ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1410386
Interdisciplinary Medical Journal 2023;14(50):181-189.

Relationship between atrial fibrillation and P wave dispersion in inpatients with COVID-19

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Abstract

Objective: Various cardiac arrhythmias, primarily atrial fibrillation (AF), have been reported to occur in 7% to 22% of patients hospitalized due to coronavirus disease 2019 (COVID-19). It has been shown that P wave dispersion (PWD) predicts the development of AF in different clinical situations and is closely related to the inflammatory process. The aim of this study is to determine the relationship between PWD and the development of new-onset AF in hospitalized patients due to COVID-19.

Method: 51 COVID-19 patients who developed AF and 72 COVID-19 patients who did not develop AF were included in the study as the control group retrospectively. Electrocardiography (ECG) was performed in all patients and PWD was calculated. In addition, demographic data, imaging findings and laboratory test results of all COVID-19 patients were obtained from the institutional digital database and recorded.

Results: Patients who developed AF were older and had a higher frequency of hypertension and heart failure ($p<0.05$ for all). Patients who developed AF during hospitalization had higher neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP) ($p<0.05$ for all)). The PWD value was significantly longer in the AF group ($p<0.05$). In addition, a significant positive correlation was observed between PWD and cTn-I, CRP and NLR.

Conclusion: Our study showed that PWD predicts new-onset AF during follow-up of COVID-19 patients and is associated with inflammatory markers. Multivariate logistic regression analysis showed that PWD is an independent predictor of AF development. We believe that pretreatment PWD assessment in COVID-19 patients may be useful in estimating the risk of AF.

Keywords: P Wave Dispersion, COVID-19, Atrial Fibrillation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in a global pandemic (1-3). While the majority of COVID-19 cases manifest with a mild clinical course, some individuals develop a severe disease phenotype (1-3). Those experiencing a severe clinical course are typically of advanced age, presenting with increased comorbidities such as coronary artery disease (CAD), hypertension, diabetes mellitus (DM), and heart failure (HF) (1-3). Particularly in hospitalized patients, various cardiac complications, predominantly arrhythmias, may ensue (4). Diverse studies report an incidence of arrhythmias in hospitalized patients ranging from 7% to 22%, with atrial fibrillation (AF) being the most commonly

Cite this article: Eren H, Omar MB, Kaya Ü, Akkan S, Demizbaş Z. Relationship between atrial fibrillation and P wave dispersion in inpatients with COVID-19. Interdiscip Med J. 2023;14(50):181-189. https://doi.org/10.17944/interdiscip.1410386

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Received: July 30, 2021
Accepted: August 25, 2023

observed (4-6). AF, the most prevalent arrhythmia associated with aging and various cardiovascular comorbidities, is unsurprisingly frequent in COVID-19 patients undergoing inpatient care due to a shared risk profile. The Italian Ministry of Health has reported AF development in 19-22% of hospitalized COVID-19 patients (7,8).

P-wave dispersion (PWD) is defined as the difference between the maximum and minimum P-wave durations assessed on the standard electrocardiogram (ECG) (9). Increased PWD is well-established to be particularly associated with various atrial-origin arrhythmias such as AF (10). PWD serves as a simple and useful electrocardiographic parameter predicting the development of AF in various clinical scenarios (11,12).

In COVID-19 pathology, increased systemic inflammation, heightened adrenergic stimulation, myocardial injury secondary to hypoxia, and microvascular thrombosis resulting from endothelial inflammation occur (13-16). All these processes may lead to changes in atrial tissue through electrical and structural abnormalities in the context of COVID-19 disease, potentially impacting P-wave parameters. Therefore, in this study, the objective was to determine the relationship between PWD values and the development of AF in patients hospitalized due to COVID-19, with the aim of elucidating the potential link between PWD and AF in the context of COVID-19-induced cardiac alterations.

METHOD

Study Population and Patient Selection

This multicenter study was conducted through a retrospective review of the records of patients hospitalized between May 20, 2020, and January 15, 2021. A total of 61 patients who developed AF during the follow-up were included in the study. All patients were treated in accordance with the guidelines outlined in the Turkish Ministry of Health COVID-19 treatment protocols (17). In order to avoid bias, no exclusion criteria were defined, except for valvular AF, individuals with a history of pre-existing AF, pregnancy or breastfeeding, and those with mechanical heart valve prostheses. After excluding 10 patients, a total of 51 patients constituted the group. Subsequently, 72 COVID-19 patients who did not develop AF were randomly selected to form the control group. The diagnosis of new-onset AF was confirmed through daily electrocardiograms, bedside monitors, or Holter devices. Additionally, patients were regularly examined during daily follow-ups, and pulse examinations were conducted systematically. Patients with insufficient information in their hospital records were excluded from the study.

