Erciyes Med J 2022; 44(4): 375–81 • DOI: 10.14744/etd.2021.06791
ORIGINAL ARTICLE – OPEN ACCESS

Assessment of P Wave Peak Time and P Wave Dispersion in Patients with COVID-19 Infection

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ABSTRACT

Objective: This study aims to evaluate P wave distribution (PD) and P wave peak time (PWPT) in COVID-19 patients.

Materials and Methods: A total of 140 participants were recruited in our study. The COVID-19 group included 74 subjects, and the control group included 66 individuals. Between the two groups, PD was compared for electrocardiographic P-wave measurements, including abnormal P wave axis, P wave terminal force in V1 (PWTF), P wave max duration (P_{max}), and PWPT.

Results: It was determined that the P_{max} and PD values of the patients infected with the COVID-19 virus were higher than the control group ($p<0.001$). $PWPT_{D2}$ ($p<0.001$), $PWPT_{V1}$ ($p<0.001$) and abnormal P wave axis ratio ($p<0.05$) were found to be significantly longer in COVID-19 patients. Serum CRP and WBC values were found to be significantly higher in COVID-19 patients ($p<0.001$, $p<0.001$, respectively). Also, a significant and positive correlation was detected between CRP and P_{max}, PD, $PWPT_{D2}$ and $PWPT_{V1}$. There was the same correlation relationship between WBC with P_{max}, PD, $PWPT_{D2}$ and $PWPT_{V1}$.

Conclusion: Significant prolongation of PWPT and PD in COVID-19 patients may be predictive in determining the risk of developing atrial fibrillation.

Keywords: Atrial fibrillation, COVID-19, P wave peak time, P wave dispersion

INTRODUCTION

Coronavirus disease (COVID-19), coronavirus-2 (SARS-CoV-2) is a new RNA virus characterized by severe acute respiratory syndrome, acute pneumonia and severe respiratory distress syndrome. Although COVID-19 mainly affects the lungs, cardiovascular involvement has also been shown to be common (1). Acute cardiovascular events complicating the clinical course of SARS-CoV-2 may be one of the causes of poor survival. Arrhythmia is one of the most common cardiac findings during this disease, and especially atrial fibrillation was found to be increased in COVID-19 patients in a recent study (1, 2). Atrial fibrillation (AF), which is the most widespread rhythm disorder in clinical practice, is important because it causes hemodynamic instability and thromboembolic events (3). Although the causes for triggering AF are not clear, risk factors such as advanced age, diabetes mellitus, and hypertension are thought to play a role in the development of AF (4). Moreover, accumulating evidence has shown that inflammation and inflammatory factors, the autonomic nervous system, and oxidative stress play significant roles in the AF pathogenesis (5, 6). COVID-19 infection may cause, myocardial oxygen supply/demand mismatch, direct myocardial cell injury, hypoxia, enhanced systemic inflammation, increased thrombosis, catecholamine surge and oxidative stress imbalance, all of which may be related to the AF formation (7, 8). Therefore, the risk of new-onset AF (NOAF) may increase in COVID-19 due to all these mentioned mechanisms.

Various clinical, electrocardiographic, and echocardiographic factors have been shown to be predictors of AF in previous studies. Among these parameters, electrocardiography is especially crucial because it is easily accessible easy to interpret. The P wave peak time (PWPT) parameter is a newly defined ECG finding and studies have been published recently on the relationship between various cardiovascular events (9). In line with these data, long-term PWPT has been shown and accepted to be associated with a higher risk of paroxysmal AF (10). In addition, other studies have shown that P wave distribution (PD) and maximum P wave duration (P_{max}) can be predictors of AF (11).

In this study, we aimed to evaluate classical P wave parameters with PWPT, a new ECG parameter in COVID-19 patients.

MATERIALS and METHODS

Our study was designed as a single-center, aretrospectif case-control study in confirmed COVID-19 infected patients followed and treated in our hospital.

