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Research Article

Comparison of Cardiovascular Disease Risk Indicators in Bipolar Disorder Patients with Healthy Controls

Yasar Kapici[1], Selcuk Ayhan[2], Bulut Guc[3], Atilla Tekin[4]

[1]Kahta State Hospital, Deparment of Psychiatry, Adıyaman,Türkiye
[2]Adıyaman Training and Research Hospital, Department of Cardiology, Adıyaman, Türkiye
[3]Balıklıgöl State Hospital, Department of Psychiatry, Şanlıurfa,Türkiye
[4]Adıyaman University, Faculty of Medicine, Department of Psychiatry, Adıyaman, Türkiye

Abstract

Aim: It is important to assess the likelihood of cardiovascular disease in patients with bipolar disorder (BD). In this study, indicators of increased cardiovascular disease risk on electrocardiogram (ECG) and laboratory were evaluated.

Material and Methods: In the present investigation, we studied the demographic details, ECG variables, and blood test results of 90 healthy controls (HC) and 97 patients we followed for BD diagnosis.

Results: Age and gender trends were similar between the BD and HC groups (p=0.844 and p=0.664). BD had a higher mean number of fragmented QRS (fQRS) than the HC group, and fQRS was more frequent (p=0.002 and p=0.007). The frontal QRS-T angle was wider in the BD group than it was in the HC group (p=0.038). Monocyte-to-lymphocyte ratio (MLR), monocytes to high-density lipoprotein cholesterol (HDL-C) ratio (MHR), and atherogenic index of plasma (AIP) were statistically greater in BD patients (p=0.021, p<0.001, and p<0.001).

Conclusion: In brief, the report indicates that impaired ventricular repolarization is related to an elevation in the frontal QRS-T angle in BD. As a result, BD patients have a greater risk of cardiovascular mortality and ventricular arrhythmias. As a result, clinicians ought to have a greater understanding of the frontal QRS-T angle and conduct an ECG examination on regular controls.

Keywords: Bipolar disorder, frontal QRS-T angle, fragmented QRS

INTRODUCTION

Manic and depressive episodes characterize bipolar disorder (BD), a serious mental illness that lasts a lifetime. During a manic episode, symptoms such as an increase in the amount of speech, flight of ideas, exuberance, grandiose delusions, risky behaviors, increased libido, insomnia, increased energy, and agitation are observed. In a depressive episode, the patient experiences anhedonia, feelings of unworthiness and guilt, suicidal ideas, introversion, and low energy (1). The lifelong frequency of BD is predicted to be between 5% and 5%, with an average prevalence of 1.3 percent in the community.

Average life expectancy in BD decreases due to cardiovascular diseases (3). Atypical antipsychotics and lithium used in the treatment of BD are thought to elevate the incidence of cardiovascular disease. Cardiovascular mortality is thought to increase 1.5 to 2.5 times in BD (4). Hypertension can be seen in 33%, hyperlipidemia in 27%, and diabetes in 15% of BD patients (5). Using atypical antipsychotics in the therapy can cause insulin resistance, weight gain, and obesity (6).

Myocardial depolarization and repolarization heterogeneity are thought to be reflected in the frontal QRS-T angle. The frontal QRS-T angle is the actual difference between the T axis, which shows myocardial repolarization, and the QRS axis, which shows myocardial depolarization. The electrocardiogram (ECG) easily measures this brand-new

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Corresponding Author: Yasar Kapici, Kahta State Hospital, Deparment of Psychiatry, Adıyaman, Türkiye
E-mail: dryasarkapici@gmail.com

measure. The available evidence suggests that frontal QRS-T might be a cardiovascular disease marker (7). The ECG sign of a scar in the myocardium is the fragmented QRS (fQRS). The QRS complex identifies fQRS as a notching. It is generally accepted that fQRS can predict cardiovascular diseases (8).

Kalelioğlu et al. demonstrated that BD depressive state is accompanied by increased AIP. The significant correlations between AIP and other conventional cardiovascular risk factors indicate that AIP may be more useful than absolute lipid parameters to identify BD individuals at high risk for cardiovascular disorders (9). Nunes et al. reported that AIP was increased in BD patients when compared with healthy controls (10).

