

Comparison of Frontal QRS-T Angle in Patients with Panic Disorder and Healthy Control Group: A Preliminary Study

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ABSTRACT

Background: Autonomic instability is blamed for panic disorder pathophysiology. It has been suggested that this may raise the risk of cardiovascular disease. A new proposal for ventricular depolarization and repolarization impairment is the frontal QRS-T angle.

Methods: In this cross-sectional study, 61 patients with panic disorder and 73 healthy controls were included. The severity of panic disorder was evaluated using the Severity Measure for Panic Disorder—Adult. Electrocardiography, echocardiography, hemogram, and biochemistry data were recorded.

Results: Patients with panic disorder had a greater frontal QRS-T angle than healthy controls. In panic disorder patients, the values for hemoglobin, eosinophil count, and high-density lipoprotein cholesterol were all significantly lower than healthy controls. In comparison to healthy controls, panic disorder patients had significantly higher values for total cholesterol, fasting triglycerides, low-density lipoprotein cholesterol, platelet-to-lymphocyte ratio, and monocyte-to-high-density lipoprotein cholesterol ratio. Significant correlations were found between frontal QRS-T and Severity Measure for Panic Disorder—Adult, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio. The frontal QRS-T value is positively and significantly predicted by the neutrophil-to-lymphocyte ratio value according to the linear regression analysis for the frontal QRS-T angle [$F(6.54)=8.375$, $P<.001$, adjusted $R^2: 0.424$].

Conclusion: The current study found that the frontal QRS-T angle increased with the severity of the disease in patients with panic disorder. Frontal QRS-T angle may help to estimate cardiovascular disease risk in patients with panic disorder. This relationship may be necessary in terms of cardiovascular events and inflammatory conditions.

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INTRODUCTION

About 5% of the population suffers from the common psychiatric ailment known as panic disorder (PD). In addition to recurrent panic attacks, panic disorder is mentioned in the presence of fear of having a panic attack and phobic avoidance behaviors. Patients with PD show avoidance behaviors when it may be challenging to get help, and they frequently present to emergency services.¹

Cardiovascular diseases (CVD) and cardiovascular mortality are reported to be more common in PD, according to studies.^{2,3} Palpitations and arrhythmias due to autonomic nervous system (ANS) dysfunction are associated with panic attacks in PD patients. Autonomic nervous system dysfunction causes an increased risk of ventricular arrhythmia and its recurrence. An increase in resting heart rate and activation of the sympathetic system is observed due to ANS dysfunction.⁴

The frontal QRS-T angle (fQRS), a novel indicator of ventricular depolarization and repolarization heterogeneity, illustrates the angle between the QRS and T axis in the frontal plane.⁵ Wide fQRS angles have been linked in studies to an elevated risk of sudden cardiac death. Greater fQRS angle has been linked to a higher incidence of arrhythmia, according to reports. Compared to QT prolongation and left ventricular hypertrophy, the fQRS angle more accurately predicted the likelihood of arrhythmia and cardiac mortality.⁶

To the best of our knowledge, there is limited information on the relationship of fQRS-T angle and psychiatric disorders. The findings of a recent study show that the fQRS-T angle is wider in patients with schizophrenia than in healthy controls (HC) and that there is a relationship between the severity of the negative symptoms and the fQRS-T angle duration of disease in patients with schizophrenia.⁷ It has

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been claimed that the fQRS-T angle may be related to the severity of symptoms in PD patients. Therefore, the current study seeks to assess the CVD risk in PD patients by comparing the fQRS angle in electrocardiography (ECG) with the healthy control group.

MATERIAL AND METHODS

Study Design

The present study had a cross-sectional nature. This study was carried out in a district state hospital in Turkey. Between January 1, 2022, and April 1, 2022, 61 PD patients and 73 HC were included consecutively. The ethics committee of Adiyaman University gave its clearance to the study (Decision Date: December 14, 2021, and Decision Number: 2021/10-09). The Declaration of Helsinki was followed in conducting the study. Participants' informed consent was acquired.