Cite this article as:
Keleşoğlu Ş, Elçik D. Assessment of P Wave Peak Time and P Wave Dispersion in Patients with COVID-19 Infection. Erciyes Med J 2022; 44(4): 375-81.

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Submitted
12.03.2021

Accepted
14.12.2021

Available Online
31.12.2021

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Table 1. Baseline clinical and laboratory features of the study groups

Variables	Control group (n=66)	COVID-19 (n=74)	p
Age (years)	49.56±10.70	52.31±16.03	0.241
Male/female	36/30	44/30	0.558
Systolic Blood Pressure, mmHg	123.7±12.6	122±11.9	0.426
Diastolic Blood Pressure, mmHg	75.9±8.4	76.1±8.8	0.902
Glucose, mg/dl	98.1±24.2	101.7±17.3	0.311
Creatinine mg/dl	0.8±0.17	0.85±0.20	0.081
Glomerular filtration rate	96.37±22.13	93.59±24.05	0.479
Aspartate aminotransferase, IU/l	21.36±6.53	22.22±11.41	0.589
Alanine aminotransferase, IU/l	20.83±11.68	23.10±17.05	0.365
Troponin	0.10±0.00	0.10±0.00	0.987
Hemoglobin, g/dl	13.80±1.71	14.34±2.21	0.112
White blood cell, 10^3 uL	8.69±3.10	17.92±4.04	**<0.001**
Platelet, 10^3 uL	252.3±64.83	256.68±71.88	0.708
CRP, mg/L	6.06±8.29	73.62±51.65	**<0.001**

Data are expressed as mean±standard deviation for normally distributed data and percentage (%) for categorical variables. CRP: C-reactive protein

The study was carried out in an institute designated as a 'COVID-19 Hospital' by the Turkish Ministry of Health to admit porobable or confirmed cases of COVID-19. Patients older than 18 years of age with a sinus rhythm initial rhythm on a 12-lead electrocardiogram and a definitive diagnosis of SARS-CoV2 in the presence of symptoms and positive polymerase chain reaction (PCR) were analyzed. Exclusion criteria in the study were diabetes mellitus, coronary artery disease (CAD), hypertension (HT), heart failure diagnosis, detection of severe valve pathology, variable branch block, previous diagnosis of atrial fibrillation, chronic kidney disease, thyroid disorder, poor ECG recordings.

This study included 74 patients hospitalized in our hospital with the diagnosis of COVID-19 in July 2020. Sixty-six randomized

Table 2. Electrocardiographic and echocardiographic characteristics of the study population

Variables	Control group (n=66)	COVID-19 (n=74)	p
LVEF	66.71±5.88	64.38±4.27	**<0.05**
LA Diameter	3.36±0.31	3.40±0.29	0.595
Heart Rate, beat/min	77.78±6.65	80.14±11.01	0.133
QRS duration, ms	87.96±10.09	91.83±48.38	0.525
QT, ms	381.39±23.13	379.41±27.53	0.649
QTc, ms	420.18±15.83	416.31±17.11	0.169
P wave parameters			
PR, ms	148.57±27.28	165.72±22.46	**<0.001**
P wave max time, ms	97.06±8.82	110.72±8.92	**<0.001**
P wave min time, ms	59.46±6.22	59.81±8.26	0.785
P wave dispersion, ms	37.48±10.75	50.16±10.77	**<0.001**
P wave peak time D2, ms	49.03±7.34	56.63±7.54	**<0.001**
P wave peak time V1, ms	47.39±6.62	55.09±6.90	**<0.001**
P wave terminal force, V1, ms	37.95±10.80	40.45±11.46	0.187
P wave terminal force, V1 >40, n (%)	18 (27.27)	30 (40.54)	0.099
Average P wave axis	54.53±16.07	58.6±20.18	0.214
Biphasic P wave (+/-), n (%)	10 (15.15)	14 (18.91)	0.555
Abnormal P wave axis, n (%)	10 (15.15)	25 (33.78)	**<0.05**

