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DETERMINING THE RISK OF CARDIOVASCULAR DISEASE IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER

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Summary

Background: *In Schizophrenia (SCZ) and Bipolar Affective Disorder (BAD) patients using the Framingham Heart Risk Scoring (FHRS), we aimed to investigate the possible cardiac arrhythmia risk by calculating electrocardiogram (ECG) parameters (QT, QTc, Tpe, and TPE/QTc ratios), which are ventricular repolarization markers.*

Subjects and methods: *A total of 140 BAD and 253 SCZ patients were included in the study. Age, blood test results (fasting blood glucose, LDL-HDL-TC levels, hemogram values), blood pressure and heart rate, smoking status, antihypertensive drug use, and FHRS were calculated from the patient files, and sociodemographic information was recorded. In addition, ECG calculations were performed, and QT, QTc, TPe, TPe/QTc ratios and heart rate were measured.*

Results: *When we evaluated the cardiac risk indexes of SCZ and BAD patients, we detected that FHRS was higher in smokers, female patients, and those with other medical diseases such as diabetes mellitus (DM) ($p<0.05$). In addition, we found that QTc rates, markers of ventricular repolarization, were associated with FHRS, the number of antipsychotics used, patient age, disease duration, and the number of hospitalizations. TPe and QT rates were found to increase in parallel with FHRS. In addition, a positive correlation was found between QTc rates in females, patients with DM, and those using additional medical drugs. ($p<0.05$)*

Conclusions: *In BAD and SCZ patients, diabetes diagnosis, other medical drug use, a high Framingham heart score, the number of antipsychotics, the disease duration, the patient's age, and an increased number of hospitalizations may increase the risk of cardiac arrhythmia. Therefore, possible cardiac risk should be considered in patients with chronic drug use, such as BAD and SCZ. Regulating the treatment and follow-up of this group of patients against possible cardiac risks will reduce cardiac mortality and morbidity.*

Key words: *Schizophrenia, Bipolar Affective Disorder, Framingham Heart Risk Score, Electrocardiogram*

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INTRODUCTION

Compared to the general population, the incidence and prevalence of cardiovascular disease are higher in patients with Schizophrenia (SCZ) and Bipolar Affective Disorder (BAD) (Colton & Manderscheid, 2006, Viron & Stern, 2010). Cardiovascular diseases (including coronary artery disease) are the most common cause of death in people with SCZ. Among the causes of increased cardiovascular disease potential, psychopharmacological treatments, less use of national health services, lifestyles, obesity, dyslipidemia, hypertension, diabetes, and increased smoking can be counted (De Leon & Diaz 2005; Meng et al., 2012, Stubbs et al., 2016). In addition, the use of antipsychotic drugs in many psychiatric diseases, especially SCZ and BAD, has become widespread. In recent years, cumulative knowledge has shown that the cardiac side effects of this group of drugs are of vital importance (Pérez-Piñar et al., 2016). Cardiac side effects related to antipsychotics include weight gain, lipid and glucose metabolism disorders, metabolic syndrome, and increased risk of cardiovascular disease, orthostatic hypotension, tachycardia, arrhythmia, sudden cardiac death, cardiomyopathy, and myocarditis (Correll et al., 2015). The metabolic syndrome, which causes cardiovascular problems, is a cause of mortality and morbidity, especially in patients with SCZ and BAD disorder (Babić et al., 2010; Kozumplik et al., 2010). Therefore, the effects of drugs should be considered in the treating mental illnesses.

Framingham Heart Risk Score(FHRS) is a tool for assessing the risk of cardiovascular disease based on multiple risk factors. weaThe calculation is made using the variables age, gender, systolic blood pressure (SBP), antihypertensive use, smoking, history of Diabetes Mellitus(DM), and body mass index (D'Agostino et al., 2001). The difference between the longest QT interval and the shortest QT interval on the ECG is called the

QT dispersion (QTd). It is accepted that QTd dispersion indicates regional heterogeneity in myocardial repolarization. The higher the QTd, the less homogeneous the ventricular repolarization, and thus the greater the ventricular instability. Therefore, it gives an idea of the risk of serious ventricular arrhythmias and, therefore, sudden cardiac death (Macfarlane et al., 1998). The interval between the peak point and the end of the T wave (TPe) is considered an index of the transmural dispersion of ventricular repolarization (Kors et al., 2008). TPe/QT and TPe/QTc ratios can be defined as the electrocardiographic index of ventricular arrhythmogenesis (Gupta et al., 2008).

