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An investigation of cardiac effects in patients presenting to the pandemic clinic with suspected COVID-19

COVID-19 şüphesi nedeniyle pandemi polikliniğine başvuran hastalarda kardiyak etkilenmenin araştırılması

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ABSTRACT

Aim: COVID-19 is a virus capable of causing cardiovascular complications. This study investigates whether any cardiac effect is present in patients presenting with suspected COVID-19 in the light of Electrocardiography (ECG) findings.

Material and Method: This prospective study involved patients with chest pain presenting to the pandemic clinic with suspected COVID-19. Patients were divided into two groups based on their PCR results, PCR-positive and -negative. All participants' demographic characteristics, presentation symptoms and the duration thereof, physical examination findings, laboratory results, and ECG findings were recorded. Patients with positive PCR results were invited for checks on the 15th day, when repeat ECG was performed.

Results: A-50 patients with positive PCR results and 50 with negative PCR results were included in the study. The mean age of the entire patient group was 52.30±16.02 years, and 56% were women. No difference was determined between the positive and negative PCR result patients in terms of age or sex (p=0.116; 0.687, respectively). Presentation high sensitive cardiac Troponin (hs-cTn) levels were significantly higher in the patients with positive PCR results than in the PCR-negative patients (p<0.001). Rates of detection of ST-T change at presentation ECG were 38% in the patients with positive PCR results and 16% in those with negative PCR results (p=0.023). ST-T alteration persisted at 15th day ECG in 36% of the patients with positive PCR results. P-wave amplitude and mean heart rate were significantly higher at presentation ECG in the patients with positive PCR results than at ECG on day fifteen (p=0.038; <0.001 respectively).

Conclusion: A cardiac effect does occur in patients with COVID-19, and this can be shown by means of ECG findings. The increase in P-wave amplitude at presentation ECG in patients with positive PCR results may represent a marker of COVID-19-related cardiac overload. ECG should be performed both at presentation and in the following days on COVID-19 patients presenting with chest pain, and care should be taken against potential ischemic ST-T alterations.

Keywords: COVID-19, electrocardiography, emergency department, troponin

ÖZ

Amaç: COVID-19 kardiyovasküler komplikasyonlara neden olabilen bir virüstür. Bu çalışmada, COVID-19 şüphesi ile başvuran göğüs ağrılı hastalarda kardiyak etkilenme olup olmadığı Elektrokardiyografi (EKG) bulguları eşliğinde araştırılmıştır.

Gereç ve Yöntem: Bu çalışma, Pandemi polikliniğine COVID-19 şüphesi ile başvuran göğüs ağrılı hastalar üzerinde prospektif olarak yapıldı. Hastalar PCR sonucuna göre: PCR sonucu pozitif ve negatif olmak üzere iki gruba ayrıldı. Tüm katılımcıların demografik özellikleri, başvuru şikayetleri ve şikayetlerinin mevcudiyet süresi, fizik muayene bulguları, laboratuvar sonuçları ve EKG bulguları kaydedildi. PCR sonucu pozitif olan hastalar, 15. günde kontrole çağırılarak yeniden EKG çekildi.

Bulgular: Çalışmaya 50 PCR sonucu pozitif ve 50 PCR sonucu negatif hasta dahil edildi. Tüm hastaların yaş ortalaması 52.30±16.02/yıl ve %56'sı kadındı. PCR sonucu pozitif olanlarla PCR sonucu negatif olanlar arasında yaş ve cinsiyet bakımından farklılık saptanmadı (Sırasıyla p=0.116; 0.687). Başvuru yüksek duyarlıklı kardiyak Troponin (hs-cTn) düzeyi, PCR sonucu pozitif olanlarda PCR sonucu negatif olanlara göre anlamlı olarak daha yüksekti (p<0.001). Başvuru EKG'sinde ST-T değişikliği saptanma oranı PCR sonucu pozitif olanlarda %38 iken, PCR sonucu negatif olanlarda ise %16 idi (p=0.023). PCR sonucu pozitif olan hastaların %36'sının 15. gün EKG'sinde ST-T değişikliği izlenmeye devam ediyordu. PCR sonucu pozitif olan hastaların başvuru EKG'sinde P-dalga amplitüdü ve ortalama kalp hızı değeri 15. gün EKG'sine göre anlamlı olarak daha yüksekti (Sırasıyla p=0.038; <0.001).