LVEF: LV ejection fraction; LA; Left atrium; QRS duration: The time from the beginning to the end of the QRS complex; QT interval: The time from the beginning of the QRS complex to the end of the T wave; QTc: Corrected QT; PR interval: The time from the beginning of the P wave to the first deflection of the QRS complex

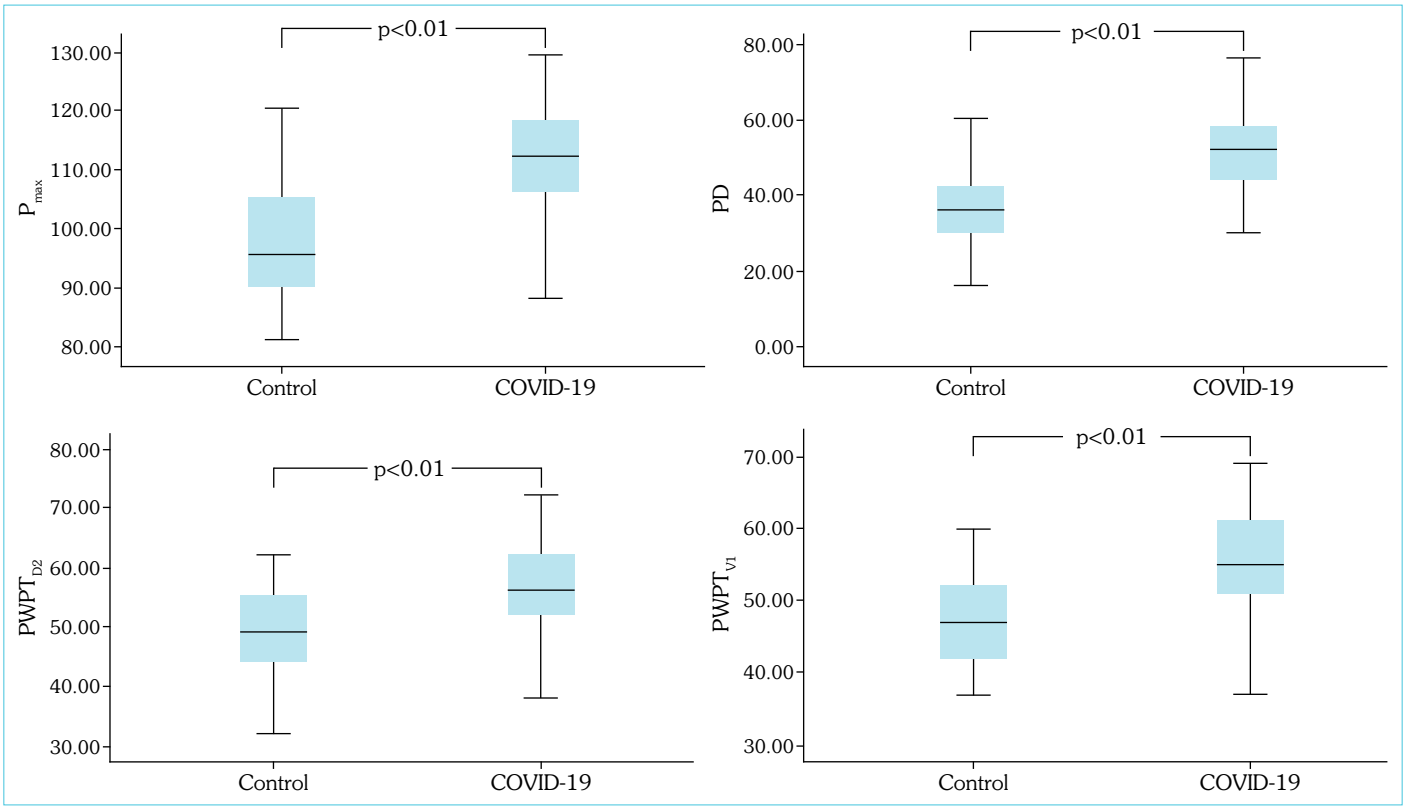

Figure 1. Change Pmax, PD, $PWPT_{D2}$ and $PWPT_{V1}$ between study groups

PD: P wave distribution; PWPT: P wave peak time

healthy volunteers were included in the study for comparison. ECG evaluation of all participants was found to be in sinus rhythm. Blood parameters including complete blood count and serum biochemistry and detailed medical history, 12-channel electrocardiography were obtained from all patients at the time of hospitalization. The study was evaluated and approved by the Local Medical Ethics Committee (Ethics number: 104, Kayseri City Hospital Clinical Research and Ethics Committee) and was conducted following the principles of the Declaration of Helsinki.

Electrocardiography

ECG recordings were performed simultaneously with a Philips electrocardiography (ECG) device before COVID-19 treatment, with at least 3 QRS complexes with all leads of 25 mm/sec, 1 mV amplitude, and standard 12 leads. The P wave duration in all derivations was measured manually with the help of calipers and magnifying lenses to reduce errors in measurements. All measurements were made by two different cardiologists, unaware of each other. The average of two measurements were evaluated for comparison. Large screen measurements were found to be similar overall.