Due to the deterioration of BD patients' functionality over time, changes in treatment compliance, and the treatments they receive, it is essential to assess the likelihood of cardiovascular disease. Monocyte to HDL ratio (MHR), AIP and lipid panel are used in cardiovascular disease risk assessment. In addition, there is information in the literature that Neutrophil lymphocyte ratio (NLR) is increased in cardiovascular diseases. ECG is a quick, inexpensive, simple, and quick-to-access test that can be evaluated quickly. In the present investigation, we studied the demographic details, ECG variables, and blood test results of 90 healthy controls (HC) and 97 patients we followed for BD diagnosis. We could not find any study in the literature evaluating frontal QRS-T angle and fQRS in BD patients. In this sense, the data to be obtained from this study can evaluate the risk of cardiovascular disease in the chronic period in BD patients. In addition, the evaluation of laboratory data related to cardiovascular disease risk will help to explain the differences in the mentioned ECG parameters. We wanted to use ECG parameters to figure out the chances of heart conditions in BD.

MATERIAL AND METHOD

Study Design

The current study is interpretive and comparative. The Local Ethics Committee accepted the research protocol (Approval date: 2021-09-21; IRB Number: 2021/7-1). Permission was secured from all subjects before the project. The examination was implemented following the Declaration of Helsinki. This study was carried out in Adıyaman Training and Research Hospital Psychiatry Clinic. The patients in this study were being followed up and treated in our psychiatry clinic with the diagnosis of BD. The ECGs of the patients were evaluated by a cardiology specialist with 10 years of experience.

Study Group

The sample size was calculated as 103 using G*Power (3.1 Version, Dusseldorf, Germany) (The power of test: 0.8, alpha significance level: 0.05, Cohen's d effect size: 0.71). The examination included 113 BD patients as classified by The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). This research did not include people who had hypertension (3), coronary artery disease (1), valve disease (1), arrhythmia (1), or were not between the ages of 18 and 65 (2). In addition, 8 BD patients with poor quality ECG recording were not included in the study. The study included 90 HC without psychiatric or organic disease. The participants' age, gender, smoking status, hemogram, biochemistry, blood pressure, and ECG parameters were used. The squared ratio of a person's height to their weight was used to calculate their BMI. BD patients were diagnosed by psychiatry specialists with the structured clinical interview for DSM-5 (SCID-V) (11). These BD patients did not have any additional psychiatric disorders. BD patients were in the euthymic period during our study.

Electrocardiogram Examination

Each subject was recorded while lying in a supine position using a 12-lead ECG with a value of 10 mm/mV, a velocity of 25 mm/s, and a frequency range of 0.16–100 Hz. The parameters for the QRS and QT interval were created methodically. By setting a constant heart rate of 60, the QT interval is corrected (QTc). Bazett's method adjusts the QT interval to account for heart rate (12). The ECG machine's documentation included the QRS and T axes, which were easily accessible. The report checked them, and the exact difference between the QRS and T axes was used to calculate the frontal QRS-T angle (Figure 1). Using this difference, if the angle is greater than 180°, the angle is calculated by subtracting 360° from it. Notching in the QRS complex is the definition of fQRS (Figure 2).

