



## Cardiac Findings after COVID-19 Treatment and Completed Quarantine Process

### COVID-19 Tedavisi ve Karantina Süreci Tamamlandıktan Sonraki Kardiyak Bulgular

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#### ABSTRACT

**Objective:** Our aim was to determine late-term which cardiac effects were in hemogram, biochemical parameters, cardiac biomarkers, Electrocardiography (ECG) and Transthoracic echocardiography (TTE) and which cardiac complaints were in the patients admitted to the Cardiology outpatient clinic after the Coronavirus disease 2019 (COVID-19) treatment and quarantine process was completed.

**Method:** 132 consecutive patients included in this retrospective study. ECG and TTE were performed, hemogram, biochemical parameters, cardiac biomarkers; high sensitive cardiac troponin T (hs-cTn), N terminal Pro B type natriuretic peptid (NT-pro BNP) and D-dimer were studied in all patients on admission.

**Results:** In this study, we found the following findings in the patients: the most common co-morbidity was hypertension in 39 (29.5%) patients, the most common complaints of the patients presenting to the Cardiology outpatient clinic was chest pain in 48 (36.40%) patients, the most common ECG finding was sinus tachycardia in 11 (8.3%) patients, the most common TTE finding was mild tricuspid regurgitation in 63 (47.70%) patients. In this study we have found systolic pulmonary artery systolic hypertension rate 6.10% and the rate was higher than compared to the normal population. It was remarkable that pericardial hyperchocogenicity was detected in 18 (13.60%) patients. We detected elevated D-dimer levels were detected in 24 (18.20%) patients, elevated NT-pro BNP levels in 15 (11.40%) patients and elevated hs-cTn levels in 9 (6.8%) patients.

**Conclusion:** The patients should be evaluated in the Cardiology outpatient clinic to investigate whether they have late-term cardiac effects due to COVID-19 infections.

**Keywords:** COVID-19, electrocardiography, transthoracic echocardiography

#### ÖZ

**Giriş:** Amacımız, Coronavirus disease 2019 (Covid-19) tedavisi ve karantina süreci tamamlandıktan sonra Kardiyoloji Polikliniğine başvuran hastaların geç dönemde hangi kardiyak şikayetler ile başvurduğunu ve biyokimyasal parametrelerde, kardiyak biyobelirteçlerde, elektrokardiyografi (EKG) ve transtorasik ekokardiyografide (TTE) hangi kardiyak bulguların olduğunu tespit etmektir.

**Yöntem:** Bu retrospektif çalışmaya ardışık 132 hasta dahil edildi. EKG çekildi, TTE yapıldı. Tüm hastalarda başvuruda hemogram, biyokimyasal parametreler, kardiyak biyobelirteçler; yüksek duyarlılıklı kardiyak troponin T, N terminal pro B tipi natriüretik peptid ve D-dimer çalışıldı.

**Bulgular:** Kardiyoloji Polikliniğine başvuran hastalarda en sık görülen ko-morbidite hipertansiyon 39 (%29,50), en sık görülen kardiyak şikayet göğüs ağrısı 48 (%36,40), en sık EKG bulgusu sinüs taşikardisi 11 (%8,3), en sık TTE bulgusu hafif triküspit yetersizliği 63 (%47,70). Bu çalışmada sistolik pulmoner arter hipertansiyon oranının %6,10 bulduk ve bu oran normal popülasyona göre daha yüksekti. Perikardiyal hiperekojenitenin 18 (%13,60) hastada saptanması dikkat çekiciydi. Yüksek D-dimer seviyesi 24 (%18,20) hastada, yüksek NT-pro BNP seviyesi 15 (%11,40) hastada ve yüksek hs-cTn seviyesi 9 (%6,80) hastada tespit edildi.

**Sonuç:** Hastalar, Covid-19'un geç dönem kardiyak etkilerinin olup olmadığını araştırmak için Kardiyoloji Polikliniğinde değerlendirilmelidir.