Sonuç: COVID-19 hastalarında kardiyak bir etkilenme olmakta ve bu durum EKG bulguları vasıtasıyla gösterilebilmektedir. PCR sonucu pozitif hastaların başvuru EKG'sinde saptanan P-dalga amplitüdündeki artış, COVID-19'a bağlı kardiyak yüklenmenin göstergesi olabilir. Göğüs ağrısı ile başvuran COVID-19 hastalarına hem başvuru anında hem de ilerleyen günlerde EKG çekimi yapılmalı ve oluşabilecek iskemik ST-T değişikliklerine karşı dikkatli olunmalıdır.

Anahtar Kelimeler: COVID-19, elektrokardiyografi, acil servis, troponin

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INTRODUCTION

Following its emergence in the Chinese city of Wuhan in 2019, COVID-19 spread rapidly across the world (1). Although the virus essentially causes dry cough, sore throat, fever, lethargy, malaise, muscle and joint pain, or gastrointestinal tract symptoms, it may also worsen to give rise to pneumonia and respiratory failure (1). In addition, due to the direct and indirect effects of the virus, several fatal complications associated with the cardiovascular system may also be observed. These complications include acute coronary syndrome, myocarditis, heart failure, cerebrovascular stroke, pulmonary embolism, and disseminated intravascular coagulopathy (2,3). Cardiac damage responsible for these complications can be shown both by Electrocardiography (ECG) findings and by measuring such biomarkers as cTn, creatine kinase (CK), brain natriuretic peptide (BNP), and D-dimer (4).

The aim of this study was to investigate the presence or absence of a cardiac effect in patients with chest pains presenting to the pandemic clinic on suspicion of COVID-19 in the light of ECG findings.

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 10.12.2020, Decision No: 20/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This prospective study was performed with patients with suspected COVID-19 presenting with chest pains to the Kırıkkale University Medical Faculty pandemic clinic. Written voluntary consent was obtained from all participants.

Establishment of the Study Groups

Patients with suspected COVID-19 presenting to the pandemic clinic were divided into two groups based on PCR results from nasopharyngeal swabs, PCR result-negative and PCR result-positive. All patients' presentation symptoms, the duration thereof, demographic characteristics (age, sex, chronic disease, and medication use status), and laboratory and PCR results were recorded. Additionally, patients with positive PCR results were invited to control visits on the 15th day, at which time repeat ECG was performed and the results were again recorded.

Patients with previously diagnosed cardiovascular system diseases (coronary artery disease, hypertension, heart failure, dysrhythmia, cor pulmonale, valve diseases, etc.), using any medications capable of affecting the cardiovascular system, with no chest pains at time of presentation, aged under 18, with missing data, or refusing to consent to participate were excluded from the study.

ECG Performance and Interpretation

ECG was performed using a 12-lead, six-trace Nihon Kohden-1350K device. The procedure was carried out by a specialist ECG technician at a room temperature of 25o C. The ECG results were evaluated by an emergency medicine specialist using an ECG goniometer. P-wave amplitude, width, and morphology, PR interval, QRS complex, QT interval (calculated using Bazett's formula), T-wave amplitude, width, and morphology, ST-T alteration, heart rate, rhythm, and flow axis were evaluated and recorded for all patients.

Statistical Analysis

Data analysis was performed on Statistical Package for Social Sciences) for Windows version 21.0 software (IBM Corporation, Armonk, New York, USA). Variables were expressed as number (n), percentage (%), mean, and standard deviation (±SD). Normality of distribution was assessed using the Kolmogorov-Smirnov test. The independent sample t-test was used for intergroup comparisons in case of normal distribution, and the Mann-Whitney U-test in case of non-normal distribution. Qualitative data were compared using the chi-square test. The presentation and day 15 ECG results of PCR-positive patients were compared using the paired sample t-test. The results were evaluated at a 95% confidence interval, and p values <0.05 were regarded as statistically significant.

RESULTS

The study was completed with 50 PCR-positive and 50 PCR-negative patients, after 4723 of the 4823 patients presenting to the pandemic clinic had been excluded for meeting the exclusion criteria (**Figure 1**).