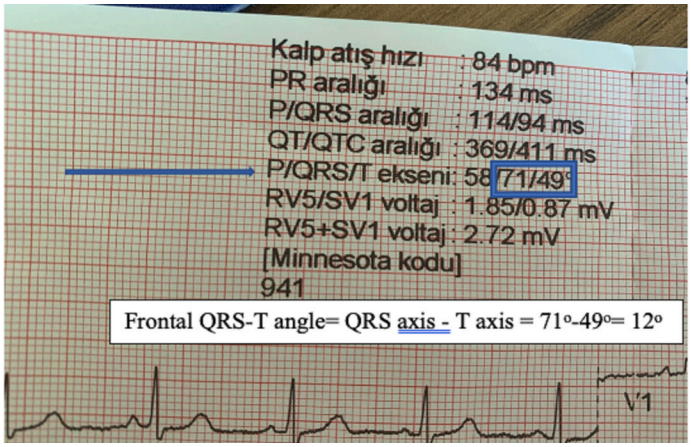

Figure 1. Calculation of frontal QRS-T angle in electrocardiogram

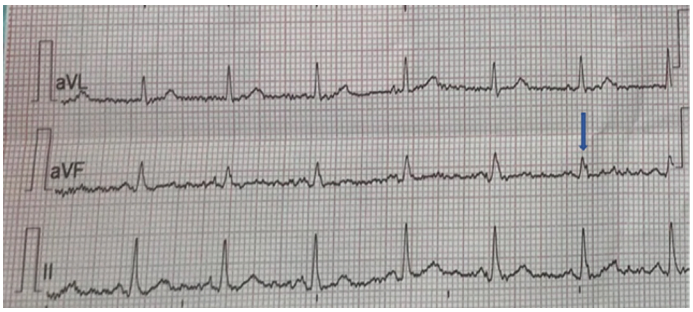

Figure 2. Fragmented QRS in electrocardiogram

Laboratory Analyses

On admission to the hospital, a venous blood sample was taken. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (Total-C), and fasting triglyceride levels were measured. White blood cells (WBC), total blood cell counts, and biochemistry results were assessed. NLR, monocyte lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) are computed. Additionally, the MHR and the neutrophils to albumin ratio (NAR) were evaluated. The logarithm (fasting triglyceride/HDL-C) is used to AIP.

Statistical Analysis

The SPSS application 26.0 (SPSS Inc., Chicago, IL, USA) was implemented for the statistics processing. The numerical measures were represented by mean values and standard deviations, whereas the qualitative measures were represented by percentages. The Kolmogorov-Smirnov test was carried out to look at patterns in the data. Independent samples t test was used for normally distributed data, and Mann-Whitney U test was used for data not normally distributed. Chi-square tests were performed between study groups to compare qualitative measures.

RESULTS

Sociodemographic and clinical parameters of BD patients are shown in Table 1. Accordingly, the mean disease duration of the BD patients was 11.89±8.08 and the mean number of hospitalizations was 3.01±3.91. The comparison of sociodemographic and ECG parameters of BD patients and HCs is shown in Table 2. The mean age of BD patients was 37.4±7.12, and the mean age of HCs 37.88±10.6. There were 46 females and 51 males in the BD group. There were 42 females and 48 males in the HC group. In the BD and HC groups, age and gender did not vary statistically (p=0.844 and p=0.664). There was notable dissimilarity in the BMI between the BD and the HC groups (p<0.001). In the BD group, smoking rates were remarkably greater than those in the HC group (p<0.001).

Table 1. Sociodemographic and clinical characteristics of bipolar disorder patients

Marital Status	Single=48 (49.5) Married=41 (42.3) Divorced=8 (8.2)
Education Level	Primary school graduate=39 (40.2) High school graduate=26 (26.8) University graduate=25 (25.8) Illiterate=7 (7.2)
Working Status	Not working=64 (66) Working=33 (34)
Family History of Psychiatric Disease	25 (25.8)
Alcohol and Substance Use	Alcohol use=5 (5.2) Substance use=0 (0)
Duration of Ilness, Years	11.89±8.08
Number of Hospitalizations	3.01±3.91
Treatment (Mood Stabilizers)	Valproic acid=48 (49.5) Lithium=22 (22.7) Lamotrigine=5 (5.2) Carbamazepine=4 (4.1)
Treatment (Antipsychotics)	Quetiapine=42 (43.3) Olanzapine=21 (21.6) Aripiprazole=12 (12.4) Risperidone=12 (12.4) Clozapine=5 (5.2) Paliperidone (Depot)=3 (3.1) Chlorpromazine=2 (2.1) Haloperidol=2 (2.1) Amisulpride=2 (2.1) Zuclopenthixol decanoate=2 (2.1) Trifluoperazine=1 (1.0) Paliperidone (Oral)=1 (1.0)
Treatment (Others)	SSRI and SNRI=26 (26.8) Tricyclic antidepressant=6 (6.2) Benzodiazepines=3 (3.1) Methylphenidate=1 (1.0) Modafinil=1 (1.0)

n (%) and m±sd was used to present variables. SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin and norepinephrine reuptake inhibitor

Table 2. Comparison of sociodemographic features and electrocardiographic parameters of bipolar disorder patients and healthy controls

