

P wave peak time and P wave dispersion in severe COVID-19 infection

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Abstract. – OBJECTIVE: With this study, we aimed at evaluating the association between electrocardiographic P wave indices and the severity of COVID-19 infection indicated as intensive care unit (ICU) admission.

PATIENTS AND METHODS: We included 247 patients who were hospitalized with a diagnosis of COVID-19 infection and underwent 12 lead standard Electrocardiography (ECG). P wave indices, P wave dispersion (Pdis), P wave peak time in V1 lead (PWPT_{V1}), and D2 lead (PWPT_{D2}) were measured using admission ECG. Comparisons were performed between ICU admitting and non-ICU admitting patients.

RESULTS: 160 patients were hospitalized in normal wards, and 87 patients were admitted to ICU. Pdis, PWPT_{V1}, and PWPT_{D2} were prolonged in ICU admitted patients compared with the normal ward admitted patients [40 (30-50) ms vs. 50 (40-55) ms; $p<0.001$, 61 ± 9 ms vs. 68 ± 9 ms; $p<0.001$, and 55 ± 7 ms vs. 64 ± 7 ms; $p<0.001$, respectively]. In multiple logistic regression analysis, PWPT_{V1} and PWPT_{D2} were independent predictors of ICU admission. A cut-off point of 67.5 ms PWPT_{V1} has a sensitivity of 62.1% and a specificity of 69.4% (AUC=0.710, 95% CI: 0.642-0.777, $p<0.001$) and a cut-off point of 62.5 ms PWPT_{D2} has a sensitivity of 60.9% and a specificity of 83.6% (AUC=0.819, 95% CI: 0.777-0.871, $p<0.001$).

CONCLUSIONS: Admission ECG atrial indices Pdis and PWPT were associated with intensive care unit admission in newly diagnosed COVID-19 patients.

Key Words:

COVID-19, Electrocardiography, P wave dispersion, P wave peak time, Intensive care.

SARS-CoV-2 is the causative agent of Coronavirus disease 2019 (COVID-19) and the determinants of the severe COVID-19 remain uncertain. Heterogeneity of COVID-19 clinical manifestations may vary from mild, rapidly improving symptoms to an accelerated decline requiring intensive care. The circulatory and respiratory systems are the mainly affected organs; however, little data are available on the use of a basic and common test such as standard electrocardiogram (ECG) as a prognosticator.

Several ECG indices were evaluated in COVID-19 prognosis and severity¹⁻⁴. Atrial functions and atrial indices are closely related to cardiac and respiratory parameters that are prone to deteriorate during the COVID-19 disease course. A recent study evaluated P wave dispersion (Pdis) in newly diagnosed COVID-19 patients⁵. P wave peak time (PWPT), the time from the beginning of the P wave to its peak, is a novel index of atrial depolarization and recent studies showed the association with several cardiac conditions⁶⁻⁸. Also, severe inflammation during COVID-19 may induce electrophysiological changes and atrial remodeling that may influence atrial indices on surface ECG. In this context, atrial ECG indices, specifically Pdis and PWPT may have a prognostic value in the COVID-19 trajectory. Hitherto, no study investigated PWPT in COVID-19. This study aimed at investigating the possible association between atrial ECG indices, specifically Pdis and PWPT, measured on surface ECG and severity of COVID-19 infection, indicated as intensive care unit (ICU) admission.

Introduction

The world has been facing a pandemic caused by the severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) since the end of 2019.

Patients and Methods

In this single-centered, retrospective, observational study, we recruited 247 patients with COVID-19 diagnosis based on positive Reverse

Transcriptase-Polymerase Chain Reaction (RT-PCR) assay from a nasal and/or throat swab according to the COVID-19 Treatment guideline. Patients who were admitted to the Pandemia Clinics of Cankiri State Hospital and hospitalized with a diagnosis of COVID-19 infection and underwent simultaneous standard ECG examination between April 2020 and September 2020 were included. Laboratory tests including biochemistry, complete blood count (CBC) and C-reactive protein (CRP) were obtained at admission. Blood samples for complete blood count (CBC) were taken into standardized tubes containing potassium ethylenediaminetetraacetic acid tubes (dipotassium EDTA). Plasma levels of biochemical parameters were tested using an automated biochemistry analyzer. The plasma level of C-Reactive Protein (CRP) was measured using a turbidimetric immunoassay method. Data were retrospectively extracted from the digitally archived patients' files. Patients with atrial fibrillation, conduction abnormalities, atrioventricular block, pacemaker rhythm, and patients under 18 years old were excluded from the study. The study was approved by the Ethics Review Committees of the Cankiri Karatekin University. Approval of the study protocol and a waiver from the need to provide written informed consent were obtained from the Ethics Review Committees of the Cankiri Karatekin University.