Some of the psychotropic drugs used in patients with schizophrenia and bipolar disorder cause metabolic and especially cardiac side effects. Predicting cardiac risk may be helpful in arranging the treatment of this patient group. In this study, we aimed to identify possible cardiac dysfunction in the early period without clinical symptoms by calculating the 10-year risk of developing Coronary Heart Disease (CHD) and ventricular repolarization indicators QT, QTc, TPe, and TPe/QTc using the FHRS in inpatients with SCZ and BAD. To avoid morbidity, we used ECG to identify potential pathologies.

SUBJECTS AND METHODS

Participants

Our study is a retrospective study consisting of patients in the inpatient wards of our hospital. Our study consisted of patients hospitalized in the inpatient wards of our hospital. Between 2018 and 2021, a total of 3105 patients who were hospitalized in the last three years were examined, and patients who met the criteria and had complete data (140 BAD and 253 SCZ patients) were included in the study. The inclusion criteria for the study were as follows: being between the ages of 18 and 65; being diagnosed with SCZ and BAD bipolar or schizophrenia; having complete ECG and laboratory data in their files; having a calculated FHRS score; not having a history of cardiac surgery; and not having undergone electroconvulsive therapy (ECT) in the last six months. Patients with incomplete information were not included in the study. The FHRS score was calculated according to the file findings. FHRS was calculated by determining the patient's age, blood test results (fasting blood glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC) levels, hemogram values), blood pressure and heart rate, smoking, and antihypertensive drug use obtained from patient files; then, FHRS and other clinical parameters of the patients were compared. The ECGs in the patient files were taken from the first ECGs taken during hospitalization. In ECG evaluations, QT interval dispersion was accepted as the difference between the maximum and minimum QT intervals in any of the leads. Prolonged QTc refers to patients with QTc>440 ms. An experienced cardiologist evaluated ECGs. A 12-lead, 25 mm/min rate, and 10 mm/mV standard ECG were used. PR, R-R, QRS, QT intervals, QTc, heart rate, rhythm, axis, and conduction, and QRS, ST, and T wave abnormalities were measured for each ECG. Statistical methods determined the differences between the measurements. Hospitalized patients between 18 and 65, diagnosed with SCZ and BAD, whose file data were completely accessible, were included in the study. Ethical committee approval was received from the Ethics Committee of XXX Mental Health and Diseases Training and Research Hospital. (Approval Number: 9, Date: 01.02.2021)

Instruments

Sociodemographic Data Form: The physician-researcher completed the sociodemographic data form. The form contains questions about the age, height, weight, marital status, educational status, employment status, smoking, alcohol-drug use, psychiatric-physical disease history, family history of the psychiatric-physical disease, hemogram-biochemistry parameters, SBP, and diastolic blood pressure (DPS) of the patients participating in the study.

Electrocardiographic Evaluation: Standard 12-lead ECG (25 mm/sec, 10 mm/mV) recordings of the patients at rest were included and evaluated in the study. The QT interval was measured as the distance from the beginning of the Q wave to the end of the T wave (where it reaches the T-P line). No measurement was made in the leads where the end of the T wave could not be identified. QT (QTc) corrected (QTc) according to the heart rate was calculated with the Bazett formula [QT(ms)/RR(s)1/2]. P wave duration, RR interval, PR interval, QRS duration, QT interval, and TPe interval were measured manually. The TPe/QT ratio and TPe/QTc ratio were calculated from these measurements. The TPe interval was measured from the peak to the end of the T wave. The end of the T wave was defined as the intersection of the tangent to the downward slope of the T wave and the isoelectric line (Macfarlane et al., 1998).

Framingham Heart Risk Score Calculation: The American Heart Association developed a risk assessment system based on FHRS study data. In this system, by using gender, age, smoking, family history, presence of cardiovascular disease, presence of diabetes, high fasting blood glucose levels (>100 mg), height, weight, SBP, DBP, antihypertensive use, TC, HDL, LDL, and triglyceride parameters, the risk of myocardial infarction or sudden cardiac death/coronary death within ten years is calculated (Kannel et al., 1976).