**Anahtar Kelimeler:** COVID-19, elektrokardiyografi, transtorasik ekokardiyografi

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## INTRODUCTION

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) which causes corona virus disease 2019 (COVID-19) has resulted in a world health crisis. In December 2019, COVID-19 was first described in Wuhan, China, in patients complaining of flu-like symptoms. World Health Organization declared Covid-19 as a pandemic on March 11, 2020 (1). The exact effects of COVID-19 on the cardiovascular system are not well determined but several case reports and reviews have been published. Myocarditis in COVID-19 has been recognized as the cause of death in some patients (2). COVID-19 can directly cause cardiacandvascular injuries such as pericarditis, myocarditis, myocardialinfarction, heartfailure, arrhythmias, orthromboembolicevents (3).Such cardiac complication sares how both during the course of COVID-19 treatment and after the COVID-19 treatment is completed. In this study, our aim was to determinelate-term cardiac effects of COVID-19. Biochemical parameters including cardiac biomarkers, electrocardiography (ECG) andtransthoracic echocardiography (TTE) were performed. Cardiac complaints of the patients who admitted to the cardiologyout-patient clinic after completion of COVID-19 treatment and the quarantine process.

## MATERIALS AND METHODS

This study was an observational retrospective study. Republic of Turkey Ministry of Health gave permission to do the research. This research was ethically conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board and waived the requirement for informed consent. The protocol was approved by the local ethics committee.132 consecutive patients who were treated for COVID-19, completed quarantine process and admitted to the cardiology out-patient clinic between January 2, 2021 and February 2, 2021 were included in this retrospective study. All clinical, laboratory and outcome data were extracted from electronic medical records using a standardized data collection form and patient's file from archive.

Cardiac complaints of the patients such as chest

pain, shortness of breath, palpitation and back pain were recorded. Demographic features of the patients age, female gender, chronic diseases [diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), chronic kidney disease (CKD), chronic hemodialysis, chronic peritoneal dialysis, chronic obstructive pulmonary disease (COPD), documented coronary artery disease, stroke history, cirrhosis] were recorded. Laboratory data on admission (glucose, creatinine, sodium, potassium, white blood cell, hemoglobin, hematocrit, glomerular filtration rates, D-dimer, high-sensitive cardiac troponin T(hs-cTn) and N terminal pro-B type natriuretic peptide (NT-proBNP) were recorded. The ECGs was performed bycardiology out-patient clinic nurses. Findings such as resting heart rate per minute, presence of normal sinus rhythm and atrial fibrillation, PR interval, QRS duration, QTc interval, presence of atrioventricular block, bundle branch block, sinus tachycardia and sinus bradycardia were recorded on the ECGs of the patients. TTE was conducted by the cardiologists at the cardiology out-patient clinic. Diameters was measured with M-mode. Ejection fraction was measured using Simpson method. Left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), valve regurgitation, systolic pulmonary artery pressure (SPAP), pericardial effusion, pericardial hyperechogenicity were recorded.

Patients over the age of 18, diagnosed with COVID-19 with polymerase chain reaction test (PCR)positivity and admitted to the cardiology out-patient clinic after completion of COVID-19 treatment and the quarantine process, for cardiac control or due to cardiac complaints such as chest pain, shortness of breath, palpitation and back pain were included in the study.

Patients under 18 years of age, hospitalized patients, patients with chronic heart failure (EF lower than 50%), acute renal failure, chronic renal failure [glomerular filtration rate (GFR)below60ml/min/1.73 m<sup>2</sup>],acute liver failure,cirrhosis, history of tuberculosis, history of autoimmune conditions, hyperthyroidism, hypothyroidismand patients on hemodialysis or peritoneal dialysis were excluded from the study.

SPSS software for Windows (release 15.0.0, SPSS, Chicago, IL) was used for statistical analysis. The Kolmogorov-Smirnov test was used to determine the normality of the variables. Continuous variables were reported as mean±standard deviation or median (IQR). Categorical variables were reported as the number (percentage) of participants.

## RESULTS

In the study we included patients over the age of 18, diagnosed as COVID-19 with PCR positivity and admitted to the cardiology out-patient clinic after completion of COVID-19 treatment and the quarantine process, for cardiac control or due to cardiac complaints.