The 12-lead ECG was recorded at a paper speed of 25 mm/s and 10 mm/mV amplitude during rest in the supine position at admission before the initiation of the treatment. One cardiologist, who was blinded to the clinical status of the patients, measured ECG intervals. Measurements were performed with the caliper and magnifying lens for defining the ECG deflection. P wave dispersion is defined as the difference between the maximum and minimum P wave durations measured at all ECG leads⁹. P wave Peak Time at lead D2 ($PWPT_{D2}$) was measured as the duration from the beginning to the peak of the P wave was measured from lead D2 and P wave Peak Time at lead V1 ($PWPT_{V1}$) was defined as the interval between the beginning of the P wave to the nadir of the negative deflection in patients with biphasic or pure negative P wave morphology¹⁰ (Figure 1).

All Chest Computed Tomography using Toshiba Aquilion (Toshiba Medical Systems Corporation, Ōtawara, Tochigi, Japan) scans were acquired in the supine position during inspiratory breath-hold. Acquired images were transferred to

the picture archiving and communicating system (PACS) and evaluated by one expert radiologist who was blinded to the laboratory and ECG characteristics of the patients. Lung involvement, location of involved lung lobes (upper right, middle right, lower right, upper left, and lower left lobes), number of involved lobes, the pattern of lung involvement (ground glass, consolidation, reticular, honeycomb), and involvement distribution (central, subpleural or diffuse involvement) were reported.

Statistical Analysis

Statistical analyses were carried out with IBM SPSS for Windows Version 23.0 (IBM Corp., Armonk, NY, USA) package program. The level of significance was accepted as $p < 0.05$. Quantitative variables were summarized as mean \pm standard deviation or median (25-75th percentile) and categorical variables by numbers and percentages. Parametric test assumptions (normality and homogeneity of variances) were checked before comparing the groups in terms of quantitative variables. Shapiro-Wilk's test was used to examine whether the quantitative variables showed normal distribution. The homogeneity of the variances of the compared groups was tested with the Levene's test. When parametric test assumptions were provided, *t*-test was used in independent groups in comparison of groups, and Mann Whitney U test was used when para-

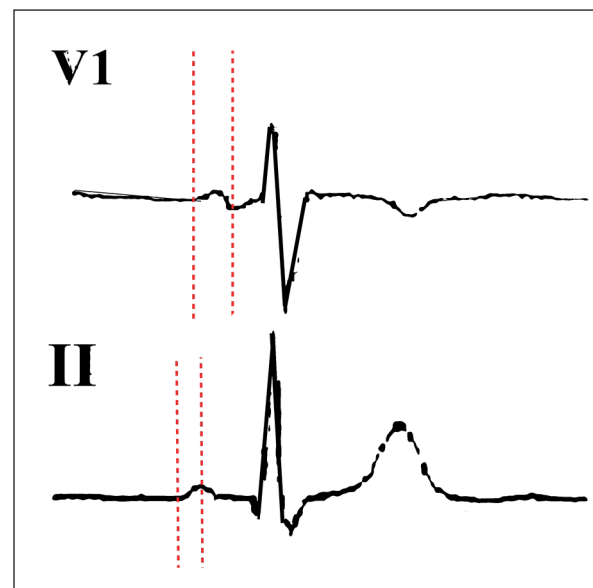


Figure 1. Measurement of P wave peak time on D2 and V1 leads.

metric test assumptions were not met. Chi-square or Fisher's exact test were used to compare the groups in terms of categorical variables. Factors predicting ICU admission were tested using step-wise multiple logistic regression analysis. The cut-off points of P wave dispersion and PWPT that determine admission to intensive care were calculated by ROC curve analysis.

Results

We included 87 ICU admitting and 160 normal wards hospitalized patients. Demographics, comorbidities, clinical characteristics, and laboratory analysis are summarized in Table I. ICU admitted patients were older and ICU admission was more frequent among male patients. Diabetes Mellitus, hypertension, and smoking were also more frequent in ICU admitted patients. The frequency of hyperlipidemia was similar between the two groups. Blood glucose and creatinine levels were higher in ICU admitted patients [113.5 (100-135) mg/dl vs. 147 (119-184) mg/dl, $p<0.001$ and 0.85 (0.7-1) mg/dl vs. 1.10 (0.81-1.42) mg/

dl, $p<0.001$ respectively]. Leukocyte and C-reactive protein levels were significantly higher in ICU admitted patients [5,680 (4,740-7,527)/mm³ vs. 6,870 (5200-9390)/mm³, $p=0.004$ and 15.7 (3.5-79.5) mg/l vs. 101.8(51.2-178.3) mg/l respectively]. On the other hand, hemoglobin and platelet levels were lower in ICU admitted patients [13.62±1.76 g/dl vs. 12.92±2.23 g/dl, $p=0.012$ and 203 (164-253)/mm³ vs. 177(128-215)/mm³, $p=0.002$ respectively].