Demographic characteristics, cardiovascular risk factors, comorbidities, medication usage, smoking habits, and laboratory values of the patients included in the study were recorded.

Diagnosis of COVID-19

Patients meeting the criteria for a potential SARS-CoV-2 infection according to the Turkish Ministry of Health COVID-19 Treatment Guidelines and the World Health Organization (WHO) underwent viral screening using molecular methods (17,18). Throat and nasopharyngeal swab samples were collected from all patients in this study to detect SARS-CoV-2 RNA. Real-time reverse transcription polymerase chain reaction (RT-PCR) molecular method was employed for the analysis of SARS-CoV-2 virus RNA. The RT-PCR test was conducted in accordance with WHO guidelines, utilizing the SARS-CoV-2 (2019 nCoV) qPCR Detection Kit (Bioeksen R&D Technologies Co Ltd, Istanbul, Türkiye) recommended by the Turkish Ministry of Health (17,19). Cases with detectable SARS-CoV-2 RNA by the RT-PCR method were considered as confirmed cases of COVID-19. The definition of comorbidities was based on relevant guidelines, and elevated cardiac troponin I values, with at least one value above the 99th percentile upper reference limit, were characterized as myocardial injury.

ECG

All ECGs of the patients included in the study were assessed before the initiation of treatment. 12-lead ECGs (Mortara, Jackson, USA) were recorded in the supine position at rest, with a speed of 25 mm/s and a voltage of 10 mm/mV. To minimize measurement errors, all ECGs were scanned, transferred to a personal computer, and then examined at 400% magnification using Adobe Photoshop software. All measurements were performed manually on the screen using appropriate programs. The baseline ECGs of all patients were reviewed, and all exhibited a sinus rhythm. The first detectable point of atrial depolarization from the isoelectric line was defined as the onset of the P-wave. Subsequently, the

turning point on the isoelectric line was defined as the end of the P-wave. ECG derivations where the beginning or end of the P-wave could not be precisely determined were excluded from the analysis. P-maximum (P-max) was determined as the P-wave duration in any derivation with the longest interval, while P-minimum (P-min) was defined as the P-wave duration in any derivation with the shortest interval. PWD was calculated by subtracting P-min from P-max, as measured in any of the 12 ECG derivations. A cutoff value of at least 36 ms was established to categorize PWD, as previously demonstrated (20). P-wave amplitude was defined as the vertical distance between the peak of the P-wave and the isoelectric line, calculated in millivolts from derivations V1 and D2. The PR interval was defined as the distance between the onset of the P-wave and the onset of the QRS complex. QRS duration was defined as the distance from the end of the PR interval to the end of the S-wave. QT interval was defined as the interval from the beginning of the QRS complex to the end of the T-wave. QT interval measurements were taken from all derivations, and the longest QT interval was recorded. The R–R interval was measured, and heart rate (HR) was calculated, and corrected QT intervals (QTc) were calculated using the Bazett formula: QTc=QTH (R–R interval) (21). All ECG measurements were made in three consecutive beats, and the average of three measurements was taken for analysis. Two independent cardiologists, blinded to other patient information, performed all ECG measurements. These values were calculated three times for each study patient. Intraobserver and interobserver variations for measurements were calculated as 3.5% and 3.2%, respectively.

Transthoracic Echocardiography (TTE)

Echocardiography was performed on all patients using the Philips Affiniti 50C system (Philips Medical Systems, Netherlands) in the left lateral position. Measurements were taken simultaneously with a single-lead electrocardiogram recording, and the average of three cardiac cycles was recorded. Measurements were conducted in accordance with the recommendations of the American Society of Echocardiography (22).

Laboratory Measurements

Following the immediate diagnosis of COVID-19 and during hospitalization, routine blood laboratory tests were conducted. Routine blood test results, including serum cTn-I, were obtained from the institutional digital database, and values below the 99th percentile upper reference limit were considered normal. Hemogram, biochemical parameters, cTn-I, D-dimer, ferritin, and CRP measurements were performed for all patients. Using hemogram measurements, NLR and PLR were calculated.