The admission of the patients to the cardiology out-patient clinic was median 30 (14-150) days after the completion of the quarantine process.

87 (66%) of the patients were women and 45(34%) of the patients were men. The mean age was 43.76±13.45 years. The accompanying comorbidities of the all the patients were as follows: DM 17 (12.9%), HT 39 (29.5%), HL 20 (15.2%), CAD 16 (12.1%), COPD 6 (4.5%), stroke history 1 (0.8%), metallic mitral valve prosthesis 1 (0.8%). The basic clinical characteristics of the patients, including age, gender, comorbidities are listed in Table 1.

Age (mean±SD), years		43.76±13.45	
		n	%
Sex	Male	45	34
	Female	87	66
Hypertension		39	29.5
Diabetes mellitus		17	12.9
Hyperlipidemia		20	15.2
Coronary artery disease		16	12.1
Chronic obstructive pulmonary disease		6	4.5
Stroke		1	0.8
Mitral valve prosthesis		1	0.8
n: number SD: standard deviation			

Chest pain, shortness of breath, palpitation and back pain were present in 48 (36.40%), 21 (15.90%), 27 (20.50%) and 18 (13.63%) patients, respectively (Table 2).

	n	%
Back pain	18	13.63
Angina	48	36.4
Dyspnea	21	15.9
Palpitation	27	20.5
n: number		

Median resting heart rate was 79.00 (66.10-99.00) beatper minute, atrial fibrillation was present in 2 (1.5%), sinus tachycardia in 11 (8.3%), sinus bradycardia in 3 (2.3%), right bundle branch block in 6 (4.5%), left bundle branch block in 1 (0.8%), atrial extrasystole in 7 (5.3%), ventricular extrasystole in 5 (3.8%) patients. Mean PR interval, median QTc interval and median QRS duration were 148.99±19.63 millisecond (ms), 399.00 (377.90-427.10) ms, and 85.50 (75.00-102.00) ms, respectively. Short PR interval was present in 7 (5.3%) patients. Long PR interval was detected in 2 (1.5%) patients. Long QTc was found in 5 (3.8%) patients. Left ventricular hypertrophy was present in 5 (3.8%) patients. ECG findings of the patients are shown in Table 3.

Median LVEF was 60% (60-65), LV hypertrophy was present in 14 (10.60%), LV diastolic dysfunction in 15 (11.40%), mild mitral regurgitation in 32 (24.20%), moderate mitral regurgitation in 3 (2.30%), mild tricuspid regurgitation in 63 (47.70%) patients. Median SPAP was 25.00 mmHg (20.00-35.00), Pericardial hyperechogenicity was present in 18 (13.60%), mild aortic regurgitation in 8 (6.10%), systolic pulmonary arterial hypertension (sPAH) in 8 (6.10%) patients. TTE findings of the patients are shown in Table 4.

Median glucose level was 98 (84.00-140.30) mg/dl and median creatinine level was 0.70 (0.60-1.00) mg/dL.

**Table 3 : Electrocardiography Findings of the Patients**

	bpm	ms	median	IQR	mean ± SD	n	%
<b>Heart rate</b>	79.00		66.1	96.0			
<b>Tachycardia</b>						11	8.3
<b>Bradycardia</b>						3	2.3
<b>Right bundle branch block</b>						6	4.5
<b>Left bundle branch block</b>						1	0.8
<b>Atrial extrasystole</b>						7	5.3
<b>Ventricular extrasystole</b>						5	3.8
<b>PR interval</b>					148.99 ± 19.630		
<b>QTc interval</b>		399.0	377.9	47.1			
<b>Left ventricular hypertrophy</b>						5	3.8
<b>QRS duration</b>		85.5	75.0	102.0			
<b>Short PR interval</b>						7	5.3

bpm: beats per minute, IQR: Inter Quantile Range, n: number, SD: standard deviation, ms: millisecond