The PR interval was defined as the time interval from the onset of the P wave to the onset of the QRS complex. The time between the onset of the isoelectric line of the P wave (PW) and the peak reflection peak was considered the P wave peak time (PWPT), and this evaluation was measured from leads V1 ($PWPT_{V1}$) and D2 ($PWPT_{D2}$). Biphasic and negative PW was defined as the time from the origin of the PW in V1 to the crest of the negative PW. We only measured negative waves ≥0.1 mv as a biphasic PW, ignoring those below this value. We found the P wave terminal force (PWTF) by extending the force and interval of the negative terminal component of the PW in V1. We considered PWTF ≥40ms as abnormal. We set the abnormal PW axis as less than 0° or greater than 75°. Maximum PW time was accepted as the longest duration of PW and longest atrial conduction time on ECG. The difference between the longest and shortest P wave was accepted as the P wave distribution ($PD=P_{max}-P_{min}$) and calculated (10, 12, 13).

Echocardiography

Conventional echocardiography was carried out with the Philips Epiq 7 ultrasound system (Philips, Andover, Mass., USA). To reduce the risk of COVID-19 transmission, only left ventricular ejection fraction (LVEF) and left ventricular dimensions were examined to detect myocardial damage. Conventional echocardiographic images were acquired from the apical and parasternal views. The Simpson method was used for the calculation of LVEF.

Statistical Analysis

Statistical analysis was performed using the SPSS Statistical Package for Windows version 21.0 (SPSS Inc, Armonk, NY, USA). The distribution characteristics of the findings were analyzed using the Kolmogorov-Smirnov test. Independent Sample t-test was used for parametric scale variables. The χ^2 test was used for univariate analysis of the categorical variables. Numerical parametric variables were given as mean±SD; categorical variables were defined as percentages. Correlation analyses were performed using Pearson correlation analysis. A 2-sided $p<0.05$ was considered significant.