Statistical Analysis

All measurements were evaluated for normal distribution using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), and categorical variables as percentages. For the comparison of groups, the student-t test or Mann-Whitney U test was used for continuous variables, and the chi-square test for categorical variables. Enter method regression analysis was applied for multivariate analysis of independent variables that could predict the development of AF. Variables with an unadjusted p-value < 0.10 were included in the multivariate model to identify predictors of new-onset AF development. Statistical significance was defined as $p < 0.05$. SPSS version 22.0 (SPSS 22.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

A total of 532 patient records admitted due to COVID-19 were retrospectively reviewed. It was determined that AF developed in 61 patients during hospitalization (11.4%). Ten patients were excluded from the study due to exclusion criteria, leaving 51 patients included in the analysis. Additionally, 72 COVID-19 patients without AF were randomly selected to form the control group. All data between the groups with and without AF were compared.

The demographic and clinical characteristics of both groups are presented in Table 1. The mean age was significantly higher in the AF group (74.8±9.3 vs. 65.7±12.1, $p<0.001$). No statistically significant differences were observed between the groups in terms of gender, DM frequency, smoking, body mass index (BMI), hyperlipidemia (HL) frequency, coronary artery disease (CAD), chronic obstructive pulmonary disease, and history of prior stroke or embolism ($p>0.05$). However, in patients with AF, hypertension (68.6% vs. 40.1%, $p<0.001$), heart failure (13.7% vs. 6.9%, $p<0.001$), admission oxygen saturation (87.5% vs. 91.2%, $p<0.001$), intensive care admission rate (21.5% vs. 16.6%,

p<0.001), CHA_2DS_2VASc score (2.48±0.56 and 1.73±0.76, p<0.001), intubated patient count (7.8% vs. 4.2%, p<0.001), and frequency of inotropic agent use (9.8% vs. 5.5%, p<0.001) were higher. There was no statistically significant difference in medication use between the two groups. AF developed within the first 96 hours after hospitalization in 36 patients and within the first week in the remaining 15 patients. Among these 51 patients, 11 were monitored in the intensive care unit.

Table 1: Comparison of the demographic characteristics of the study population.

	AF group (n=51)		Control group (n=72)		p value
Age (year)	74.8 ± 9.3		65.7 ± 12.1		<0.001
Gender (male)	31	61.1%	45	62.5%	0.643
BMI kg/m²	30.2±8.5		29.8±7.3		0.271
Hypertension, count (%)	35	68.6%	29	40.1%	<0.001
Diabetes mellitus, count (%)	13	25.4%	17	23.6%	0.328
Hyperlipidemia, count (%)	18	35.3%	25	34.7%	0.321
Coronary artery disease, count (%)	6	11.7%	8	11.1%	0.501
Heart failure, count (%)	7	13.7%	5	6.9%	<0.001
Cigarette, count (%)	15	29.4%	21	27.7%	0.253
COPD, count (%)	5	9.8%	7	9.7%	0.427
CVA or history of embolism, count (%)	2	3.9%	3	4.1%	0.738
CHA2DS2VASc	2.48±0.56		1.73 ±0.76		0.021
Intensive care hospitalization, count (%)	11	21.5%	12	16.6%	0.003
Need for intubation, count (%)	4	7.8%	3	4.2%	0.012
Use of inotropic, count (%)	5	9.8%	4	5.5%	0.023
Use of anticoagulants, count (%)	51	100%	72	100%	0.786
Admission oxygen saturation (%)	87.5±7.2		91.2±6.4		0.004

Abbreviations: AF; atrial fibrillation, BMI; body mass index, CHA2DS2VASc; congestive heart failure (1), hypertension (1), age>75 (2), Diabetes mellitus (1), Previous cerebrovascular accident or transient ischemic attack (2), history of vascular disease (1), age 65-74 (1), female gender (1), COPD; chronic obstructive pulmonary disease, CVA; cerebrovascular accident

Laboratory findings of the patients are presented in Table 2. In the AF group, WBC (7.9±3.2 vs. 6.3±1.4, p=0.003), neutrophil count (5.7±2.1 vs. 3.9±1.9, p<0.001), NLR (6.4±2.1 vs. 4.7±1.9, p=0.012), PLR (274.1±96.2 vs. 213.3±77.9, p=0.023), ferritin (739.2±201.2 vs. 431.2±141.4, p<0.001), D-dimer (5821±1234 vs. 3021±1064, p=0.031), cTn-I (0.063±0.013 vs. 0.025±0.09, p<0.001), and CRP (47.1±19.3 vs. 29.4±11.9, p<0.001) levels were significantly higher compared to the non-AF group. Lymphocyte count (1.2±0.4 vs. 1.5±0.5, p=0.002) was significantly lower in the AF group. No statistically significant differences were observed between the groups in terms of other laboratory values (p>0.05).