Study Sample

Sixty-one volunteers diagnosed with PD according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) were included in the study.⁸ Those who were not between the ages of 18 and 65, those with known cardiac disease, endocrinological disease, other psychiatric disease, and those using beta blockers were excluded from the study. The study did not include PD patients using tricyclic antidepressants, antihistamines, and antipsychotics. Seventy-three HC without a known disease were included in the study. The healthy control group was selected from the people who came to get a driver's license, a job entrance examination, or a healthy report. Participants were not using any antiarrhythmic drugs such as calcium channel blockers or beta blockers. Some sociodemographic (age, gender, and smoking status) and clinical (hemogram, biochemistry, systolic and diastolic blood pressures, echocardiography, and ECG parameters) features of the participants were recorded.

The Severity Measure for Panic Disorder—Adult

The Severity Measure for Panic Disorder—Adult (SMPD-A) is a self-report scale recommended by the American

Psychiatric Association and used to determine PD severity. The SMPD-A scale consists of 10 items, and each item is scored from 0 to 4 (0=never, 4=always). The Severity Measure for Panic Disorder—Adult questions the symptoms of PD patients in the last 7 days and the effects of these symptoms on their lives.⁹ A Higher SMPD-A score is associated with more severe PD. In the present study, the SMPD-A scale was used to detain disease severity in patients with PD.

Electrocardiography and Echocardiography Examination

Two independent cardiologists blindly assessed each patient's 12-lead ECG. Using a CardioFax S instrument, the 12-lead ECG recordings (50 mm/s, 10 mm/mV) were made while the patient was lying flat (Nihon Kohden, Tokyo, Japan). Utilizing the ECG data, the resting heart rate was calculated, and measurement errors were minimized by using calipers and magnifying glasses. The period of time from the QRS complex's beginning to its conclusion was called the QRS duration. The time from the beginning of the QRS complex to the conclusion of the T-wave was used to compute the QT interval. By applying Bazett's formula, the QT interval was adjusted for heart rate.¹⁰

The automatic ECG machine reports included frontal QRS and T-wave axis. These axes were used to determine the f(QRS-T) angle, which is the exact difference between the frontal plane QRS axis and the frontal plane T axis. If the angle is more than 180°, it was computed by deducting from 360°.

All study participants underwent transthoracic echocardiographic examinations using the Vivid 5 Pro brand ECO device from General Electric, Horten, Norway. In the lateral decubitus posture, parasternal long-axis and short-axis pictures were obtained, and 4-chamber and 2-chamber views were obtained via the apical window. The Simpson's approach was used to calculate the left ventricular ejection fraction (LVEF).¹¹

Laboratory Analysis

At the time of hospital admission, venous blood samples were tested. The Architect c8000 Chemistry System (Abbott Diagnostics, Abbott Park, Ill, USA) commercial kits were used to determine total cholesterol, fasting triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels. Using the automated hematology analyzer CELL-DYN Ruby (Abbott Diagnostics), total white blood (WBC) counts were calculated, including neutrophil lymphocyte counts, and expressed as 1000 cells/mm³. Calculations were also made for hemoglobin, albumin, and platelet count. Platelet-to-lymphocyte ratio (PLR) is computed as the number of platelets divided by the lymphocyte count, while neutrophil-to-lymphocyte ratio (NLR) is determined by dividing the neutrophil count by the lymphocyte count.

MAIN POINTS

- Widening of the frontal QRS-T angle has been associated with an increased risk of cardiovascular disease.
- It is thought that there is a deterioration in the autonomic nervous system and heart rate variability in panic disorder, and therefore the risk of cardiovascular disease may be increased.
- In this study, we found the frontal QRS-T angle to be significantly higher in patients with panic disorder.
- We also determined that inflammatory parameters may be related to the frontal QRS-T angle.

Abbott Diagnostics' biochemistry kits and Architect c8000 Chemistry System were used to measure the levels of C-reactive protein (CRP).

Statistical Analysis

All analyses were conducted using the IBM Statistical Package for Social Sciences 26.0 package program (IBM SPSS Corp.; Armonk, NY, USA). While qualitative factors were given numbers and percentages, quantitative variables were reported as mean and standard deviation values. The normality assumption of the data was tested with Kolmogorov-Smirnov. Independent sample *t*-tests were used to compare numerical variables, whereas Mann-Whitney *U*-test, which is a nonparametric test, was used in cases where the assumption of normality was not provided. Chi-square tests were used to compare qualitative factors within the research group. Since the fQRS-T angle does not fit the normal distribution, the correlations between the fQRS-T angle and other factors were assessed using the Spearman correlation test. Linear regression analysis was utilized. If the *P* values were lower than .05, it was regarded as statistically significant.