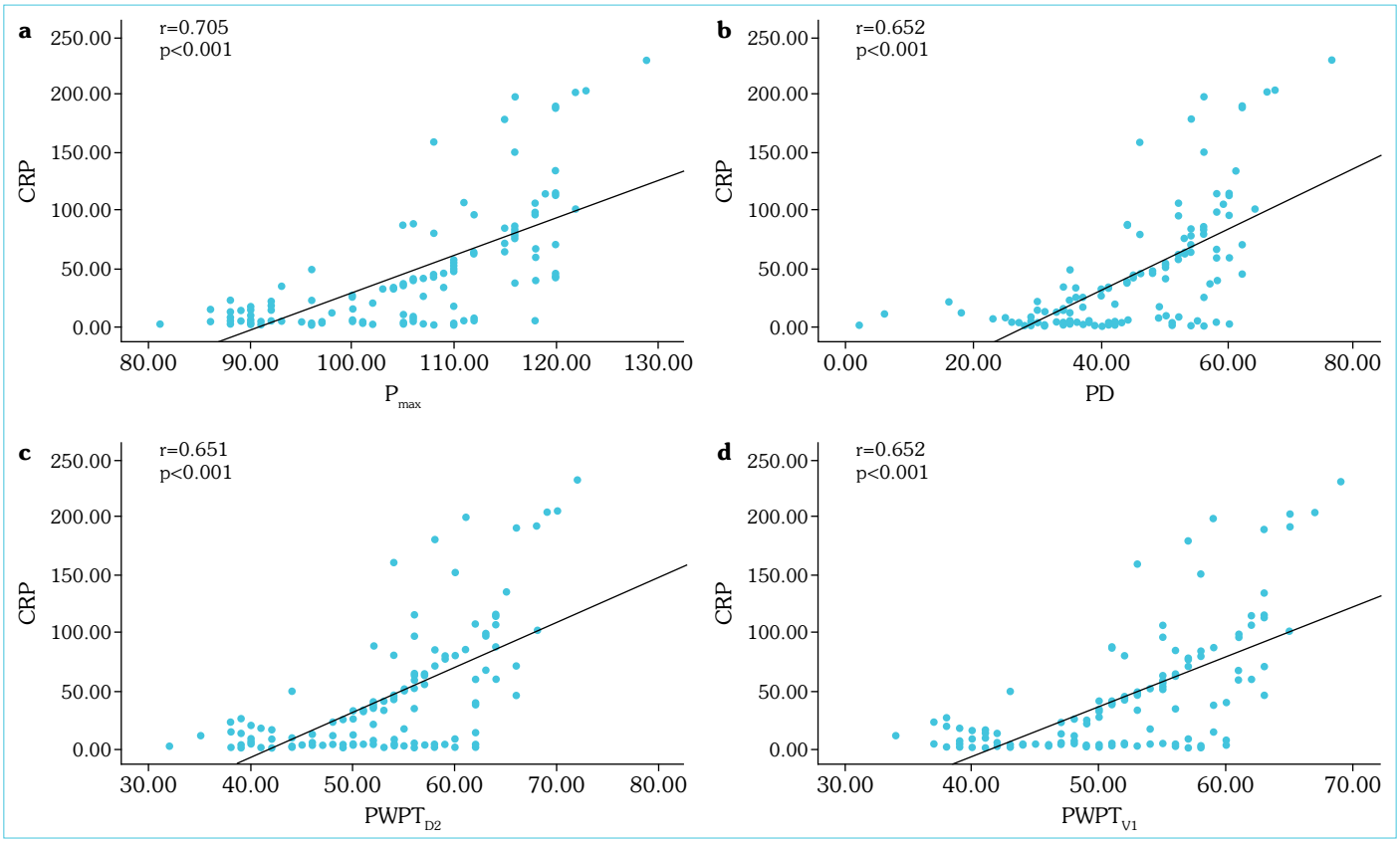

Figure 2. (a)Correlation between CRP and Pmax. (b) Correlation between CRP and PD. (c) Correlation between CRP and $PWPT_{D2}$. (d) Correlation between CRP and $PWPT_{V1}$

CRP: C-reactive protein; PD: P wave distribution; PWPT: P wave peak time

RESULTS

A total of 140 participants were included in our study. 74 people (44 men) in the group with COVID-19 infection and 66 people (36 men) in the control group were included in the study. Basal characteristics and basal laboratory values of the groups are shown in Table 1. There was no statistically significant difference between the COVID 19 infected group and the control groups in terms of gender and age distribution (p> 0.05). Serum CRP and white blood cell (WBC) levels were significantly higher in COVID-19 patients (p<0.01). Other blood parameters were similar between groups.