Table 2: Comparison of laboratory characteristics of the study population.

	AF group (n =51)	Control group (n=72)	p value
WBC (10^3 µl)	7.9±3.2	6.3±1.4	0.003
Neutrophil (10^3 µl)	5.7±2.1	3.9±1.9	<0.001
Lymphocyte (10^3 µl)	1.2±0.4	1.5±0.5	0.002
Monocyte (10^3 µl)	0.58±0.23	0.57±0.29	0.435
Platelet (10^3 µl)	233.5±78.8	229.9±74.7	0.245
Ferritin	739.2±201.2	431.2±141.4	<0.001
CRP (mg/l)	47.1±19.3	29.4±11.9	<0.001
Troponin I (ng/mL) (cut off=0.021)	0.063±0.013	0.025±0.09	<0.001
D-Dimer (ng/mL)	5821±1234	3021±1064	0.031
Hemoglobin (g/dl)	12.9±1.3	13.5 ± 1.6	0.510
Glucose (mg/dl)	97.2±8.8	95.9±8.9	0.345
Aspartate aminotransferase (IU/l)	31.1±6.8	29.8±8.1	0.248
Alanine aminotransferase (IU/l)	29.8±8.4	27.3±9.1	0.123
Creatinine (mg/dl)	0.93±0.21	0.87±0.23	0.712
Sodium (mEq/l)	139.1±3.3	137.2±3.1	0.162
Calcium (mg/dl)	9.43±.2.32	9.34±1.98	0.123
Potassium (mmol/l)	4.12±0.74	4.23±0.62	0.279
NLR	6.4±2.1	4.7±1.9	0.012
PLR	274.1±96.2	213.3±77.9	0.023

Abbreviations: AF; atrial fibrillation, CRP; C-reactive protein, NLR; neutrophil/ lymphocyte ratio, PLR; platelet/lymphocyte ratio

The electrocardiographic and echocardiographic values of both groups are presented in Table 3. Maximum P-wave duration (111.2±12.9 vs. 96.8±7.5, p<0.001), minimum P-wave duration (69.2±8.9 vs. 60.1±6.3, p<0.001), and PWD value (47.1±9.2 vs. 36.1±5.1, p<0.001) were significantly higher in patients with AF. PR interval (147.1±17.2 vs. 139.3±14.3, p=0.003), P-wave amplitude in lead V1 (0.131±0.011 vs. 0.122±0.07, p<0.001), P-wave amplitude in lead D2 (0.139±0.013 vs. 0.125±0.008, p<0.001), and left atrial diameter (38.5±3.3 vs. 35.6±3.1, p=0.013) were significantly higher in the AF group. There were no statistically significant differences between the groups in terms of other electrocardiographic and echocardiographic results (P>0.05).

Significant parameters found in univariate regression analysis were included in multivariate logistic regression analysis. In multivariate logistic regression analysis, PWD

(Odds ratio (OR): 3.345, 95% CI: 1.607-7.697, p<0.001), age (OR: 1.099, 95% CI: 1.026-1.715, p=0.002), hypertension (OR: 2.134, 95% CI: 1.242-6.789, p=0.002), and CRP (OR: 1.321, 95% CI: 1.213-1.713, p=0.005) were predictors for the development of AF in hospitalized COVID-19 patients (Table 4). Particularly, among these parameters, PWD was the strongest independent determinant of AF development. It was observed that 45 patients with AF returned to sinus rhythm upon discharge, while 6 did not.

Table 3: Comparison of electrocardiographic and echocardiographic characteristics of the study population.