**Table 4: Transthoracic Echocardiography Findings of the Patients**

	mmHg	median	IQR	n	%
<b>Left ventricular hypertrophy</b>				14	10.6
<b>Ejection fraction</b>		60	65		60.0
<b>Left ventricular diastolic dysfunction</b>				15	11.4
<b>Mild mitral regurgitation</b>				32	24.2
<b>Moderate mitral regurgitation</b>				3	2.3
<b>Tricuspid regurgitation</b>				63	47.7
<b>Systolic pulmonary arterial pressure</b>	25.0	20	35		
<b>Pericardial effusion</b>				2	1.5

IQR: Inter Quantile Range, n: number

Median urea, mean GFR, median sodium and median potassium levels were 26.00 (15.00-39.00) mg/dl, 103.48±16.70, 139.00 (136.00-142.00) mmol/L and 4.20 (3.80-4.80) mmol/L, respectively. Median alanine amino transferase level was 17.00 (8.00-36.00) U/L and median aspartate amino transferase level was 18.00 (13.20-28.60) U/L. Median CRP level was calculated as 2.50 (0.45-13.10)mg/L. Median thyroid stimulating hormone was 1.50 (0.90-3.08) IU/ mL. Median hemoglobin level, mean hematocrit, mean white blood count (WBC) and median thrombocyte count were 13.10 (11.04-15.68) mg/dL, 40.04±4.42%, 7.40±2.43 10<sup>3</sup>/L and 254.00 (188.40-348.80) 10<sup>3</sup>/L, respectively. Median hs-cTn level was 3.30 (3.00-12.00) ng/L and median NT-proBNP level was 53.50 (13.32-203.90) pg/mL. Median D-dimer level was calculated as 0.20 (0.20-0.84) µg/ml. Anemia was present in 23 (17.40%) patients. High CRP was found in 28 (21.20%), high WBC in 19 (14.40%), low thrombocyte in 1 (0.8%), high thrombocyte in 5 (3.8%), high hs-cTn in 9 (6.8 %), high D-dimer in 24 (18.20%) µg/ml and high NT-proBNP in 15 (11.40%) patients. Laboratory findings of patients on admission are shown in Table 5.

**Table 5: Laboratory Findings of Patients on Admission**

	n	%	
Glucose (mg/dl) median (IQR)	98.00 (84.00-140.30)		74-106mg/dl
Urea (mg/dl) median (IQR)	26.00 (15.00-39.00)		10-50 mg/dL
Creatinine (mg/dl) median (IQR)	0.70 (0.60-1.00)		0.5-0.9 mg/dL
Sodium (mmol/L) median (IQR)	139.00 (136.00-142.00)		135-148 mmol/L
Potassium (mmol/L) median (IQR)	4.20 (3.80-4.80)		3.4-4.5 mmol/L
Glomerular filtration rate mean $\pm$ SD	103.48 $\pm$ 16.70		
Alanine aminotransferase (U/L) median (IQR)	17.00 (8.00-36.00)		0-33 U/L
Aspartate aminotransferase (U/L) median (IQR)	18.00 (13.20-28.60)		0-32 U/L
CRP (mg/L) median (IQR)	2.50 (0.45-13.10)		0-5 mg/L
Thyroid stimulating hormone ( $\mu$ IU/mL) median (IQR)	1.50 (0.90-3.08)		0.270-4.20 $\mu$ IU/mL
White blood count ( $10^3/\mu$ L) mean $\pm$ SD	7.40 $\pm$ 2.43		3.98-10.04 $10^3/\mu$ L
Hemoglobin (g/dl) median (IQR)	13.10 (11.04-15.68)		11.7-16.0 g/dL
Hematocrit (%) mean $\pm$ SD	40.04 $\pm$ 4.42		35-47%
Thrombocyte ( $10^3/\mu$ L) median (IQR)	254.00 (188.40-348.80)		150-388 $10^3/\mu$ L
High sensitive cardiac troponin T (ng/L) median (IQR)	3.30 (3.00-12.00)		0-14 ng/L
D-Dimer ( $\mu$ g/mL) median (IQR)	0.20 (0.20-0.84)		0-0.5 $\mu$ g/ml
NT-proBNP (pg/mL) median (IQR)	53.50 (13.32-203.90)		0-125 pg/mL
High CRP	2 8	21.2 0	
High white blood count	1 9	14.4 0	
Anemia	2 3	17.4 0	
Low thrombocyte	1	0.80	
High thrombocyte	5	0.80	
High sensitive cardiac Troponin T	9	6.80	
High D-Dimer	2 4	18.2 0	
High NT-ProBNP	1 5	11.4 0	
bpm: beats per minute, IQR: Inter Quantile Range, n: number, SD: standard deviation, ms: millisecond, mg/dl: milligram/deciliter, mmol/L: millimole/liter, $\mu$ IU/mL: micro international unit/milliliter, $\mu$ g/mL: microgram/ milliliter, $\mu$ L: microliter, mg/L: milligram/liter, pg/mL: picogram/ milliliter, NT-proBNP: N terminal Pro B type natriuretic peptid, CRP: C reactive protein, ng/L:nanogram/liter, U/L: unit/liter			