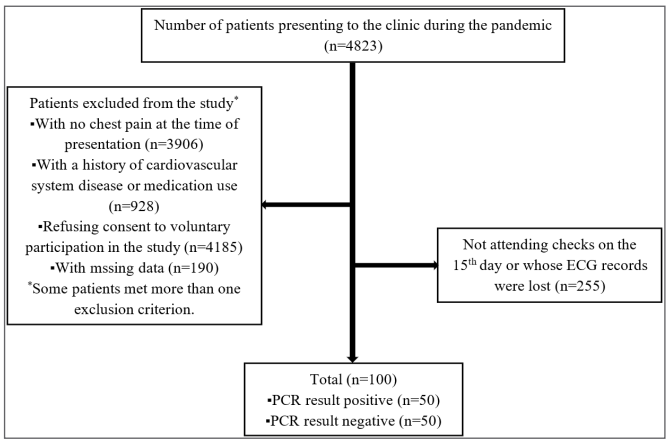

Figure 1. Patient selection and the constitution of the study groups

The mean age of the entire patient group was 52.30±16.02 years (range 21-94), and 56% were women. No difference was determined between the groups in terms of age or sex (p=0.116 and 0.687, respectively). Eighty-nine percent of the patients had no chronic disease and were not on medication. Disregarding chest pain, the most common presentations

symptoms were lethargy/malaise (50%), followed by myalgia/arthralgia (39%) and dyspnea (23%) (**Table 1**).

Table 1. A comparison of the study groups' demographic characteristics

	PCR (+) (n=50)	PCR (-) (n=50)	Total (n=100)
Age (years), (mean±SD)	54.98±17.02	57.66±17.72	52.30±16.02
Gender			
Male, n (%)	21 (42.0)	23 (46.0)	44 (44.0)
Female, n (%)	29 (58.0)	27 (54.0)	56 (56.0)
History of medication use			
Yes, n (%)	5 (10.0)	6 (12.0)	11 (11.0)
No, n (%)	45 (90.0)	44 (88.0)	89 (89.0)
Additional disease			
Diabetes mellitus, n (%)	2 (4.0)	1 (2.0)	3 (6.0)
COPD, n (%)	2 (4.0)	--	2 (2.0)
Psychiatric disease, n (%)	1 (2.0)	4 (8.0)	5 (5.0)
Thyroid disease, n (%)	--	1 (2.0)	1 (1.0)
More than one disease, n (%)	3 (6.0)	4 (12.0)	7 (14.0)
Unremarkable, n (%)	45 (90.0)	44 (88.0)	89 (89.0)
Presentation symptom (except for chest pain)			
Headache, n (%)	7 (14.0)	2 (4.0)	9 (9.0)
Sore throat, n (%)	6 (12.0)	3 (6.0)	9 (9.0)
Cough, n (%)	7 (14.0)	4 (8.0)	11 (10.0)
Myalgia/Arthralgia, n (%)	20 (40.0)	19 (38.0)	39 (39.0)
Lethargy/fatique, n (%)	25 (50.0)	25 (50.0)	50 (50.0)
Fever, n (%)	4 (8.0)	--	4 (4.0)
Dyspnea, n (%)	9 (18.0)	14 (28.0)	23 (23.0)
Anosmia, n (%)	4 (8.0)	2 (4.0)	6 (6.0)
Number of symptom days			
≤1 day	10 (20.0)	13 (26.0)	23 (23.0)
2-3 days	34 (68.0)	27 (54.0)	61 (61.0)
≥3 days	6 (12.0)	10 (20.0)	16 (16.0)

COPD, Chronic obstructive pulmonary disease

No difference was observed between the two groups in terms of physical examination findings (**Table 2**). However, hs-cTn levels were significantly higher in the PCR-positive group than in the PCR-negative group (p <0.001) (**Table 3**).

Table 2. A comparison of the study groups' physical examination findings

	PCR (+) (n=50)	PCR (-) (n=50)	p*
	mean±SD	mean±SD	
Body temperature (oC)	36.63±0.53	36.63±0.57	0.986
Heart rate (beats/min)	91.66±14.02	90.26±14.18	0.621
Respiration rate (/min)	22.30±10.04	21.10±2.15	0.410
Systolic blood pressure (mmHg)	138.18±21.76	132.44±17.55	0.150
Diastolic blood pressure (mmHg)	83.96±11.26	82.42±11.24	0.495
Oxygen saturation (%)	95.84±2.10	96.28±2.26	0.316

*Independent sample t-test

The incidence of ST-T alteration at presentation ECG was significantly higher in the PCR-positive group (38.0%) than in the group with negative PCR results (16.0%) (p=0.023) (**Table 4**). Comparison of ECG at time of presentation and after 15 days in the PCR-positive group revealed that P-wave amplitude and heart rate were significantly higher at presentation than on the 15th day (p=0.038; <0.001, respectively) (**Table 5**).

