiple territories in 2 patients, respectively (Table 3).

When the results were compared with regard to the presence of MPD; age, sex, cardiovascular risk factors, LV functional parameters and RV dimension did not statistically differ between patients with MPD and patients without MPD. However, cardiac biomarkers including creatine kinase (CK)-MB [12.85 (11.79-15.65) vs. 9.05 (6.62-12.25); p: 0.016] and troponin-I [0 (0-0.093) vs. 0 (0-0); p: 0.011] was detected statistically higher in patients with MPD than in patients without MPD. Interestingly, poste-

TABLE 1: Baseline characteristics of the COVID-19 history group.

Age (y)	49.83±10.88
Sex (male/female)	14/16
HR (beats/min)	87±14
SBP (mm Hg)	130.50±15.41
DBP (mm Hg)	82.96±8.82
BSA (m^2)	1.86±0.13
BMI (kg/m^2)	29.42±4.03
NYHA class	
I (asymptomatic) n, (%)	0 (0)
II (mild) n, (%)	28 (93.33)
III (moderate) n, (%)	2 (6.66)
IV (severe) n, (%)	0 (0)
Other symptoms	
Cough n, (%)	4 (13.33)
Chest pain n, (%)	5 (16.66)
Hypertension n, (%)	12 (40)
Hyperlipidemia n, (%)	2 (6.7)
Diabetes mellitus n, (%)	5 (16.7)
Current smoking n, (%)	6 (20)
CK-MB (u/L)	11.5 (6.38-26.06)
Troponin I (ng/mL)	0 (0.00-0.30)
BNP (pg/mL)	26.62 (2.98-112.80)
D-dimer (µg/mL)	0.26 (0.18-8.24)
Ferritin (ng/mL)	36.52 (2.50-252.80)
Haemoglobin (g/dL)	13.6±1.54
Thrombocytes	266 (239-327.5)
Leukocytes	7.57±1.59
Lymphocytes	2330 (1885-2635)
FVC (L)	3.24 (1.95-5.46)
FEV1 (L)	2.54 (1.64-4.59)
FEV1/FVC (%)	82.84±4.62
PEF (L/s)	88 (38-109)
FEF25-75 (L/s)	2.83 (1.34-5.68)

HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BSA: Body surface area; BMI: Body mass index; NYHA: New York Heart Association; BNP: Brain natriuretic peptide; FVC: Forced vital capacity; FEV1: Forced expiratory volume in second 1; PEF: Peak exoiratory flow; FEF25-75: Forced expiratory flow at 25-75% of forced vital capacity. Values are mean±standart deviation, median (interquartile range).

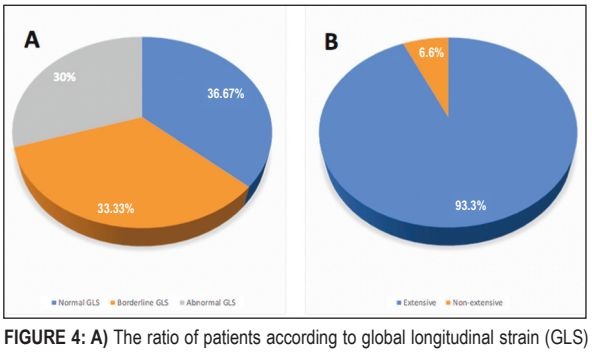

FIGURE 4: A) The ratio of patients according to global longitudinal strain (GLS) classification; **B)** The ratio of patients according to the extension of dysfunctional segment.

TABLE 2: Two dimensional, tissue Doppler imaging and speckle tracking echocardiographic findings.