	BD (n=97)	HC (n=90)	*p*
Age	37.4±7.12	37.88±10.6	0.844[1]
Gender			0.664[2]
Female	46 (47.4)	42 (46.6)	
Male	51 (52.6)	48 (53.4)	
Smoking	50 (51.5)	29 (32.2)	***<0.001***[2]
BMI, kg/m²	28.45±4.7	26.8±4.8	***<0.001***[1]
Systolic blood pressure mmHg	124.3±12.3	115.4±16.4	0.352[1]
Diastolic blood pressure mmHg	78.3±6.9	72.4±7.9	0.336[1]
Heart rate, bpm	81.09±16.23	78.49±12.84	0.304[3]
QRS, msec	89.2±8.78	89.86±8.14	0.464[1]
QT, msec	364.31±28.04	364.02±34.26	0.950[1]
QTc, msec	420.07±34.64	404.66±26.07	***0.001***[3]
Frontal QRS-T angle	27.98±16.94	24.27±19.59	***0.038***[3]
Having fQRS	73 (75.3)	48 (53.3)	***0.002***[2]
fQRS count	1.35±1.15	0.99±1.24	***0.007***[3]

n (%) and m±sd was used to present variables. [1]Independent t test was used. [2]Chi-square test was used. [3]Mann-Whitney U test was used. p<0.05 was accepted as statistically significant.
BD, bipolar disorder; HC, healthy control; BMI, body mass index; fQRS, fragmented QRS; QTc, corrected QT interval

Table 3. Comparison of laboratory parameters of bipolar disorder patients and healthy controls

	BD (n=97)	HC (n=90)	*p*
Hemoglobin, mg/dL	14.52±1.52	14.34±2.07	0.493[1]
Albumin, mg/dL	4.07±0.33	4.23±0.28	***0.001***[1]
WBC, 10^3/µL	8.03±1.99	8.16±2.23	0.836[2]
Neutrophil, 10^6/µL	4.57±1.59	4.85±1.73	0.382[2]
Lymphocyte, 10^3/µL	2.59±0.92	2.64±1.06	0.692[2]
Monocyte, 10^3/µL	0.64±0.26	0.54±1.19	***0.017***[2]
Eosinophil, 10^3/µL	0.16±0.12	0.16±0.16	0.332[2]
Basophil, 10^3/µL	0.03±0.03	0.10±0.10	***<0.001***[2]
Platelet, 10^3/µL	248.98±70.75	245.08±54.47	0.749[2]
Total-C, mg/dL	179±42.16	170.11±38.47	***0.041***[2]
LDL-C, mg/dL	95.63±32.35	77.51±29.34	***<0.001***[1]
HDL-C, mg/dL	45.82±14.17	67.48±16.32	***<0.001***[2]
Fasting Triglyceride, mg/dL	192.14±159.58	125.53±99.02	***<0.001***[2]
NLR	1.97±0.93	2.09±1.11	0.658[2]
MLR	0.27±0.20	0.22±0.12	***0.021***[2]
PLR	105.31±41.47	105.46±47.60	0.674[2]
MHR	0.014±0.006	0.008±0.003	***<0.001***[2]
NAR	1.13±0.42	1.15±0.42	0.863[2]
AIP	0.54±0.35	0.19±0.32	***<0.001***[1]

n (%) and m±sd was used to present variables. [1]Independent t test was used. [2]Mann-Whitney U test was used. p <0.05 was accepted as statistically significant.
BD, bipolar disorder; HC, healthy control; WBC, white blood cell; Total-C, total cholesterol; LDL-C, low-density cholesterol; HDL-C, high-density cholesterol; NLR; neutrophil lymphocyte ratio; MLR, monocyte lymphocyte ratio; PLR, platelet lymphocyte ratio; MHR, monocyte HDL-C ratio; NAR, neutrophil albumin ratio; AIP, atherogenic index of plasma

ECG-related Parameters

The BD and HC groups had similar QT intervals, QRS, and heart rates. The BD group had a considerably longer QTc than the HC group (p=0.001). BD had a higher mean number of fQRS than the HC group, and fQRS was more frequent (p=0.002 and p=0.007). The frontal QRS-T angle was wider in the BD group than it was in the HC group (p=0.038).

Laboratory Parameters

Comparison of laboratory parameters of BD patients and HCs is shown in Table 3. Albumin levels were low in BD patients (p=0.001), but hemoglobin concentrations were similar in both groups. In summary, the numbers of WBC, neutrophils, lymphocytes, and eosinophils were similar between the groups. The monocyte number was numerically greater (p=0.017) and the basophil number was substantially less in patients with BD (p=0.001).

Fasting triglycerides, Total-C, and LDL-C were statistically greater in BD patients (p=0.041, p<0.001, and p<0.001). BD patients had statistically lower HDL-C concentrations (p<0.001). MLR, MHR, and AIP were statistically higher in BD patients (p=0.021, p<0.001, and p<0.001).