Heart rate and PR intervals were similar in both groups of patients (83±16 bpm vs. 87±14 bpm, $p=0.082$ and 149±21 ms vs. 149±18 ms, $p=0.891$, respectively). Pmax and Pmin were prolonged in ICU admitted patients compared with the normal ward admitted patients [100 (100-110) ms vs. 120 (110-120) ms, $p<0.001$ and 60 (50-70) ms vs. 70 (60-70) ms, $p<0.001$ respectively]. Pdis was also increased in ICU admitted patients [40 (30-50) ms vs. 50 (40-55) ms, $p<0.001$]. PWPT_{v1} and PWPT_{d2} were prolonged in ICU admitted patients compared with the normal ward admitted patients (61±9 ms vs. 68±9 ms, $p<0.001$, and 55±7 ms vs. 64±7 ms, $p<0.001$, respectively).

Table I. Baseline demographic, clinical and laboratory characteristics.

	Non-intensive care unit admitting (n = 160)	Intensive care unit admitting (n = 87)	p-value
Age, years	68.3 ± 11.8	51.7 ± 18.9	< 0.001
Male	84 (57.5%)	62 (71.2%)	0.004
Female	76 (47.5%)	18 (20.7%)	
Diabetes mellitus	18 (11.3%)	28 (32.1%)	< 0.001
Hypertension	62 (38.8%)	60 (69%)	< 0.001
Hyperlipidemia	7 (4.3%)	9 (10.3%)	0.121
Non-smokers	140 (87.5%)	65 (74.7%)	< 0.001
Glucose (mg/dl)	113.50 (100-135)	147 (119-184)	< 0.001
Creatinine (mg/dl)	0.85 (0.70-1.00)	1.10 (0.81-1.42)	< 0.001
Sodium(mmol/L)	136 ± 4	135 ± 6	0.141
Potassium (mmol/L)	4.08 ± 0.48	4.12 ± 0.60	0.622
Leukocytes (/mm ³)	5,680 (4,740-7,527)	6,870 (5,200-9,390)	0.004
Hemoglobin (g/dl)	13.62 ± 1.76	12.92 ± 2.23	0.012
Platelets (/mm ³)	203 (164-253)	177(128-215)	0.002
C-reactive protein (mg/L)	15.7 (3.5-79.5)	101.8 (51.2-178.3)	< 0.001
Lung involvement	94 (58.75%)	77 (88.5%)	< 0.001
Number of involved lung lobes	1 (0-5)	5 (4-5)	< 0.001
Heart rate (bpm)	83 ± 16	87 ± 14	0.082
PR interval (ms)	149 ± 21	149 ± 18	0.891
Pmin (ms)	60 (50-70)	70 (60-70)	< 0.001
Pmax (ms)	100 (100-110)	120 (110-120)	< 0.001
Pdis (ms)	40 (30-50)	50 (40-55)	< 0.001
PWPT _{v1} (ms)	61 ± 9	68 ± 9	< 0.001
PWPT _{d2} (ms)	55 ± 7	64 ± 7	< 0.001
QRS (ms)	86.5 (80-96)	88 (80-98)	0.894
QT (ms)	360 (330-382)	355 (330-370)	0.519

Pdis: P wave dispersion, Pmax: maximum P wave duration, Pmin: minimum P wave duration, PWPT: P wave peak time.

Table II. Multivariate logistic regression analysis showing predictive factors of COVID-19-related intensive care unit admission.