DISCUSSION

This study investigated, in the light of ECG findings, the cardiac effect in patients with chest pain presenting to the pandemic clinic with suspected COVID-19. The results show that COVID-19 leads to ischemic cardiac alterations at ECG and temporary cardiac overload.

Table 3. A comparison of the study groups' laboratory findings

Reference interval		PCR (+) (n=50)	PCR (-) (n=50)	p*
		mean±SD	mean±SD	
CK (u/L)	0-145	126.10±285.50	100.28±52.20	0.531
CK-MB (u/L)	0-24	30.1±25.25	38.52±25.77	0.105
Creatinine (mg/dL)	0.6-1.1	0.86±0.18	0.82±0.17	0.297
WBC (103uL)	4-10	6500.0±1976.53	8914.02±334.24	<0.001
Neutrophil (103uL)	2-7	4053.86±1407.10	6384.74±2710.23	0.546
Monocyte (103uL)	0.12-1.2	519.21±209.90	524.80±217.02	0.896
Lymphocyte (103uL)	0.8-4	1700.0±668.32	2082.14±803.92	0.011
CRP (mg/L)	0-5	18.30±21.44	20.95±36.75	0.662
Sodium (mmol/L)	136-145	139.26±3.52	139.64±2.70	0546
Potassium (mmol/L)	3.5-5.1	4.44±0.42	4.44±0.41	0.935
Calcium (g/dL)	8.8-10.6	9.53±0.68	9.80±0.52	0.030
D-dimer (ug/L)	0-500	352.91±408.62	333.10±324.08	0.630
		median (min-max)	median (min-max)	p†
Presentation hs-cTn (ng/ml)	0-14	75 (2-1680)	4.70 (2-11)	<0.001†
Day 15 hs-cTn (ng/ml)	0-14	7.6 (2-21)	--	

CK, Creatine kinase; WBC, White blood cell; CRP, C-reactive protein; hs-cTn, High sensitive cTn, Cardiac troponin, *Independent sample t-test, †Mann-Whitney U-test

Table 4. A comparison of the study groups' demographic characteristics

	PCR (+) (n=50)	PCR (-) (n=50)	p*
	mean±SD	mean±SD	
P-wave amplitude (mV)	1.69±0.44	1.63±0.45	0.501
P-wave width (msn)	85.20±17.52	88.0±19.38	0.450
PR interval (msn)	191.6±190.40	190.40±24.32	0.824
QRS interval (msn)	78.80±10.99	80.80±13.97	0.521
QT interval (msn)	412.22±36.05	412.28±25.62	0.992
Heart rate (beats/min)	89.36±14.39	86.18±16.84	0.313
	n (%)	n (%)	p†
ST-T alteration present	19 (38.0)	8 (16.0)	0.023
T-wave morphology			
Normal	32 (64.0)	42 (84.0)	
Negative	13 (26.0)	6 (12.0)	
Biphasic	4 (8.0)	2 (4.0)	
More than one morphology	2 (2.0)	--	
Rhythm			
Normal sinus rhythm	40 (80.0)	44 (88.0)	
Sinus arrhythmia	4 (8.0)	2 (4.0)	
Sinus tachycardia	6 (12.0)	4 (8.0)	
Axis			
Normal axis	45 (90.0)	46 (92.0)	
Sol axis	5 (10.0)	3 (6.0)	
Right axis	--	1 (2.0)	
Other findings			
Unremarkable	45 (90.0)	45 (90.0)	
Pathological Q-wave	2 (4.0)	2 (4.0)	
LAFB	2 (4.0)	2 (4.0)	
VES	1 (2.0)	1 (2.0)	

LAFB, left anterior fascicular block; VES, ventricular extrasystole, *Independent sample t-test, †Chi-square test

Table 5. A comparison of the PCR-positive patients' presentation and 15th day ECG findings