	AF group (n =51)		Control group (n=72)		p value
Heart rate (beats/minute)	82.2±7.7		80.1±6.9		0.467
LVEF (%)	60.2±2.1		61.7±1.7		0.315
Left atrium diameter (mm)	38.5±3.3		35.6±3.1		0.013
PR interval (ms)	147.1±17.2		139.3±14.3		0.003
PR interval >160 ms, n (%)	23	45.1%	8	11.1%	0.007
PR interval >200 ms, n (%)	3	5.8%	4	5.5%	0.231
P-wave amplitude (mV) V1 derivation	0.131±0.011		0.122±0.007		<0.001
P-wave amplitude (mV) D2 derivation	0.139±0.013		0.125±0.008		<0.001
Maximum P-wave duration (ms)	111.2±12.9		96.8±7.5		<0.001
Minimum P-wave duration (ms)	69.2±8.9		60.1±6.3		<0.001
PWD (ms)	47.1±9.2		36.1±5.1		<0.001
PWD>36 ms, count (%)	26	50.1%	11	15.2%	<0.001
QRS width (ms)	118.9±4.7		119.2±4.5		0.325
QTc interval (ms)	396.1±9.5		392.7±8.9		0.546

Abbreviations: AF; atrial fibrillation, PWD; P-wave dispersion, LVEF; left ventricular ejection fraction.

DISCUSSION

In this study, it was found that the PWD value was longer in the group where AF developed among COVID-19 patients receiving inpatient treatment. Additionally, inflammatory markers such as CRP, NLR, and PLR, as well as the cardiac damage indicator cTn-I, were significantly higher in patients with AF. Increased PWD value was shown to be associated with the development of new-onset AF in COVID-19 patients. This study suggests that PWD value in hospitalized COVID-19 patients may be used to predict AF development.

The novel coronavirus named SARS-CoV-2 was first detected in Türkiye in March 2020 (17). The COVID-19 caused by SARS-CoV-2 has led to a global pandemic as it rapidly spread worldwide (20). Although COVID-19 was initially considered a disease characterized by respiratory symptoms, it was observed that cardiovascular diseases and complications often accompanied COVID-19 infections as the number of patients increased (4,5). Various studies have reported various cardiovascular complications such as myocardial injury, cardiac decompensation, and arrhythmias, ranging from 7% to 17% in these patients, significantly contributing to mortality (2,23). These results indicate that cardiovascular involvement is considerable in COVID-19 patients. Especially, cardiac arrhythmias are the most commonly reported cardiovascular complications in COVID-19 patients, with new-onset AF being the most common form (5,6). There are some mechanisms underlying the development of AF in COVID-19 patients (13-16). This novel virus readily attaches to type 2 alveolar cells in the lungs and the angiotensin-converting enzyme 2 receptor in myocardial tissue in humans, exerting direct cytotoxic effects on these cells (24,25). The presence of interstitial mononuclear cells in the myocardium supports this theory (26). Additionally, increased sympathetic stimulation following

Table 4: Univariate and multivariate regression analysis showing independent predictors of atrial fibrillation

	Univariate OR	95%CI	p value	Multivariate OR	95% CI	p value
PWD	2.142	1.798–7.123	0.001	3.345	1,607-7.697	<0.001
Age	1.198	1.072-3.150	0.005	1.099	1.026-1.715	0.002
Hypertension	1.856	1.370-6.145	0.001	2.134	1.242-6.789	0.002
CRP	1.141	1.056-1.634	0.002	1.321	1.213-1.713	0.005
Admission oxygen saturation	0.645	0.456-0.914	0.003	1.477	0.742-1.987	0.871
cTn-I	1.156	1.142-1.287	0.041	1.123	0.898-1.323	0.245
CHA2DS2-VASc	1.123	1.098-1.323	0.045	0.980	0.938-1.023	0.351
HF	1.348	1.087-1.657	0.034	1.333	0.719-2.472	0.362
Ferritin	1.080	1.038-1.098	0.023	1.447	0.749-2.792	0.271
NLR	1.333	1.119-2.472	0.012	0.966	0.896-1.042	0.370
Left atrium diameter	1.266	1.196-1.942	0.032	1.234	0.856-2.178	0.317
PLR	1.592	1.156-5.214	0.009	0.992	0.962-1.023	0.622

Abbreviations: CHA2DS2VASc; [congestive heart failure (1), hypertension (1), age>75 (2), Diabetes mellitus (1), Previous cerebrovascular accident or previous transient ischemic attack (2), history of vascular disease (1), age 65-74 (1), female gender (1)], CRP; C-reactive protein, cTn-I; cardiac troponin I, HF; heart failure, NLR; neutrophil/lymphocyte ratio, OR; Odds ratio, PWD; P-wave dispersion PLR; platelet/lymphocyte ratio.