	Odds Ratio	95% C.I. for Odds Ratio	p-value
Model 1			
Age - years	1.069	1.037-1.101	< 0.001
Platelet (/mm ³)	0.993	0.987-0.998	0.006
Leukocytes (/mm ³)	1.000	1.000-1.000	0.110
C-reactive protein (mg/L)	1.007	1.002-1.013	0.012
Lung involvement	1.202	1.039-1.391	0.014
Gender (male)	3.799	1.692-8.531	0.001
Diabetes Mellitus	3.194	1.355-7.528	0.008
PR interval	0.982	0.963-1.001	0.070
PWPT _{V1} (ms)	1.100	1.055-1.147	< 0.001
Model 2			
Age, years	1.070	1.037-1.104	< 0.001
Platelet (/mm ³)	0.992	0.986-0.998	0.012
Leukocytes (/mm ³)	1.000	1.000-1.000	0.039
C-reactive protein (mg/L)	1.005	0.999-1.011	0.089
Lung involvement	3.121	1.180-8.260	0.022
Gender (male)	4.214	2.153-8.247	< 0.001
PWPT _{D1} (ms)	1.219	1.143-1.300	< 0.001
PWPT: P wave peak time			

In multiple logistic regression analysis to predict ICU admission, when age, leucocyte count, platelet count, CRP level, presence of lung involvement, male gender, diabetes mellitus, PR interval, and PWPT_{V1} were included in the analysis, PWPT_{V1} was considered as an independent predictor of ICU admission (OR=1.1, 95% CI: 1.055-1.147, $p<0.001$). When age, leucocyte count, platelet count, CRP level, presence of lung involvement, male gender, and PWPT_{D2} were included in the analysis, PWPT_{D2} was also considered as an independent predictor of ICU admission (OR=1.1, 95% CI: 1.143-1.300, $p<0.001$) (Table II).

The cut-off points of Pdis, PWPT_{V1} and PWPT_{D2} that determine admission to intensive care were calculated by ROC curve analysis (Figure 2). A cut-off point of 34.5 ms Pdis had a sensitivity of 88.5% and a specificity of 41.9 % (AUC=0.663, 95% CI: 0.596-0.731, $p<0.001$), a cut-off point of 67.5 ms PWPT_{V1} had a sensitivity of 62.1 % and a specificity of 69.4 % (AUC=0.710, 95% CI: 0.642-0.777, $p<0.001$) and a cut-off point of 62.5 ms PWPT_{D2} had a sensitivity of 60.9 % and a specificity of 83.6 % (AUC=0.819, 95% CI: 0.777-0.871, $p<0.001$).

Discussion

In this study we found that atrial ECG indices, Pdis and PWPT, were associated with

the severity of COVID-19 infection, defined as the need for ICU admission. According to our results, in patients with newly diagnosed

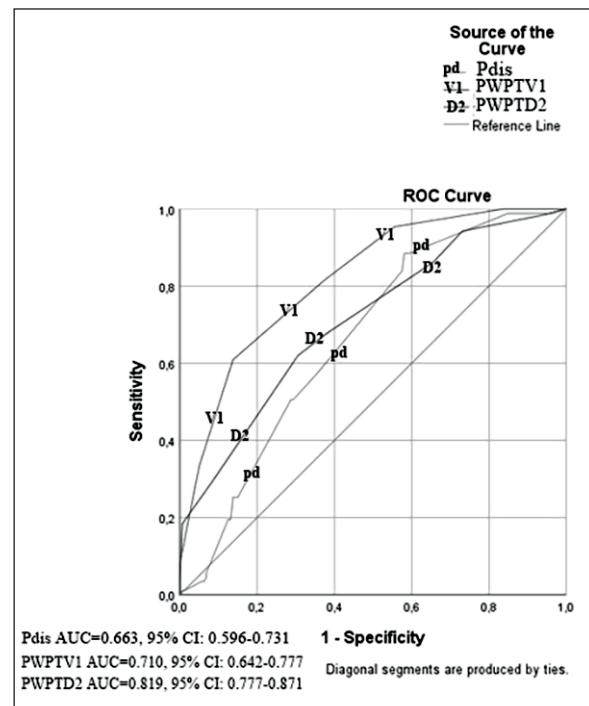


Figure 2. Receiver–operating characteristic curve analysis of P wave dispersion, P wave peak time in the lead V1 and D2 for predicting intensive care admission. (Pdis: P wave dispersion, PWPT_{V1}: P wave peak time on V1 lead, PWPT_{D2}: P wave peak time on D2 lead).

COVID-19, compared to Pdis, PWPT showed a stronger association with disease severity. These indices may have a value in risk stratification in COVID-19.

After being first identified in Wuhan, China, in December 2019, COVID-19 spread in a relatively short time and became a pandemic that affected the whole world. Despite the development of effective vaccines, with the newly emerging mutations, the death, morbidity, and burden on the health system caused by COVID-19 continue. Besides being an indicator of the disease severity, the need for intensive care is one of the important components of the shortage in the health care systems and proper utilization of limited resources during pandemic is essential. In this context, ECG is one of the extensively utilized tests, and implementations to prognostication tools and algorithms may be useful^{11,12}. Although most of the recent studies focused on rhythm disturbances, ventricular repolarization abnormalities, conduction abnormalities, and ST-T changes¹³⁻¹⁵, the role of atrial indices as a COVID-19 severity predictor was not yet adequately evaluated.