LVEF (%)	55.65±5.75
LVEDVI (mL/m^2)	41.26±9.96
LVESVI (mL/m^2)	17.46 (15.15-21.15)
IVSd (mm)	1.09±0.20
PWd (mm)	0.88±0.11
LAd (mm)	3.21±0.48
RVd (mm)	2.52±0.35
MV-E (cm/s)	67.67±12.79
MV-A (cm/s)	80.00 (46.00-130.00)
MV-E/A ratio	0.81 (0.55-2.35)
TV-E/A ratio	0.94 (0.66-1.99)
LV lateral Sm (cm/s)	9.27±2.14
LV septal Sm (cm/s)	8.07±1.33
RV lateral Sm (cm/s)	13.51±1.74
Lateral E/e'	6.62 (3.69-15.34)
Septal E/e'	9.09 (5.67-16.90)
Normal GLS n, (%)	11 (36.7)
Borderline GLS n, (%)	10 (33.3)
Abnormal GLS n, (%)	9 (30)
Mean GLS (%)	-17.45±2.32
GLS-A4C (%)	-16.69±2.80
GLS-A3C (%)	-18.55±3.06
GLS-A2C (%)	-17.07±2.80
Regional left ventricle abnormal longitudinal strain n, (%)	
Extensive	28 (93.3)
Non-extensive	2 (6.6)
Time to peak strain (ms)	297 (207-480)
Mechanical dispersion (ms)	39.5 (0-201)

LVEF: Left ventricular ejection fraction; LVEDVI: Left ventricular end diastolic volume index; LVESVI: Left ventricular end systolic index; IVSd: Interventricular septum dimension; PWd: Posterior wall dimension; LAd: Left atrium dimension; RVd: Right ventricular dimension; MV: Mitral valve; GLS: Global longitudinal strain. Values are mean±standart deviation, median (interquartile range).

rior wall dimension (PWd) was found to be significantly lower in patients with MPD than in patients without MPD (0.81±0.10 vs. 0.91±0.10, p: 0.020). Moreover, patients with MPD had significantly worse peak systolic strain rate (SR) at A2C than patients without MPD (Table 4).

RESULTS ACCORDING TO NYHA CLASS

Biventricular systolic and diastolic functional parameters were evaluated according to NYHA class in post COVID-19 patients. The patients with NYHA III had significantly lower GLS (-14.00±1.83 vs. -17.55±2.50, p: 0.035).

DISCUSSION

The present study among recovered COVID-19 patients found that (1) 63.3% of patients had 2D-STE evidence for myocardial dysfunction at 3 month follow-up, (2) extensive abnormal GLS was detected in 93.3% of patients, (3) 33.3% patients had MPD and all MPDs were observed to be reversible defects, (4) MPD was mainly located in anterior wall (60%) and mid (20%) to apical (70%) LV segments, (5) patients with MPD had higher cardiac biomarkers, lesser PW thickness and lower peak systolic SR A2C view, (6) the more impaired GLS was found in more symptomatic patients. Our results also demonstrate that patients with persistent dyspnea who recovered from COVID-19 had frequent sustained cardiac involvement in the chronic phase. This finding is also consistent with other cardiac magnetic resonance (CMR) imaging studies.[1,17]

Extensive impaired GLS was the major finding on 2D-STE in our study patients. Several studies have suggested that persistent symptomatic patients recovered from COVID-19 have LV abnormalities in CMR, including myocardial edema, inflammation and late gadolinium enhancement (LGE) lesions at inferior and inferolateral wall.[17] Likewise, a CMR study by Kravchenko et al. detected that patients with ongoing symptoms after COVID-19 infection had LGE lesions in subepicardium at basal segment of inferolateral wall and mid segment of RV attachment.[18]

TABLE 3: Myocardial perfusion scintigraphic findings.

Time to MPS (day)	94.76±5.98
MPD n, (%)	10 (33)
Reversible perfusion defect n, (%)	10 (100)
Irreversible perfusion defect n, (%)	0 (0)
Regional left ventricle segment PD n, (%)	
Apical	7 (70)
Mid	2 (20)
Basal	0 (0)
All	1 (10)
Regional left ventricle wall PD n, (%)	
Anterior	6 (60)
Inferior	2 (20)
Septal	0 (0)
Lateral	0 (0)
Multiple	2 (20)

MPS: Myocardial perfusion scintigraphy; MPD: Myocardial perfusion defect; PD: Perfusion defect.