DISCUSSION

These are the primary implications of this investigation: 1) The ECG QTc interval in the BD patient group was longer than in the HC patient group, 2) fQRS number was increased in BD patients than in HC patients, and iii.) There was a wider frontal QRS-T angle in the BD group than in the HC group.

As reported in previous studies, prolongation in the QT interval is associated with syncope, sudden death, and ventricular arrhythmias. The most important arrhythmias associated with QT interval elongation are torsades de pointes and polymorphic ventricular tachycardia. QT interval elongation can cause ventricular fibrillation due to ventricular repolarization delay. Thus, prolonging the QT interval might result in cardiac arrest (13).

High frontal QRS-T angle and increased fQRS number on ECG indicate ventricular depolarization and repolarization abnormalities. The high rate of these ECG abnormalities in the bipolar disease group in our study may explain why the probability of ventricular arrhythmia and cardiovascular mortality increased 1.5-2.5 times in the BD group compared to healthy individuals (4).

Several researches have documented that severe mental illnesses are associated with cardiovascular mortality. It has been demonstrated that patients with BD and schizophrenia have elevated cardiovascular mortality scores than the general population (14). Also, it has been established that BD patients are more prone to metabolic syndrome (15). The higher BMI, smoking rate, increased LDL-C and reduced HDL-C in the BD group could all be predictors of higher cardiovascular mortality.

Inflammatory processes, neurotrophic factors, oxidative stress, and microvascular events have been associated with cardiovascular disease risk in BD patients (16). High blood C-reactive protein, tumor necrosis factor-a, and interleukin-6 concentrations have been related to the presence of atherosclerosis in BD (17,18).

Bortolasci et al. documented that in BD patients there is an increase in fasting triglyceride level and a lower HDL-C (19). Increased oxidative stress, decreased endogenous antioxidants and anti-inflammatory agents, increased AIP were found be useful to delineate BD patients at risk for comorbid cardiovascular disorders (20).

Systemic inflammation has been shown to play a significant role in cardiac arrhythmias and conduction disturbances. The possible reason of cardiac arrhythmias and conduction disturbances seems to be related to myocardial inflammation, focal fibrosis, and ischemia within the conduction system (21). In a recent study, Kadi et al. showed that fQRS increased even in patients with rheumatoid arthritis without cardiovascular disease, in which it is speculated that inflammatory processes may play a pivotal role to produce fragmentations on ECG (22).

In 2012 Çetin et al. found that fQRS was related to increased C-reactive protein. fQRS that may result as an end effect of inflammation at cellular level can represent increased cardiac risk by different causative mechanisms in patients with acute coronary syndrome (23).

In the literature review, large-scale studies investigate repolarization abnormalities in psychiatric disorders and examine their relationship with QTc, QT interval, QT dispersion, and frontal QRS-T angle. In a study evaluating the frontal QRS-T angle with schizophrenia in May 2022, the frontal QRS-T angle was wider in schizophrenia patients than in the control group, as in our study (24). However, no studies have been published in the literature examining the possible link between frontal QRS-T angle and BD. Hence, our study is essential in terms of its contribution to the literature.

This study has some limitations. Since the drugs used by BD patients may affect the ECG parameters, it is a limitation that this information was not provided in our study. In the literature, it has been observed that antidepressants, lithium, and antipsychotic drug combinations may exacerbate the possibility of cardiovascular disease by altering the QT interval and ventricular repolarization. For this reason, it is also important whether the patient group included in our study received combined drugs or not (25). In addition, since patients' blood electrolyte and thyroid hormone concentrations will change the ventricular repolarization parameters, not examining them is another limitation of our study. More extensive laboratory and detailed studies, such as blood drug levels, are needed for the relation between BD and frontal QRS-T angle.

CONCLUSION

The findings of the current research reveal that the frontal QRS-T angle increases with impaired ventricular

repolarization in BD. Therefore, the probability of ventricular arrhythmias and cardiovascular mortality is elevated in BD patients. Therefore, clinicians should have more information about the frontal QRS-T angle and perform ECG evaluation in normal controls. Through this way, cardiovascular mortality, and morbidity can be diminished in BD patients..

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The Adıyaman University Local Ethics Committee accepted the research protocol (Approval date: 2021-09-21; IRB Number: 2021 / 7-1).*

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