	Presentation ECG (n=50)	15th day ECG (n=50)	p*
	mean±SD	mean±SD	
P-wave amplitude (mV)	1.69±0.44	1.55±0.38	0.038
P-wave width (msn)	85.20±17.52	85.20±13.88	0.761
PR interval (msn)	191.6±190.40	184.40±21.10	0.124
QRS interval (msn)	78.80±10.99	82.40±7.70	0.322
QT interval (msn)	412.22±36.05	414.04±24.26	0.765
Heart rate (beats/min)	89.36±14.39	78.28±11.70	<0.001
	n (%)	n (%)	p†
ST-T alteration present	19 (38.0)	18 (36.0)	0.799
T-wave morphology			
Normal	32 (64.0)	32 (64.0)	
Negative	13 (26.0)	13 (26.0)	
Biphasic	4 (8.0)	4 (8.0)	
More than one morphology	2 (2.0)	1 (2.0)	
Rhythm			
Normal sinus rhythm	40 (80.0)	47 (94.0)	
Sinus arrhythmia	4 (8.0)	3 (6.0)	
Sinus tachycardia	6 (12.0)	2 (4.0)	
Axis			
Normal axis	45 (90.0)	45 (90.0)	
Sol left axis	5 (10.0)	5 (10.0)	
Right axis	--	--	
Other findings			
Unremarkable	45 (90.0)	42 (84.0)	
Pathological Q-eave	2 (4.0)	5 (10.0)	
LAFB	2 (4.0)	2 (4.0)	
VES	1 (2.0)	--	

LAFB, left anterior fascicular block; VES, ventricular extrasystole, *Paired sample t test, †Chi-square test

Cardiac ischemic damage in patients with COVID-19 may occur due to direct damage to myocardial tissue or increased adrenergic stimulation, systemic inflammatory response, cytokine storm, hypoxia, hypotension or microthrombus, caused by the disease process (5-8). The cardiac damage that develops causes ST-T alterations at ECG. These changes may persist for one year on the ECGs of some patients, and are a marker of increased mortality, particularly in patients with severe COVID-19 (9-11). In one of two previous studies examining the prognostic value of presentation ECG in COVID-19 patients, McCullough et al. (11) reported an ST elevation incidence of 0.7% and a T-wave innervation incidence of 10.5%; in the other study Chorin et al. (12) reported an incidence of ST-T alteration of 17.6%. Li et al. (13) reported that the incidence of ST-T alteration increased still further among patients hospitalized in the intensive care unit (65.2%). Another study examining presentation ECGs of patients with COVID-19 pneumonia reported an incidence of ST-T alteration of 30%, and that these alterations were observed on ECGs a mean 30 (12-51) days after the first onset of symptoms (14). Bergamaschi et al. (15) reported an incidence of ST-T alteration of 5.6% among COVID-19 patients at the time of presentation, rising to 8.2% on the seventh day. The authors therefore emphasized that ischemic ST-T alterations can be detected, and a decrease in major cardiac event and mortality achieved, through serial ECG monitoring. In the present study, the incidence of ST-T alteration was significantly higher in the PCR-positive group. This is consistent with previous studies showing that the direct or indirect effect of COVID-19 causes ischemic damage to myocardial tissue. ST-T alteration at ECG was also observed in the PCR-negative patients in our study. We attributed this either to the patients having COVID-19 even if their test results were negative, or to cardiac involvement due to the effect of infection by another virus (such as influenza or RSV). In addition, the ST-T alteration in the PCR result-positive group persisted on both presentation and 15-day ECGs, suggesting that cardiac ischemic alterations also persisted in these patients after 15 days. Therefore, in exact agreement with Bergamaschi et al. (15) , we also think that regular ECG will be useful for the purpose of monitoring cardiac effects in such patients infected with COVID-19.

In addition to the diagnosis of arrhythmias, alterations in the P-wave morphology and PR interval are also useful in detecting the presence of cardiac pathologies (16). An extended PR interval is associated with conduction disorders such as AV blocks, while an increased P-wave amplitude (>2.5 mm) is a messenger of right atrial dilatation, while an extended duration (>120 msn) indicates left atrial dilatation (17). Studies have shown that prolongation of the P-wave duration is associated with an increased risk of cardiovascular disease and mortality (18). Atrial tachyarrhythmias, particularly atrial fibrillation (AF), are frequently seen in COVID-19, and diagnosis of AF is linked to the presence (or absence) of the P-wave (19). Interatrial block is a form of rhythm disorder in which conduction is delayed in the Bachman region between the right and left atria. This lays the foundation for P-wave dispersion, and thus to the development of AF (20). Yenerçağ et al. (21) reported a greater likelihood of AF development in COVID-19 patients with P-wave dispersion at ECG (>36 msn) compared to healthy. In that study, P-wave amplitude was 0.12±0.009 mV at V1 and 0.141±0.016 mV at DII, values significantly higher than in the healthy controls. No difference was determined in the present study in terms of P-wave amplitude, P-wave width, or PR interval between the PCR result-positive and –negative patients. No AF, AV block, or other dysrhythmia were observed in any patient. This may be due, in contrast to other studies in the literature, to our study involving clinically milder cases (patients with a history of cardiovascular disease and drug use were excluded from the study). To put it another way, the ECGs of less and/or non-problematic patients in cardiovascular terms were examined in the present study. On the other hand, the P-wave amplitude on admission ECG among patients with positive PCR results was significantly higher than that on the 15th day. We thought that this might be related to right atrial tension caused by the increased disease burden resulting from COVID-19. In subsequent days, as the patients responded positively to COVID-19 treatment, the disease burden may have decrease and the previously elevated right atrial tension and associated P-wave amplitude may have recovered on the 15th day and returned to normal.