TABLE 4: Comparison of COVID-19 patients with and without myocardial perfusion defect.

	Myocardial perfusion defect		
	Present (n=10)	Absent (n=20)	p value
Age (y)	54.40±9.20	47.55±11.14	0.105
Sex (male/female)	6/4	8/12	0.442
Hypertension n, (%)	6	6	0.139
Hyperlipidemia n, (%)	0	2	0.540
Diabetes mellitus n, (%)	3	2	0.300
Current smoking n, (%)	3	3	0.372
CK-MB (u/L)	12.85 (11.79-15.65)	9.05 (6.62-12.25)	0.016
Troponin I (ng/mL)	0 (0-0.093)	0 (0-0)	0.011
BNP (pg/mL)	24.03 (9.06-50.45)	26.62 (7.39-40.22)	0.538
LVEF (%)	54.67±5.54	56.14±5.93	0.519
RVd (mm)	2.51±0.52	2.52±0.25	0.927
IVSd (mm)	1.16±0.25	1.06±0.17	0.259
PWd (mm)	0.81±0.10	0.91±0.10	0.020
LAd (mm)	3.30±0.51	3.16±0.46	0.443
LV lateral Sm (cm/s)	9.20±2.31	9.30±2.11	0.906
LV septal Sm (cm/s)	7.87±0.79	8.17±1.55	0.577
RV lateral Sm (cm/s)	13.63±1.33	13.45±1.94	0.788
Mean GLS (%)	-16.81±2.39	-17.77±2.28	0.292
GLS-A4C (%)	-15.76±2.78	-17.16±2.76	0.201
GLS-A3C (%)	-18.26±3.02	-18.70±3.14	0.715
GLS-A2C (%)	-16.42±2.73	-17.39±2.85	0.379
SR-A4C			
Early diastolic (/s)	0.69±0.10	0.75±0.26	0.548
Late diastolic (/s)	0.64±0.39	0.84±0.22	0.079
Peak systolic (/s)	-0.88±0.14	-1.01±0.16	0.054
SR-A3C			
Early diastolic (/s)	0.85±0.16	0.89±0.24	0.642
Late diastolic (/s)	0.78±0.34	0.84±0.22	0.580
Peak systolic (/s)	-0.98±0.11	-1.07±0.19	0.191
SR-A2C			
Early diastolic (/s)	0.76±0.20	0.75±0.29	0.950
Late diastolic (/s)	0.71±0.39	0.89±0.30	0.196
Peak systolic (/s)	-0.87±0.10	-1.02±0.19	0.031
Time to peak strain (ms)	290.50 (275.50-409.50)	300.00 (271.75-328.25)	0.588
Mechanical dispersion (ms)	42.00 (26.25-88.25)	33.50 (17.00-68.00)	0.397

BNP: BNP: Brain natriuretic peptide; LVEF: Left ventricular ejection fraction; RVd: Right ventricular dimension; IVSd: Interventricular septum dimension; PWd: Posterior wall dimension; LAd: Left atrium dimension; GLS: Global longitudinal strain; SR: Strain rate. Values are mean±standart deviation, median (interquartile range).

Similar to findings of CMR studies, Özer et al. showed that impaired GLS was detected in 37.8% of patients in the first month after COVID-19 infection.[19] In our study, 63.3% of patients had an impaired GLS. This difference is probably due to study population. While all patients in our study were symptomatic; the patients in the study of Özer et al. were included regardless of symptoms.[19]