Pdis is an ECG indicator for alterations in the atrial electrical milieu and a predictor for atrial fibrillation¹⁶. In several conditions with increased inflammation and diseases affecting the lungs, it has been observed that Pdis is altered and the tendency to atrial fibrillation increases¹⁷⁻²¹. As being a potentially multisystemic condition, COVID-19 may affect Pdis by involving the respiratory system, circulatory system, or exaggerated inflammation. Increased volume load, inflammation of the myocardium or pericardium, increased sympathetic tone, hypoxemia, ischemia, cytokine discharge and hypercoagulability may create a proarrhythmic environment in COVID-19 patients. In a study, Yenerçağ et al⁵ found that Pdis was prolonged in newly diagnosed COVID-19 patients; however, the severity and need for ICU admission were not specified. Besides, Öztürk et al²² found a reverse correlation between the severity of lung involvement and Pdis in COVID-19 patients. They interpreted their results as patients with prolonged Pdis and less severe pneumonia may have increased risk for atrial arrhythmias and thromboembolic risk. In our study we indicated the need for ICU admission as severe COVID-19 and 10 of 87 ICU admitting patients showed no lung involvement. These 10 patients were mainly suffering cardiac or cerebrovascular complications. In this context, our results show that Pdis was not just a predictor of lung involve-

ment, but the comprehensive predictor of clinical disease severity as a whole.

PWPT indicates the time spent for excitation radiating from the sinoatrial node to the maximal sum of positive deflection from the atrium. Prolonged PWPT indicates prolonged intra- or inter-atrial conduction time as a result of increased intra-atrial pressure²³. Previous studies^{6-8,24} demonstrated the association between PWPT and severity of coronary artery disease, left ventricular end-diastolic pressure, coronary no-reflow, and left atrial volume index. This novel parameter has been nominated as a predictor of atrial fibrillation in recent studies^{25,26}. On the other hand, no study has evaluated PWPT in patients with COVID-19. To the best of our knowledge, our study is the first to investigate the association between admission PWPT and COVID-19 severity. Additionally, we found that PWPT had a better specificity for COVID-19 severity compared to Pdis. We also found that patients with prolonged PWPT had more involved lung lobes. In a recent study, patients with COVID-19 showed abnormal P wave interval behavior inconsistent with heart rate, which was associated with increased death and endotracheal intubation. Authors linked these P wave abnormalities to the antigen-antibody interaction affecting the cardiac conduction system as observed in congenital AV block of infants with circulating Lupus-related antibodies, likely produced during severe COVID-19²⁷. In this context, severe COVID-19 may be linked to abnormal atrial ECG indices *via* lung involvement affecting atrial load and stretch, bringing ischemic-embolic complications, inflammatory mechanisms like cytokine storm, inflammation of cardiac tissues (pericardium, myocardium), and making circulate abnormal antibodies interacting with the cardiac conduction systems. Further studies are needed to elucidate the actual mechanism that causes abnormal atrial ECG indices associated with severe COVID-19.

Limitations

Some limitations should be considered when evaluating the results of our study. It was a nonrandomized, single-center, retrospective study with a relatively moderate number of patients. Measurement of electrocardiographic intervals was prone to error, although some precautions have been taken to keep it at a minimum. Echocardiographic evaluation was not routinely performed due to the contagious nature of the disease and the interpretation of

the possible effects of the cardiac chamber geometry and function were not provided. Data of patients who developed arrhythmia at follow-up were not available.

Conclusions

Admission ECG atrial indices Pdis and PWPT were associated with intensive care unit admission in newly diagnosed COVID-19 patients. This is the first study evaluating PWPT in COVID-19 patients. ECG atrial indices may have a potential role in the prediction of critical patients that are likely to deteriorate.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This study did not receive any funding.

Ethical Approval

This study complies with the principles of the Declaration of Helsinki and was approved by the Ethics Review Committees of the Cankiri Karatekin University.

Authors' Contribution

Pınar Türker Duyuler: Conceptualization, Supervision, Methodology, Software, Writing - Review & Editing. Serkan Duyuler: Data curation, Writing- Original draft preparation, Supervision. Bekir Demirtaş: Resources, Visualization, Investigation. Hülya Çiçekçioğlu: Investigation, Data curation: Velihan Çayhan: Formal analysis, investigation.

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Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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