Table 1. Comparison of Sociodemographic Features and Electrocardiographic Parameters of Panic Disorder Patients and Healthy Controls

	PD (n=61) M ± SD or n (%) or Med. (Min:Max)	HC (n=73) M ± SD or n (%) or Med. (Min:Max)	<i>P</i>
Age	33.93 ± 8.68	32.88 ± 9.6	.567 ¹
Gender			.838 ²
Female	39 (63.9)	49 (67.1)	
Male	22 (36.1)	24 (32.9)	
Smoking	24 (39.3)	26 (35.6)	.657 ²
Systolic blood pressure mmHg	119.7 ± 7.48	120 ± 7.96	.822 ¹
Diastolic blood pressure mmHg	67 (55:82)	72 (55:82)	.104 ³
LVEF, %	63 (58:68)	63 (59:68)	.928 ³
Heart rate, bpm	81.7 ± 13.85	78.67 ± 12.49	.185 ¹
QRS, msec	88.25 ± 5.28	89.23 ± 7.48	.344 ¹
QT, msec	362 (324 : 440)	366 (298 : 434)	.712 ³
QTc, msec	408 (378 : 480)	404 (295 : 488)	.230 ³
fQRS-T angle	37 (0 : 131)	21 (0 : 117)	<.001 ³
SMPD-A	27.31 ± 4.57	N/A	

fQRS, fragmented QRS; fQRS, frontal QRS-TSMPD-A; HC, healthy controls; LVEF, left ventricular ejection fraction; PD, panic disorder; QTc, corrected QT interval; SMPD-A, Severity Measure for Panic Disorder-Adult.

¹Independent *t*-test was used. ²Chi-square test was used. ³Mann-Whitney *U*-test was used. *P* < .05 was accepted as statistically significant.

Statistically significant *p* values are shown in italics/bold

Table 2. Comparison of Laboratory Parameters of Panic Disorder Patients and Healthy Controls

	PD (n=62)	HC (n=64)	<i>P</i>
Hemoglobin, mg/dL	14.1 ± 2.09	14.31 ± 2.05	.549 ¹
Albumin, mg/dL	4.29 ± 0.3	4.26 ± 0.65	.804 ¹
WBC, 10 ³ /μL	7.64 ± 1.75	8.21 ± 2.23	.105 ¹
Neutrophil, 10 ⁶ /μL	4.64 ± 1.29	4.93 ± 1.76	.295 ¹
Lymphocyte, 10 ³ /μL	2.25 ± 0.78	2.49 ± 0.74	.066 ¹
Platelet, 10 ³ /μL	251.61 ± 64.97	246.69 ± 60.37	.650 ¹
Monocyte, 10 ³ /μL	0.54 ± 0.23	0.53 ± 0.19	.627 ¹
Eosinophil, 10 ³ /μL	0.08 (0 : 0.64)	0.1 (0:1)	.005 ²
Basophil, 10 ³ /μL	0.08 (0 : 0.64)	0.09 (0:0.27)	.768 ²
Fasting Triglycerid, mg/dL	142 (47:415)	100 (34:380)	<.001 ²
Total Cholesterol, mg/dL	181 (33:290)	157 (109:270)	.005 ²
LDL-C, mg/dL	102.87 ± 30.77	74.6 ± 28.77	<.001 ¹
HDL-C, mg/dL	50.31 ± 14.09	67.4 ± 15.99	<.001 ¹
CRP, mg/dL	0.26 ± 0.14	0.23 ± 0.09	.198 ¹
NLR	2.11 (0.94:5.82)	1.84 (0.89:5.89)	.187 ²
PLR	126.85 ± 55.48	108.46 ± 49.9	.046 ¹
MHR	0.01 (0:0.03)	0.008 (0:0.02)	<.001 ²
CAR	0.05 (0.04:0.22)	0.05 (0.03:0.67)	.138 ²

CAR, CRP albumin ratio; CRP, c-reactive protein; HC, healthy controls; HDL-C, high-density cholesterol; LDL-C, low-density cholesterol; MHR, monocyte HDL-C ratio; NLR, neutrophil lymphocyte ratio; PD, panic disorder; PLR, platelet lymphocyte ratio; WBC, white blood cell.