It is known that more reduction in GLS was detected in more symptomatic patients during both acute COVID-19 infection and convalescence phase.[20,21] In line with these previous studies, GLS was found to be significantly lower in patients with NYHA III symptoms in our study. This relationship suggests that the presence of cardiac dysfunction may lead to significant contribution to adverse outcomes such as hospitalization and presenting to out-patient clinic for heart failure symptoms in convalescence phase of COVID-19 infection. So that, close monitoring among COVID-19 recovered subjects may be

required to elucidate long term cardiovascular outcomes. In addition, the main reason for symptoms may be coronary microvascular disease (CMD) and the prognosis may be worse due to higher cardiac biomarkers in more symptomatic patients. In the study by Yang et al., high sensitive troponin, CK-MB and myoglobin were detected significantly higher in non-recovery patients with 28 day follow up as well as CK-MB and myoglobin were detected risk predictors for adverse outcomes.[22] Besides showing adverse outcomes, elevated cardiac biomarkers may be the sign of functional capacity. In the United Kingdom, a multicenter observational study including COVID-19 and elevated troponin was designed. The relationship of cardiac biomarkers with functional capacity will be examined in a follow up step of this study.[23] We think that the results of this study will support our findings in the future.

Impaired myocardial perfusion was seen in 23% of symptomatic patients recovered from COVID-19 without coronary artery disease.[24] In our study, we detected MPD in 33.3% of patients. The main reason for this difference may be the time to MPS imaging. Çap et al. performed MPS imaging at a median day of 150 whereas the mean time of MPS was 94.76±5.98 days.[24] The thrombus may regress over time. Drakos et al. showed the best example of this situation in their study. They performed repeated stress CMR imaging in a patient and detected increase in global myocardial perfusion reserve (MPR) within 5 months as well as observed improved clinical outcomes.[25]

The exact mechanism of ongoing myocardial injury in COVID-19 patients has not been still well understood. The possible pathomechanisms may be abnormal cytokine release due to the activation of complex signalling pathways and the presence of coronary microvascular thrombus, which may cause persistent CMD. Persistent CMD can also lead to myocardial injury and heart failure. The CMR imaging study by Drakos et al. made a significant contribution to description of CMD associated with COVID-19. In this study, the patients after 1-6 months of recovery from COVID-19 infection had significantly lower resting coronary sinus flow and global MPR.[25] However, the exact pathophysiological mechanism of CMD could not be explained in the study. Due to limited evidence from clinical trials, the cardiac pathological trials may be needed to adequately evaluate the exact pathophysiological etiology of CMD in post COVID-19 patients.

There may be a relationship between PW dimension and peak systolic SR at A2C view in post COVID-19 patients with MPD. A thin PW can be associated with increase in regional wall stress according to Laplace's law.[26] Increase in PW stress can lead to deteriorate peak systolic SR at A2C view. 2D-STE may be helpful for detecting early changes in systolic function in PW in post COVID-19 patients with symptoms.

LIMITATIONS

Our study has some limitations. It was a single center and retrospective design. Our study sample size was relatively small and had not a control group. In addition, coronary angiography was not performed in patients with MPD due to small defect size. It would be interesting to define the ratio of epicardial coronary lesions in this population. Our study is not a follow up study. We only included patients with persistent symptoms after 3 months of COVID-19 infection. Larger studies with long term follow up are required to better elucidate the change of MPD and myocardial functional parameters.

CONCLUSION

Persistent dyspnea after COVID-19 infection may be associated with cardiac dysfunction in patients without pulmonary sequelae. Ischemic and non-ischemic etiology may cause cardiac dysfunction in this population as well as noninvasive imaging modalities can be helpful in establishing the correct diagnosis and providing information about the extent and localization of the disease.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise,

working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tuğçe Çöllüoğlu, Murat Acat;* ***Design:*** *Orhan Önalan;* ***Control/Supervision:*** *Yeşim Akın;* ***Data Collection and/or Processing:*** *Tuğçe Çöllüoğlu, Ömer Özsaraç;* ***Analysis and/or Interpretation:*** *Yeşim Akın, Orhan Önalan;* ***Literature Review:*** *Tuğçe Çöllüoğlu;* ***Writing the Article:*** *Tuğçe Çöllüoğlu, Murat Akın, Ömer Özsaraç;* ***Critical Review:*** *Orhan Önalan, Yeşim Akın;* ***References and Fundings:*** *Tuğçe Çöllüoğlu;* ***Materials:*** *Tuğçe Çöllüoğlu.*

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