Statistical Analysis

Data were analyzed using the SPSS-22 program. Frequency tables were created for sociodemographic questions. To examine the differences in variable averages for measurements that adhere to the normality assumption, the independent two-sample T-test was applied for the variables with two groups and the one-way ANOVA for the variables with three or more groups. For the variables with an insufficient number of groups, Mann-Whitney U

Table 1. Sociodemographic Characteristics of Sample

Variables	Groups	N	(%)
Diagnosis	SCZ	253	% 64,4
	BAD	140	% 35,6
Sex	Female	201	% 51,1
	Male	192	% 48,9
Use of Additional Medicinal Drugs	No	315	% 80,2
	Yes	78	% 19,8
Psychotropic drugs in the last 6 months	No	142	% 36,1
	Yes	251	% 63,9
Smoking	No	168	% 42,7
	Yes	225	% 57,3
Substance	No	352	% 89,6
	Yes	41	% 10,4
Number of APs in the last 6 months	No	164	% 41,7
	1 AP	140	% 35,6
	2 AP	89	% 22,6
Medical Disease	No	288	% 79,6
	DM	39	% 10,8
	HT/CHD	20	% 5,5
	Hypothyroidism	15	% 4,1
Medical Drug	No	324	% 82,4
	Antihypertensive+ Antilipidemic	27	% 6,9
	Antidiabetic	19	% 4,8
	Other	23	% 5,9
AP in last 6 months	No	152	% 38,7
	Atypical	213	% 54,2
	Typical	28	% 7,1
MS in last 6 months	No	282	% 71,8
	Valproate	69	% 17,6
	Lithium	35	% 8,9
	Other	7	% 1,8
AD Type in last 6 months	No	348	% 88,5
	SSRI	35	% 8,9
	SNRI	10	% 2,5

AD: Antidepressant, AP: Antipsychotic, MS: Mood stabilizer, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin Noradreanlin Reuptake Inhibitor, HT: Hypertension, CHD: Coronary Heart Disease, SCZ: Schizophrenia, BAD: Bipolar Affective Disorder

analysis was applied for the variables with two groups, and nonparametric Kruskal-Wallis H analysis was applied for the variables with three or more groups. Pearson correlation analysis between normally distributed measurement values and variables and Spearman correlation analysis between nonnormally distributed measurement values and variables were applied to learn the relationship and direction between the measurement values. All analyses were performed at the alpha = 0.05 level. $p<0.05$ was accepted as statistically significant in all tests.

RESULTS

Sociodemographic Characteristics of the Sample

A total of 393 people participated in the research. A total of 140 participants were BAD (35.6%), and 253 were SCZ patients (64.4%). Of the participants, 201 were female (51.1%), and 192 were male (48.9%). Other sociodemographic characteristics of the participants are shown in Table 1.

Difference analyses of clinical variables with TC and ECG parameters (QT, QTc, and Tpe)

The women's mean TC value (179.86±40.58) was substantially different and more significant than the mean for men (170.05±38.28) ($p = .014<0.05$). The mean TC value (187.96±46.39) of those who used additional drugs was significantly different and larger ($p = .005<0.05$) than the mean of those who did not use additional drugs (171.87±37.29). The mean QT value of those who did not use Antipsychotic(AP)'s in the previous six months (375.15±31.04) was significantly different and higher than the mean of those who used two APs in the previous six months (362.91±28.39) ($p = .008<0.05$). Women's mean QTc values (424.22±16.12) were significantly different and higher than men's (418.34±16.33) ($p = .001<0.05$). The mean QTc value (429.08±16.83) of those using additional medication was significantly different and more significant than the mean (419.43±15.83) of those not using additional medication ($p = .001<0.05$). Nonusers' mean QTc value (421.95±16.64) was significantly different and higher than substance users' (416.21±14.07) ($p = .035<0.05$).