¹Independent *t*-test was used. ²Mann-Whitney *U*-test was used. *P* < .05 was accepted as statistically significant.

RESULTS

According to the statistical analysis, the fQRS-T angle was higher in PD patients than in HC (Table 1). The comparison of laboratory parameters is presented in Table 2. Accordingly, hemoglobin, eosinophil count, and HDL-C values were significantly lower in PD patients. Total cholesterol, fasting triglyceride, LDL-C, PLR, and MHR values were significantly higher in PD patients than in HC. The correlation analysis of the fQRS angle with age, disease severity, and inflammation parameters in PD patients is shown in Table 3. According to Table 4, fQRS angle and disease severity, NLR and PLR were significantly correlated. A linear regression model was created to evaluate for predictive effect of some clinical variables on fQRS-T angle ($F_{(6,54)} = 8.375$, $R^2 = 0.482$, adjusted $R^2 = 0.424$, and $P < .001$). According to the linear regression analysis for the fQRS-T angle, the NLR value positively and significantly predicts the fQRS-T angle.

DISCUSSION

This study investigated the effect of fQRS-T angle change in ECG and disease severity in PD patients. We reported

Table 3. Spearman Correlation Analyses of Frontal QRS-T Angle with Age and Inflammatory Parameters in PD Patients

Frontal QRS-T Angle	
Age	$r = -0.14$ $P = .267$
SMPD-A	$r = 0.39$ $P = .002$
NLR	$r = 0.58$ $P < .001$
PLR	$r = 0.29$ $P = .024$
CAR	$r = 0.05$ $P = .678$
MHR	$r = -0.08$ $P = .563$

CAR, CRP albumin ratio; HDL-C, high-density cholesterol; MHR, monocyte HDL-C ratio; NLR, neutrophil-to-lymphocyte ratio; PD, panic disorder; PLR, platelet lymphocyte ratio; SMPD-A, Severity Measure for Panic Disorder—Adult.

$P < .05$ was accepted as statically significant.

that PD patients' fQRS angle values were significantly greater than those of the HC group. In addition, we found that total cholesterol, fasting triglyceride, LDL-C, PLR, and MHR values increased significantly in the PD patient group. Additionally, we demonstrated a favorable correlation between the fQRS angle and PD severity as well as the prognostic power of NLR on the fQRS angle.

Panic disorder has also been shown to be associated with inflammation in previous studies. It has been shown that interleukin (IL)-1B and interleukin-2R are higher than proinflammatory cytokines in PD patients compared with the control group.¹² In a different study, it was discovered that individuals with a high score on the severity scale for PD had significantly higher levels of IL-6 than those in the control group.¹³ Due to our determination of the predictive effect of NLR on fQRS-T in the PD group, we suggested that inflammation in PD may disrupt myocardial depolarization

and repolarization concordance, leading to arrhythmias and sudden cardiac events.

Previous research have shown that ventricular arrhythmias and sudden cardiac death are both related to a broad fQRS angle.¹⁴ An abnormal fQRS-T angle indicates the underlying myocardial ion channel disorders resulting in aberrant ventricular repolarization. Although there is no direct causality between PD and CVD, it has been stated that the potential for CVD increases indirectly due to reasons such as sympathetic system activation, stress, atherosclerosis, and myocardial perfusion defects.¹⁵ Also, in 2015, a meta-analysis investigated CVD in PD patients and showed that the risk of developing coronary artery disease in PD patients increased by 1.47 times. In the same study, a relationship was found between PD and cardiovascular events, death due to coronary artery disease, ventricular fibrillation, sudden cardiac death, and acute myocardial infarction.³ High MHR was related with carotid intima-media thickness in 1 study and is considered an indicator of subclinical atherosclerosis.¹⁶