Acute phase reactant levels, liver and kidney function tests, complete blood count, coagulation tests, and cardiac biomarkers are frequently used in COVID-19 for diagnosis, follow-up, and predicting prognosis (22-24). One study reported that increasing leukocytosis and cTnI levels significantly raised ICU admission rates among COVID-19 patients (1.5- and 2.2-fold, respectively) (22). Another study emphasized changes in leukocytosis and albumin levels as important markers in the evaluation of admission to the ICU (a 2-fold increase and 0.8-fold decrease, respectively) (24). A study comparing PCR (+) and (-) patients reported significantly lower serum CRP, WBC, and neutrophil, lymphocyte, monocyte, and eosinophil counts and significantly higher ALT, AST, and LDH values in the patients with PCR (+) results (25). Chinese researchers reported significantly lower WBC and platelet values in PCR (+) patients compared to PCR (-) patients, while no difference was observed in terms of CRP, sedimentation, or lymphocyte and neutrophil counts (26). Albumin is a negative acute phase reactant, and the decrease in plasma Calcium (Ca^{++}) levels may due to decreased albumin in patients with COVID-19. Other factors that reduce Ca^{++} levels in patients with COVID-19 include diarrhea-related gastrointestinal losses and vitamin-D deficiency (27). WBC, lymphocyte counts, and Ca^{++} levels in this study were significantly lower in the PCR (+) patients than in the PCR (-) patients. This is consistent with the results of previous studies. However, it should also not be forgotten that although there was no statistically significant difference between the two groups in terms of Ca^{++} levels, serum Ca^{++} levels were within physiological limits.

Limitations

There are a number of limitations to this study. First, although large numbers of patients presented to the pandemic clinic due to COVID-19, many had to be excluded from the study due to the fear and psychological effects produced in the community by COVID-19 and lockdowns, and individuals being unwilling to attend hospital (for 15-day controls) unless absolutely necessary. This had an adverse impact on our patient numbers and the study findings. A second limitation concerns the accuracy of the tests used in the diagnosis of COVID-19 patients. The accuracy value of the RT-PCR test performed at the time of the study was different from the current accuracy, and this may have affected the grouping of patients with positive and negative PCR results. Finally, in our study, individuals with previously diagnosed cardiovascular system diseases were excluded from the study. We therefore accepted their ECGs as normal since they had no cardiovascular problems. Moreover, the protocol applied by the Turkish Ministry of Health in the treatment of PCR-positive patients consisted of favipiravir and hydroxychloroquine, and azithromycin or floroquinolone in suspected patients, and it is not known for certain whether the patients included in the present study were using these medications regularly or not, nor the effects of those medications on ECG findings (apart from the QT interval) (28). This may also have affected our results.

CONCLUSION

The incidence of ST-T alteration at ECG was significantly higher among the PCR-positive patients than in the PCR-negative patients. The significantly higher presentation hs-cTn levels observed among the PCR-positive patients also confirms that COVID-19-related ischemic changes occur in these patients. Moreover, P-wave amplitudes were also higher at presentation ECG among the PCR-positive patients compared to the 15th day ECG.

These findings all suggest that a cardiac effect does occur in patients with COVID-19 and that this can be detected with ECG alterations. An increased P-wave amplitude at presentation ECG in PCR-positive patients may be indicative of COVID-19-related cardiac overload. ECG should be performed both at presentation and in subsequent days on COVID-19 patients presenting with chest pain, and care must be taken regarding potential ischemic ST-T alterations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 10.12.2020, Decision No: 20/01).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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