The mean QTc value (433.94±17.23) of those with DM and other medical diseases was significantly different and more prominent than the mean (418.97±15.97) of those without an additional medical disease. ($p = .001<0.05$). The mean QTc value (421.99±16.52) of those who did not use Antidepressant (AD)'s in the last six months was significantly different and greater than the mean QTc (415.17±15.04) of those who used Selective Serotonin Reuptake Inhibitor (SSRI)s in the last 6 months ($p = .032<0.05$). The mean TPE value of those who had not used APs in the previous six months (84.42± 6.96) was significantly higher than the mean TPE value of those who had used two APs in the previous six months (82.15± 6.88) ($p = .033< 0.05$). (Table 2)

Difference analyses of clinical variables with FHRS and ECG parameters (TPe/QT, TPe/QTc)

Men had a significantly higher mean TPe/QTc value (.22858±.01434) than women (.22291±.01158) ($p = .001<0.05$). The mean TPe/QTc value of smokers (.22698±.01336) was significantly different and larger ($p = .024<0.05$) than the mean of nonsmokers (.22393±.01304). The mean TPe/QTc value of nonsubstance users (.23107±.01415) was significantly different and more prominent than the mean TPe/QTc value of substance users (.22505±.01307) ($p = .006<0.05$). Men had significantly higher mean TPe/QTc values (.20135±.01555) than women (.19551±.01397) ($p = .001<0.05$).

The mean TPe/QTc value (.19974±.01528) of those who do not use additional medication is significantly different and larger ($p = .001<0.05$) than the mean (.19280±.01257) of those who use additional medication. The mean TPe/QTc value (.20047±.01610) of those who did not use psychotropic drugs in the last six months was significantly different and larger ($p = .036<0.05$) than the mean (.19717±.01428) of those who used psychotropic drugs in the last six months. The mean TPe/QTc value of substance users (.20396±.01296) was significantly different and greater ($p = .012<0.05$) than the mean of nonsubstance users (.19771±.01513). The mean TPe/QTc value of those without a medical disease (.19977±.01560) was significantly different and larger than the mean TPe/QTc value of those with DM with a medical disease (.19006±.01159) ($p = .003<0.05$). The mean TPe/QTc value (.19960±.01545) of those who did not use medical drugs was significantly different and larger than the mean TPe/QTc value (.19289±.01012) of those using antihypertensive and antihyperlipidemic drugs ($p = .006<0.05$). The mean TPe/QTc value of the nonmedical users (.19960±.01545) was significantly different and larger than the mean TPe/QTc value of the antidiabetic users (.18941±.01298). Women's mean FHRS (7.17±10.58) was significantly different and higher than men's (6.37±5.45) ($p = .001<0.05$).

Table 2. Difference analyzes of clinical variables with TC and ECG parameters(QT, QTc,Tpe)

Variables	TC				QT				QTc				Tpe			
	$\bar{x}$	SD	Test	p	$\bar{x}$	SD	Test	p	$\bar{x}$	SD	Test	p	$\bar{x}$	SD	Test	p
Sex																
Female	179,86	40,58	t:2,461	,014*	372,55	29,53	t:1,129	,260	424,22	16,12	t:3,588	,001	82,91	6,35	t:-1,926	,055
Male	170,05	38,28			369,12	30,65			418,34	16,33			84,20	6,94		
Use of Additional Medicinal Drugs																
No	171,87	37,29	t:-2,842	,005*	370,81	30,87	t:-,082	,935	419,43	15,83	t:-4,759	,001	83,75	6,93	t:1,494	,137
Yes	187,96	46,39			371,12	26,92			429,08	16,83			82,66	5,45		
Substance Usage																
No	176,35	39,77	t:1,883	,060	371,15	29,86	t:,537	,592	421,95	16,64	t:2,118	,035*	83,37	6,63	t:-1,430	,153
Yes	164,04	38,00			368,48	32,27			416,21	14,07			84,95	6,93		
Number of APs in the last 6 months																
No	173,31	38,92	F:1,240	,291	375,15	31,04	F:4,868	,008*	420,94	16,02	F:,462	,630	84,42	6,96	F:3,437	,033*
1 AP	173,42	38,10			370,93	29,18			420,89	16,29			83,38	6,04		
2 AP	180,89	43,42			362,91	28,39			422,83	17,62			82,15	6,88		
Medical Diseases																
No	171,54	37,17	H:9,165	,027*	369,82	30,64	H:2,692	,442	418,97	15,97	H:26,659	,001**	83,67	7,05	H:,817	,845
DM	191,71	46,18			370,46	26,42			433,94	17,23			82,43	5,46		
HT/CHD	181,15	48,02			379,45	25,51			425,75	14,40			83,20	4,86		
Hypothyroidism	187,53	42,62			372,33	33,79			426,40	16,18			83,60	6,26		
AD types in the last 6 months																
No	174,50	39,09	H:2,339	,311	371,38	30,29	H:2,352	,308	421,99	16,52	H:6,893	,032*	83,75	6,73	H:5,247	,073
SSRI	185,08	44,17			369,74	29,32			415,17	15,04			82,60	6,20		
SNRI	159,80	42,06			357,10	24,36			420,800	16,36			79,60	4,81		