The relationship between indicators of inflammation and CVD has been investigated in many studies. In particular, CRP is the most widely studied among the indicators of inflammation. In recent years, WBC has especially become the focus of many studies assessing cardiovascular risks and showing prognostic results.¹⁷⁻²⁰ Neutrophil-to-lymphocyte ratio is a more accurate predictor of cardiovascular diseases than WBC count, according to studies. Neutrophil-to-lymphocyte ratio is better predictive because it is less affected by conditions such as dehydration or exercise. Additionally, NLR is a ratio of 2 distinct immune pathways that work well together. Neutrophil-to-lymphocyte ratio is therefore recognized as a sign of metabolic stress and poor overall health.²¹⁻²³

High NLR and the risk of cardiovascular events are associated with a number of potential reasons. Inflammatory mediators are secreted by neutrophils, which causes vascular wall deterioration.²⁰ In contrast, lymphocytes control the inflammatory response and may hinder a

Table 4. Linear Regression Analyses of Frontal QRS-T Angle in PD Patients

	B	Std. Error	Beta	t	P	95 % CI	
						Lower	Upper
Constant	-24.95	21.79		-1.145	.257	-68.63	18.73
Age	0.03	0.31	0.010	0.096	.924	-0.60	0.66
SMPD-A	1.08	0.64	0.182	1.685	.098	-0.20	2.37
NLR	18.21	3.76	0.649	4.838	<.001	10.669	25.76
PLR	-0.02	0.06	-0.056	-0.432	.667	-0.154	-0.099
MHR	-136.94	464.61	-0.030	-0.295	.769	-1068.43	794.55
CAR	47.74	80.04	0.061	0.597	.553	-112.72	208.22

CAR, CRP albumin ratio; HDL-C, high-density cholesterol; MHR, monocyte HDL-C ratio; NLR, neutrophil-to-lymphocyte ratio; PD, panic disorder; PLR, platelet lymphocyte ratio; SMPD-A, Severity Measure for Panic Disorder—Adult.

Linear regression analyses were used. $P < .05$ was accepted as statically significant.

The linear regression analyses equation is $f(\text{QRS-T}) = -24.95 + 0.03 \cdot \text{Age} + 1.08 \cdot \text{SMPD-A} + 18.21 \cdot \text{NLR} - 0.02 \cdot \text{PLR} - 136.94 \cdot \text{MHR} + 47.74 \cdot \text{CAR}$.

regulatory T-cell-based antiatherosclerotic pathway.²¹ Low lymphocyte count and associated high NLR may be an early marker in conditions such as physiological stress mediated by cortisol release and myocardial damage.^{24,25} Increased cortisol levels cause a relative decrease in lymphocyte levels.²⁶

High NLR is highly linked to the development of atherosclerosis and is a standalone predictor of atheromatous plaque, according to prior research.^{27,28} Atherosclerotic plaques with neutrophil infiltration have been observed in atherectomy samples from individuals with acute coronary syndrome, and this may lead to the plaque's instability.²⁹ It has been shown that various proteolytic enzymes secreted by neutrophils, especially neutrophil elastase, mediate the degradation of components of the basement membrane and thus endothelial damage.^{21,30} The increase in the level of stress hormones released by cerebral stimulation in PD may explain the increase in inflammatory markers, increase in NLR, and the risk of cardiovascular mortality, arrhythmia, and sudden death. The correlation of NLR with fQRS-T in our study also confirms the strength of this relationship and is vital in contributing to the literature.

The present study has several limitations. The limited number of patients indicates that longer-term follow-up with a larger patient group is needed to reach a general conclusion. This study fails to provide data on the prognostic value of the fQRS-T angle in PD patients. Future research should consider thyroid hormone levels as a factor that may alter inflammation in order to produce more accurate results. Another limitation of the study is the absence of participant body mass index information. The inability to calculate the spatial QRS-T angle in our study is another limitation. Finally, although we found significant correlations between fQRS-T angle and inflammatory parameters, the correlation coefficients were relatively smaller. It means that there were weak or moderate relationships between these variables. Further studies may help to reinterpret the results of the current study.

The current study demonstrated that in PD patients, the fQRS angle expanded as the disease's severity increased. It can predict cardiovascular risk in PD patients by looking at the fQRS angle in the ECG in the outpatient clinic. This relationship may be necessary in terms of cardiovascular events and inflammatory conditions.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Adiyaman University, (Decision Date: December 14, 2021, and Decision Number: 2021/10-09).

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

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