infection, hypoxia, cytokine storm secondary to inflammation, increased tendency for coagulation, intravascular volume, and neurohormonal abnormalities can indirectly affect the cardiovascular system (27). All these pathophysiological mechanisms can lead to a proarrhythmic effect. With the effect of these mechanisms, various arrhythmias, particularly AF, can occur during COVID-19 infection (5,6). Pan et al. found in their study that arrhythmia developed in 16.7% of cases hospitalized due to COVID-19 (2). Guo et al. showed that arrhythmias frequently developed in COVID-19 patients they followed during hospitalization (4). Similarly, the Italian Ministry of Health reported that 19-22% of hospitalized COVID-19 patients developed AF in their studies (7,8). In this study, new-onset AF was detected in 11.4% of patients. These results support the idea that arrhythmic events are not rare in COVID-19 patients.

Previous information indicates the presence of an increased inflammatory state and elevated levels of TNF-α, IL-6, and IL-1β in patients with SARS-CoV-2 infection (23). It is now known that inflammation plays a significant role in the development of AF, beyond traditional risk factors (27). Therefore, SARS-CoV-2 infection may induce a severe inflammatory response associated with the formation of AF (14-16). This relationship has been explained by the infiltration of inflammatory cells into the atrium, myocyte necrosis, and fibrosis formation. Previously, it has been reported that inflammatory mediators such as CRP, IL-6, and TNF-α, especially released during the inflammatory process, induce the development of AF (27). Additionally, some studies have shown that an increase in serum CRP levels is associated with an increased risk of AF development and a high rate of AF recurrence after catheter ablation (28,29). Moreover, CRP level and NLR are significant indicators of systemic inflammation in COVID-19 patients (14). A study investigating the early stages of COVID-19 found that CRP levels reflect disease severity and should be used as a key indicator for disease monitoring (30). Yang et al. demonstrated high NLR levels in patients with COVID-19 (14). A meta-analysis reported that increased NLR levels in COVID-19 patients may be associated with poor prognosis (31). In this study, CRP and NLR levels were significantly higher in patients who developed AF. Therefore, it can be said that increased systemic inflammatory activity is more prevalent in these patients. Multivariate regression analysis found that the CRP level in blood taken upon admission to the hospital is an independent predictor of AF development in SARS-CoV-2 patients. The significantly higher levels of inflammatory markers such as CRP, procalcitonin, erythrocyte sedimentation rate, and NLR in COVID-19 patients who developed AF compared to those who did not support this study (32). WBC value and subtypes such as NLR and PLR have been reported as indicators of inflammation in various cardiovascular diseases. NLR, especially in recent years, in addition to traditionally used inflammatory markers, is a systemic inflammatory marker that is inexpensive and easily obtainable and can be used for risk classification in various cardiovascular diseases, and an increase in NLR has been reported as a predictor of AF development (33). PLR, similar to NLR, is another inflammatory marker that has been studied in various cardiovascular patient groups in recent years and has proven prognostic importance (34,35). An increase in PLR has also been reported to be associated with adverse cardiovascular events (34). Gungor et al. reported that an increase in PLR values is an independent predictor of paroxysmal AF (36). In this study, it was determined that SARS-CoV-2-infected patients who developed AF had higher WBC, NLR, and PLR levels at the time of admission compared to those without AF. The higher levels of inflammatory markers such as CRP, NLR, and PLR in patients with AF support the view that the severity of infection may be a trigger for AF.

Regional delays in atrial depolarization can lead to an uneven P-wave duration. This heterogeneity, termed P-wave dispersion (PWD), is defined as the difference between the longest and shortest P-wave durations recorded from surface ECG derivations (37). PWD has been used to assess the risk of developing AF in various clinical conditions, including cardiovascular diseases (11). In many studies, increased PWD measurement has been reported as a sensitive and specific ECG predictor for AF (10). When compared with the control group, higher PWD values were found in the group that developed AF. Our results indicate the importance of PWD measurement due to the increased risk of AF development in COVID-19 patients. Increased inflammatory activity leads to tissue damage in atrial myocardium, and resulting fibrosis causes atrial remodeling. This can alter the membrane potential in atrial myocytes and lead to heterogeneous refractory periods in atrial conduction. These changes may be reflected as prolonged P-wave duration and increased PWD on surface ECG (37). Similarly, in this study, it was determined that P-wave parameters were prolonged in patients who developed AF. In many studies, PWD value has been closely associated with inflammation (37-38). Yenerçağ et al., in their study comparing patients diagnosed with COVID-19 with healthy adults, demonstrated that PWD values were higher in COVID-19 patients than in healthy individuals (38). According to these results, inflammation occurring in COVID-19 patients may lead to an increase in PWD, causing the development of atrial arrhythmias. Additionally, in this study, PWD was found to be the strongest independent predictor indicating the development of AF.