The electrocardiographic and echocardiographic parameters of the patient and control groups are shown in Table 2. There was no difference between the groups in echocardiographic parameters, LVEF, and LA diameters. On the contrary, when TAPSE, Right diameter and systolic PAP from right heart echocardiographic data were evaluated, a statistically significant difference was found between the two groups (p=0.001) (Table 2). Compared to the control group, P_{max} and PD were found to be higher in the COVID-19 patient group and statistically significant (P_{max} 110.72±8.92 and 97.06±8.82, p<0.01; PD 50.16±10.77 and 37.48±10.75 ms, p<0.01, Table 2, Figure 1). When P_{min} was evaluated between the two groups, it was found to be similar and no statistical difference was observed (p=0.785).

In COVID 19 patients, $PWPT_{D2}$ (56.63±7.54 vs. 49.03±7.34, p<0.001), $PWPT_{V1}$ (55.09±6.90 vs. 47.39±6.62, p<0.001) and abnormal P wave axis ratio (33.78% vs. 15.15%), p<0.05) were significantly longer than the control group. Statistically similarity was found between the two groups in other P wave parameters. Other electrocardiographic features are presented in the table (Table 2).

The correlation analysis between the data revealed a statistically positive correlation curve between CRP and P_{max}, PD, $PWPT_{D2}$ and $PWPT_{V1}$ (r=0,705 p<0,001; r=0,652, p<0,001; r=0,651, p<0,001; r=652, p<0.001, respectively) (Fig. 2). There was the same correlation between WBC with P_{max}, PD, $PWPT_{D2}$ and $PWPT_{V1}$ (r=0,655 p<0,001; r=0,569, p<0,001; r=0,524, p<0,001; r=565, p<0.001, respectively) (Fig. 3).

Of the 70 patients diagnosed with COVID-19, 42 needed an intensive care unit (ICU), while three of these patients were diagnosed with new-onset AF (NOAF). NOAF developed in these patients in the first three days of hospitalization. In these patients, initial ECG had present prolonged P_{max} (122 msn, 120 msn, 118 msn respectively), PD (66, 62, 58, respectively), $PWPT_{D2}$ (69 msn, 66 msn, 63 msn, respectively) and $PWPT_{V1}$ (65 msn, 63 msn, 61 msn, respectively). Meanwhile, all were receiving hydroxychloroquine (HCQ), azithromycin, favipiravir, and ceftriaxone treatment. None of these patients had significant ECG changes, such as drug-induced QTc prolongation, compared to the initial ECG.