## DISCUSSION

In the study we included patients over the age of 18, diagnosed as COVID-19 with PCR positivity and admitted to the cardiology out-patient clinic after completion of COVID-19 treatment and the quarantine process, for cardiac control or due to cardiac complaints. The majority of the patients were women; three of them were in postpartum period, one of them was a 35-week pregnant woman. 21 year-old 35-week pregnant patient was hospitalized with symptoms of chest pain and palpitation. She had high WBC and D-dimer levels. A total of six patients were diagnosed with acute pericarditis. Two of them were hospitalized because they had acute pericarditis with pericardial effusion. We have defined this clinical situation as a delayed complication of COVID-19 infection. The other four patients were treated at out-patient clinic.

In this study, the most common co-morbidity was HT, seen in 39 (29.5%) patients. As mentioned in previous literature, hypertension is a risk factor for COVID-19. This finding was supported by our study. The most common complaint of the patients presenting to the cardiology out-patient clinic was chest pain, seen in 48 (36.40%) patients. The characteristic of this chest pain was pleuritic. It did not meet the typical angina criteria. Acute coronary syndrome was not detected in any patient. A 45-year-old woman had a positive cardiovascular stress test and invasive coronary angiography was performed which revealed non-critical coronary stenosis.

When the echocardiographic findings were analyzed, the most common finding was mild tricuspid regurgitation. Mild tricuspid regurgitation was mostly considered physiological. We used Bernoulli equation to measure the SPAP. We detected sPAH in 8 (6.10%) patients. Moreira EM et al. found the prevalence of echocardiographic pulmonary hypertension to be 2.6% (95% CI: 2.0; 3.2) in the general population (4). In our study, we think that such a high rate of sPAH, compared to the normal population, was a result of secondary pulmonary hypertension due to the damage of the lung. In addition to this finding, pericardial hyperechogenicity was detected in 18 (13.60%)

patients. Pericardial hyperechogenicity was observed especially, adjacent to the left ventricular lateral wall in four-chamber view and left ventricular posterior wall in parasternal long axis view. As with other viral infections, it has been postulated that COVID-19 may trigger cascades of inflammatory pathways which can potentially result in multi-organ injury including heart, lung, and the serosal surface encompassing them. When COVID-19 elicits this inflammatory response, it is reasonable that this may lead to pericarditis and pericardial effusion similar to other viral infections (5). SARS-CoV-2 which belongs to coronavirinae sub family, is a single-strand RNA coronavirus, which enters human cells mainly by binding the angiotensin-converting enzyme 2 (ACE2) receptor (6). ACE2 is mainly located at human oral pharynx, upper airway, heart, liver, kidney, intestine, neuron, and testis. (7). Generally, COVID-19 predominantly presents with respiratory symptoms and pulmonary injury, but as cases have multiplied, there has been increasing awareness of its cardiovascular involvement (8). Some cases of pericardial involvement during and after symptomatic COVID-19 infection have been reported. In a case study, the presence of COVID-19 in the pericardial fluid was detected using PCR on pericardial fluid (9). Until polymerase chain reaction testing for COVID-19 on pericardial fluid becomes more available, work-up to rule out other causes should be completed before considering COVID-19 as the cause of the disease (10). In this study other echocardiographic findings were not different from the normal population.