Increased age, heart failure, and hypertension are among the key risk factors for the development of new-onset AF (39, 40). All these risk factors lead to an increase in atrial pressure and atrial remodeling, causing slowing of

atrial conduction and the formation of a substrate for AF (40). In this study, hypertension and HF were more frequent in patients who developed AF, and age and CHA2DS2-VASc score were significantly higher compared to the other group. These results suggest the development of atrial myopathy in the group with AF and an increased arrhythmic sensitivity of atrial tissue. Furthermore, these results support the increased PWD value in the group of patients who developed AF. Our current data support the hypothesis that these factors could play a significant role in the development of AF in COVID-19 patients. Additionally, cTn-I levels were found to be significantly higher in patients who developed AF. This result suggests that the occurring ventricular dysfunction may lead to increased left atrial pressure, contributing to the development of AF (41). In conclusion, it has been reported that the risk of developing AF is high in COVID-19 patients with a high PWD value, and we believe that these patients may require closer monitoring. These results confirm the results of previous studies emphasizing the role of inflammation in the pathogenesis of AF.

Limitations

There were several limitations in this study. Firstly, the sample size was small, and a larger cohort study is needed to confirm our results. Secondly, other inflammatory parameters, detailed echocardiographic measurements, and IL-6 with erythrocyte sedimentation rate couldn't be evaluated due to the fact that it was a retrospective study, the study conditions were limited, there was a possibility of viral infection, and the urgency of COVID-19. Thirdly, partly due to limitations in the available data and partly due to potential delays in the diagnosis of atrial arrhythmias during the COVID-19 pandemic, the exact onset of AF may not be accurately determined. Therefore, it is challenging to distinguish the temporal relationship between factors associated with the development of AF and their occurrence during the hospitalization. It is also worth noting that these data only pertain to hospitalized patients. Unhospitalized COVID-19 patients may have different predictors and outcomes for developing AF. However, since the likelihood of developing AF is higher in the most critical patients regardless of viral etiology, it is likely that the patients with the highest probability of developing AF were admitted to the hospital. Finally, since our follow-up only extended until discharge from the hospital, the impact of atrial arrhythmias on the post-hospitalization clinical course of the patients was not examined in this analysis. Additionally, there was no post-discharge follow-up to evaluate the occurrence of atrial arrhythmias after hospitalization.

CONCLUSION

In this study, it was found that new-onset AF occurred in 11.4% of hospitalized COVID-19 patients. The PWD is an easily accessible, cost-effective, and noninvasive ECG parameter, assessing the risk of AF development. It was determined to be high in COVID-19 patients who developed AF in this study. Furthermore, a significant relationship among PWD, CRP and NLR was identified. The evaluation of these ECG P-wave measurements in newly diagnosed COVID-19 patients may be beneficial in predicting the risk of AF development before treatment. Given the increased risk of AF development in COVID-19 patients with high PWD values, closer monitoring is anticipated. The presence of AF is associated with the increased clinical symptoms of severe COVID-19, high levels of inflammation, and markers of cardiac injury. Large-scale, long-term studies are needed to support our data.

ACKNOWLEDGEMENT

Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

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

Financial Support

The Authors report no financial support regarding content of this article.

Ethical Declaration

Ethical approval was obtained from Hospital's Research Ethical Committee with date 11.02.21 and number (FSMEAH-KAEK 2021/19 , and Helsinki Declaration rules were followed to conduct this study.

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Author Contributions

Concept: HE, MBO, ÜK, SA, ZD, Design: HE, MBO, ÜK, SA, ZD, Supervising: HE, MBO, ÜK, SA, ZD, Financing and equipment: HE, MBO, ÜK, SA, ZD, Data collection andentry: HE, MBO, ÜK, SA, ZD, Analysis and interpretation: HE, MBO, ÜK, SA, ZD, Literature search: HE, MBO, ÜK, SA, ZD, Writing: HE, MBO, ÜK, SA, ZD, Critical review: HE, MBO, ÜK, SA, ZD

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