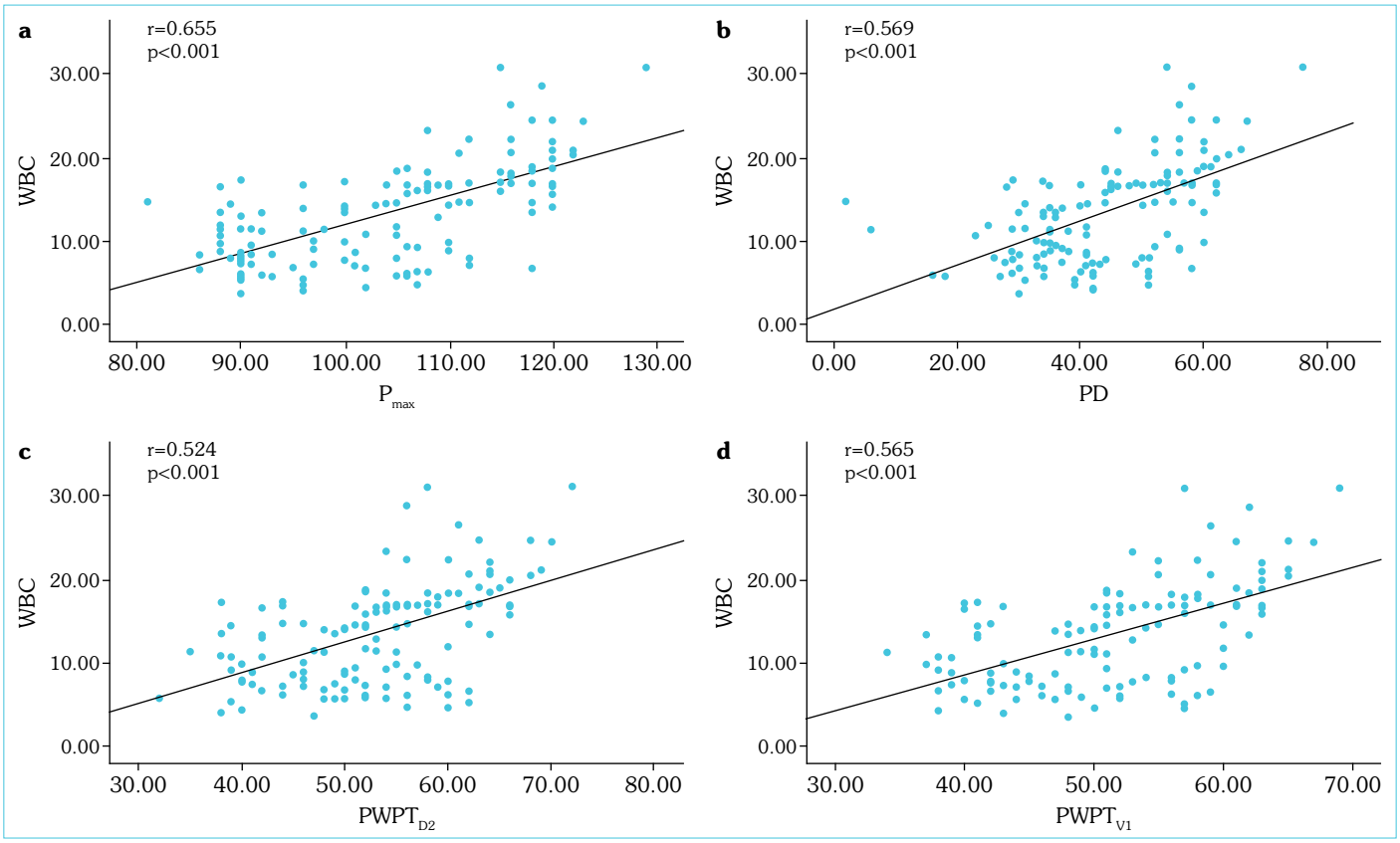

Figure 3. (a) Correlation between WBC and Pmax count. (b) Correlation between WBC and PD count. (c) Correlation between WBC and $PWPT_{D2}$ count. (d) Correlation between WBC and $PWPT_{V1}$ count

WBC: White blood cell; PD: P wave distribution; PWPT: P wave peak time

DISCUSSION

Two crucial findings detected in COVID-infected patients in this study can be listed as follows: (1) $PWPT_{D2}$, $PWPT_{V1}$, P_{max}, and PD duration were significantly higher in COVID-19 patients (2) $PWPT_{D2}$, $PWPT_{V1}$, P_{max}, and PD duration were significantly positively correlated with both CRP and WBC.

Atrial fibrillation is the most common arrhythmia that causes cardiovascular mortality and morbidity in the community and is the most common especially in the elderly population (14). Therefore, there is increasing interest in determining AF preventability in those at risk of developing AF. A simple review, ECG and ECG values provide a lot of information about AF risk and have the potential to contribute significantly to AF risk estimation.

P Max and PD are simple markers that improve the heterogeneous and unstable distribution of electrical impulses from the sinus node in the right atrial wall in a standard ECG. Increased atrial heterogeneous electrical activity causes atrial reentry, facilitating the onset of AF/flutter. P_{max} and PD have been used as noninvasive markers to predict the risk of AF in different diseases and causes leading to paroxysmal AF (15–17). In our study, mean PD and P_{max} values were found to be longer in the COVID-19 patient group than in the control group.