AD: Antidepressant, AP: Antipsychotic, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin Noradreanlin Reuptake Inhibitor, TC: Total Cholesterol, DM: Diabetus Mellitus, HT: Hypertension, CHD: Coronary Heart Disease, *p<0.05, **p<0.001, t = T-Test statistic, F = F statistic, H = Kruskal Wallis-H statistic, z = Mann Whitney-U statistic

Table 3. Difference analyzes of clinical variables with FHRS and ECG parameters(TPe/QT, TPe/QTc)

Variables	TPe/QT				TPe/QTc				FHRS			
	$\bar{x}$	SD	Test	P	$\bar{x}$	SD	Test	p	$\bar{x}$	SD	Test	p
Sex												
Female	,22291	,01158	t:-4,302	,001**	,19551	,01397	t:-3,919	,001**	7,17	10,58	z:-3,460	,001**
Male	,22858	,01434			,20135	,01555			6,37	5,45		
Use of Additional Medicinal Drugs												
No	,22632	,01389	t:1,933	,054	,19974	,01528	t:3,714	,001**	5,39	6,22	z:-6,057	,001**
Yes	,22308	,01018			,19280	,01257			12,41	12,93		
Psychotropic drug in the last 6 months												
No	,22575	,01410	t:,077	,939	,20047	,01610	t:2,099	,036*	6,07	6,92	z:-,856	,392
Yes	,22564	,01284			,19717	,01428			7,18	9,22		
Smoking												
No	,22393	,01304	t:-2,262	,024*	,19751	,01435	t:-,971	,332	5,45	7,43	z:-4,595	,001**
Yes	,22698	,01336			,19900	,01552			7,77	9,06		
Substance usage												
No	,22505	,01307	t:-2,764	,006*	,19771	,01513	t:-2,535	,012*	7,03	8,87	z:-,299	,765
Yes	,23107	,01415			,20396	,01296			4,63	2,69		
Medical Disease												
No	,22669	,01415	H:10,215	,017*	,19977	,01560	H:13,746	,003*	5,02	5,40	H:57,488	,001**
DM	,22279	,00948			,19006	,01159			18,61	16,19		
HT/CHD	,21964	,01097			,19551	,01103			9,10	6,96		
Hypothyroidism	,22497	,00855			,19600	,01171			8,20	10,08		
Medical Drugs												
No	,22624	,01376	H:4,506	,212	,19960	,01545	H:12,283	,006*	5,70	6,73	H:31,852	,001**
Antihypertensive+ Antilipidemic	,22134	,01006			,19289	,01012			11,33	11,43		
Antidiabetic	,22355	,01105			,18941	,01298			16,57	17,34		
Other	,22456	,01073			,19486	,01094			8,56	9,21		
MS in the last 6 months												
No	,22508	,01333	H:4,708	,194	,19872	,01580	H:1,159	,763	6,54	8,06	H:13,381	,004*
Valproate	,22798	,01253			,19766	,01423			8,81	11,10		
Lithium	,22458	,01476			,19806	,01063			3,94	3,65		
Other	,23270	,00814			,19274	,00861			10,57	7,78		

MS: Mood stabilizer, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin Noradreanlin Reuptake Inhibitor, DM: Diabetus Mellitus, HT: Hypertension, CHD: Coronary Heart Disease, FHRS: Framingham Hearth Risk Scoring, *p<0.05, **p<0.001, t = T-Test statistic, F = F statistic, H = Kruskal Wallis-H statistic, z = Mann Whitney-U statistic