When the laboratory findings were analyzed, elevated D-dimer levels were detected in 24 (18.20%) patients. Severe COVID-19 can be complicated with coagulopathy, namely disseminated intravascular coagulation, which has a rather prothrombotic character with high risk of venous thromboembolism (11). It has been reported that COVID-19 was associated with hemostatic abnormalities and markedly elevated D-dimer levels were observed (12-13). It is unknown how long D-dimer remains high during and after the course of Covid-19 infection. We continued subcutaneous enoxaparin treatment on these patients.

We detected elevated hs-cTn levels in 9 (6.8 %) patients. The elevation of hs-cTn in the absence of acute coronary syndrome is likely to be multifactorial, including myocardial ischaemia, increased wall tension and ventricular strain, direct myocardial trauma, excess catecholamines, and possibly impaired renal clearance (14). Since patients with acute kidney disease and chronic kidney disease were not included in our study, elevated hs-cTn cannot be attributed to these diseases. Therefore, elevated hs-cTn levels were attributed to acute myopericarditis and sPAH related right ventricular increased wall tension.

We detected elevated NT-proBNP levels in 15 (11.40%) patients. NT-proBNP levels increase in heart failure (15), chronic kidney disease (16) and cirrhosis (17). Since patients with acute kidney disease, chronic kidney disease, cirrhosis were not included in our study and there was no patient with heart failure; elevated hs-cTn levels can not be attributed to these diseases. Therefore, elevated NT-proBNP levels were attributed to mitral regurgitation, tricuspid regurgitation and sPAH related right ventricular increased wall tension.

The most common ECG finding was sinus tachycardia, detected in 11 (8.3%) patients. In our study other ECG findings were not different from the normal population. COVID-19 related cardiac arrhythmias such as; high-grade AV block, new onset atrial fibrillation, polymorphic ventricular tachycardia due to a ventricular premature contraction causing a long-short sequence, and cardiac arrest with pulseless electrical activity detected in a recent case series. In our study other ECG findings were not different from the normal population (18).

Until now, a study examining the late cardiac effects seen in COVID-19 patients who have completed COVID-19 treatment and quarantine process has not been found in the literature. This study has several limitations. Firstly, our study was a single-center and retrospective study. Secondly, the number of patients participating in the study was small. In order to reveal the late cardiac effects of COVID-19, studies are needed with larger patient groups.

## CONCLUSION

We think that sPAH, pericardial hyperechogenicity, myocarditis and sinus tachycardia detected in study patients are associated with recent COVID-19 infection. If sPAH is detected in these patients, lung damage and pulmonary embolism should be sought. Chest computed tomography (CT) scan and contrast-enhanced CT scan should be performed and D-dimer level should be measured. It was also remarkable that pericardial hyperechogenicity was detected in these patients. COVID-19 pathological cardiac equalae include pericarditis with or without pericardial effusion. The patients with pericarditis should be treated with colchicine and methylprednisolone. Myocarditis should be investigated in patients with high hs-cTn and lower LVEF. Cardiac magnetic resonance imaging should be performed to investigate whether there is myocardial fibrosis in late gadolinium enhancement sequences. ECG and Rhythm holter monitoring may be performed to detect cardiac arrhythmias in patients with palpitations. Therefore, these patients should be evaluated in the cardiology out-patient clinic to investigate whether they have late-term cardiac effects due to COVID-19 infection.

## Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

## Funding

No financial support was used by authors during this study.

## Ethics Committee Approval

Republic of Turkey Ministry of Health gave permission to do the research. This research was ethically conducted in accordance with the Declaration of Helsinki (28th January 2021 and no 2021/2).

## Informed Consent

Since this study was a retrospective study, informed consent was not obtained from the patients.

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