The relationship between abnormal P wave, PW axis, PR interval, and PWTF has been demonstrated in patients with AF (12, 16, 17). Previous studies have shown that PWTF> 0.04 mm is an independent predictor of AF (18) PWPT, which was recently announced, and studies on the relationship between cardiovascular developments have gained importance recently. Moreover, Yıldırım et al. (10) demonstrated that PWPT was more sensitive than these well-known and classical ECG parameters in predicting AF. The most critical and important point here is that the calculation of PWPT is easier and more practical than other parameters such as PD, abnormal PW axis and PWTF. In our study, the ratio of $PWPT_{D2}$, $PWPT_{V1}$ and abnormal P wave axis in COVID-19 patients was calculated quite long and easily. Although the precise mechanisms that cause AF are not fully known, accumulating evidence has shown that inflammation and inflammatory factors, the autonomic nervous system, and oxidative stress play a major role in AF pathogenesis (5, 6).

COVID-19 is a new coronavirus infection that mainly affects the lungs and causes pneumonia. Some studies have shown an increased risk of NOAF in patients hospitalized for pneumonia. (19, 20). Increases in serum inflammatory cytokines, acute metabolic disorders including electrolyte abnormalities, hypoxemia and hypo/hyperthermia have been shown to trigger AF in pneumonia infection (21, 22). Furthermore, increased inflammatory state and cytokine storm have been shown to accompany pneumonia in some COVID-19 patients (23) Circulating TNF-alfa, IL-6, and IL-1β have been demonstrated to rise in patients with COVID-19. Inflammatory mediators, such as CRP, interleukin-6, and tumor necrosis factor-alpha secreted during

the inflammatory process have previously been demonstrated to induce the development of AF (24–26). As a matter of fact, in our very recent study, we found the incidence of new-onset AF to be 5% in patients hospitalized for COVID-19 pneumonia (2).

In this study, similar to previous findings in patients with pneumonia, we found that inflammatory markers, including C-reactive protein and white blood cell count, were remarkably higher in COVID-19 patients. Furthermore, there was a significant positive correlation between CRP with P_{max}, PD, $PWPT_{D2}$, and $PWPT_{V1}$. A similar correlation was also found with WBC. Considering these findings, our results demonstrate that inflammatory markers including C-reactive protein and WBC can predict the NOAF development in COVID-19 patients. These results confirm the results of previous studies, that underlined the role of inflammation in the formation of AF. COVID-19 infection can also cause direct myocardial cell damage, catecholamine surge, myocardial oxygen supply/demand mismatch, increased thrombosis, and oxidative stress imbalance, all of which a can be listed as other reasons that may cause AF (7, 8).

Limitations

The main limitation of this study is the relatively small number of patients in the study group, to see if prolonged PWPT, P_{max}, and PD develop AF in COVID-19 patients and the lack of follow-up for possible future NOAF.

CONCLUSION

To the best of our knowledge, this study is the first in the literature investigating ECG parameters such as P_{max}, PD, $PWPT_{D2}$, and $PWPT_{V1}$ duration in patients with COVID-19. In light of the findings, as mentioned earlier, an increase in inflammatory load or an increase in inflammatory markers in COVID-19 patients seems to be a risk factor for AF and increased inflammatory environment may trigger AF.

We thought that the evaluation of ECG parameters such as PWPT, PD, and P_{max}, which can be easily measured by ECG, may be more practical than tissue Doppler and strain echocardiography, especially in diseases with high contagiousness such as COVID-19. These parameters in the ECG can be used to identify patients at high risk of developing AF in highly patients with high infectiousness, such as COVID-19. Further research is needed to clarify the predictive role of P_{max}, PD, and PWPT in evaluating the development of AF in COVID-19 patients.

Ethics Committee Approval: The Kayseri City Hospital Clinical Research Ethical Committee granted approval for this study (date: 25.06.2020, number: 104).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SK; Design – SK, DE; Supervision – SK, DE; Resource – SK; Materials – SK, DE; Data Collection and/or Processing – SK; Analysis and/or Interpretation – SK, DE; Literature Search – SK; Writing – SK, DE; Critical Reviews – SK, DE.

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

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

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