The mean FHRS (12.41±12.93) of those using additional medication was significantly different and greater (p = .001<0.05) than the mean FHRS (65.39±6.22) of those who did not use additional medication. The mean FHRS of smokers (7.77±9.06) was significantly higher than that of nonsmokers (5.457±.43) (p = .001<0.05). The mean FHRS (18.61±16.19) of those with DM and a medical disease was significantly different and greater (p = .001<0.05) than the mean FHRS of those without a medical disease (5.02±5.40). The mean FHRS (18.61±16.19) of those with a medical disease of DM was significantly different and greater than that of those with a medical disease of HT or CHD (9.10±6.96). The mean FHRS (18.61±16.19) of those with a medical disease of DM was significantly different and greater than the mean average FHRS (8.20±10.08) of those with a medical disease of hypothyroidism. The mean FHRS of those who did not use MS in the last six months (6.54±8.06) was significantly different and greater than those who used lithium in the last six months (3.94±3.65). The mean FHRS of those using valproate in the last six months (8.81±11.10) was significantly different and greater than the mean of those using lithium in the last six months (3.94±3.65) (p = .004<0.05). (Table 3).

Correlation analyses of clinical variables, FHRS, ECG parameters, and cholesterol values

There is a positive and moderately significant relationship between the SBP value and the DBP value with 99% confidence (r = .513; p = .001). There was a positive and very weak correlation between SBP and HDL, QTc, number of medical drugs, and duration of disease with 95% confidence (r = .113; p = .025, r = .102; p = .044, r = .189; p = .001, r = .106; p = .036, respectively). There was a positive and weak significant correlation between SBP value and FHRS and age with 99% confidence (r = .291; p = .001, r = .231; p = .001, respectively). A positive and weak correlation exists between the DBP value and the TC value with 95% confidence (r = .100; p = .048). A positive and significant relationship exists between the DBP value and the FHRS value with 95% confidence (r = .124; p = .014). A positive and weak correlation exists between heart rate and TC and the number of psychiatric drugs with 95% confidence (r = .124; p = .014, r = .141; p = .005).

There was a negative and strong significant correlation between heart rate and QT and TPe/QTc values with 99% confidence (r = ,858; p = .001, r = .663; p = .001). A negative and moderately significant relationship exists between the pulse value and the TPe value with 99% confidence (r = .599; p = .001). There is a positive and weak significant relationship between the pulse value and the TPe/QTc value with 99% confidence (r = .370; p = .001). With 95% confidence, and there was a positive and very weak correlation between HDL value and TC, FHRS, and number of medical drug values (r = .189; p = .001, r = .194; p = .001, r = .109; p = .031).

With 95% confidence, there was a negative and very weak significant correlation between HDL value and the number of psychiatric drugs and hospitalizations (r = .124; p = .014, r = .127; p = .012). With 99% confidence, there is a positive and weak correlation between HDL value and age (r = .253; p = .001). There was a positive and weak correlation between the TC value and QTc, with several medical drug values having 99% confidence (r = .137; p = .007, r = .111; p = .028).

There is a negative and very weak significant correlation between the TC value and the TPe/QTc value with a 99% confidence (r = .136; p = .007). There is a positive and weak significant relationship between the TC value and the FHRS value with 99% confidence (r = .301; p = .001). There was a positive and moderately significant correlation between the QT value and the QTc and TPe/QTc values with 99% confidence (r = .434; p = .00, r = .530; p = .001, respectively). There is a positive and significant correlation between the QT value and the TPe value with 99% confidence (r = .721; p = .001). There is a negative and weak significant relationship between the QT value and the TPe/QTc value with 99% confidence (r = .399; p = .001). There was a positive and very weak correlation between the QT value and the FHRS, with 95% confidence (r = .105; p = .038, r = .173; p = .001). There was a positive and weak significant correlation between the QTc value and TPe, FHRS, number of psychiatric drugs, APs, and age with 99% confidence (r = .329; p = .001, r = .383; p = .001, r = .208; p = .001, r = .229; p = .001, r = .313; p = .001, respectively). There was a negative and very weak significant correlation between the QTc value and the TPe/QTc values with 99% confidence (r = .153; p = .002, r = .171; p = .001, respectively). With 99% confidence, there was a positive and very weak significant correlation between QTc and HS and the number of psychiatric hospitalizations (r = .179; p = .001, r = .140; p = .006, respectively). There is a positive and weak significant correlation between the TPe value and the TPe/QTc value with 95% confidence (r = .345; p = .001). There is a positive and robust significant correlation between the TPe value and the TPe/QTc value with 99% confidence (r = .874; p = .001). There is a positive and very weak significant correlation between the TPe value and the FHRS value with 95% confidence (r = .109; p = .031).

With 95% confidence, there is a negative and very weak significant correlation between the TPe value and

the number of medical drugs variable (r = .100; p = .048). A positive and moderately significant relationship exists between the TPe/QTc value and the TPe/QTc value with 99% confidence (r = .438; p = .001).With 99% confidence, there was a negative and very weak significant relationship between the TPe/QTc value, the number of medical drugs, and the age variable (respectively = .174; p = .001, r = .108; p = .033). There was a negative and very weak significant correlation between the TPe/QTc value and the FHRS, number of medical drugs, and number of psychiatric drugs with 95% confidence (r = .108, p = .032, r = .173, p = .001, r = .145, and p = 0.004, respectively). There is a positive and weak significant relationship between the FHRS value and the number of medical drugs and duration of disease variables with 99% confidence (r = .281; p = .001, r = .241; p = .001, respectively). There is a positive and moderately significant relationship between the FHRS value and the age variable with 99% confidence (r = .536; p = .001). (Table 4).

DISCUSSION

Many psychiatric disorders, including SCZ, BAD, and major depression, carry an excessive burden of cardiovascular morbidity and mortality (Abosi et al., 2018). A meta-analysis published in 1997 of 18 studies from Europe, North America, and Israel found a 1.5-fold increase in age-adjusted mortality in patients with chronic mental illness compared to the general population (Brown, 1997). In our study, we evaluated cardiac risk, one of the common causes of death in SCZ and BAD diseases, which are common chronic mental diseases. The FHRS showed that the 10-year risk of CHD was higher in females than in males in BAD and SCZ patients in our study group. Similarly, the estimated risk of CHD in patients with SCZ was 34% in men and 50% in women with SCZ (Cohn et al., 2004). Likewise, the fact that the FHRS was higher in patients who smoke and have other medical diseases such as DM supports the idea that the risk of CHD may increase with additional medical diseases. Recent evidence suggests that the standardized death rate for heart disease may be increasing, especially in patients with SCZ, compared to the general population (Osby et al., 2000). With the widespread use of atypical antipsychotic agents known to cause weight gain and possibly increase the risk of hyperlipidemia and diabetes, concerns about medical morbidity have intensified, particularly concerning heart disease (American Diabetes Association, et al., 2004). Although smoking is the most commonly used substance in psychiatric diseases, it is most frequently seen in SCZ patients (Glynn & Sussman, 1990; De Leon et al., 1995). Smoking was also found to be 57.3% in our study group, and the risk of CHD was found to be higher in this group. In a study, the frequency of metabolic syndrome was two times higher in patients with SCZ than general population (Cohn et al., 2004). Psychiatric disorders with a higher incidence of DM diabetes mellitus include cognitive impairment, dementia, eating behavior disorder, anxiety disorders, SCZ, BAD, and borderline personality disorder. The coexistence of mental disorders and diabetes adversely affects metabolic control and micro- and macroangiopathic complications (Abrahamian et al., 2019). In a similar study, when the incidence of autoimmune diseases in BAD and SCZ patients was examined, there was no difference between the groups in terms of diabetes. At the same time, hypothyroidism was observed more frequently in the BAD patient group (Cremaschi et al., 2017). In our patient group, DM was detected in 10.8%, hypothyroidism was found in 4.1%, and FHRS was higher in the group with DM, especially in the group with CHD, HT, and hypothyroidism. This showed that other medical diseases, especially DM, may increase cardiac risk.

Many commonly used mood stabilizer(MS), psychotropic drugs, especially antipsychotics, MS, and some antidepressants, have been independently associated with cardiometabolic risk factors such as insulin resistance, obesity, and dyslipidemia (Abosi et al., 2018). Weight gain caused by valproic acid (VPA) is associated with many metabolic disorders. The most common are hyperinsulinemia and insulin resistance, hyperleptinemia, and leptin resistance. Patients who gain weight during VPA treatment may develop dyslipidemia and the metabolic syndrome associated with long-term vascular complications such as hypertension and atherosclerosis. In addition, increased uric acid, homocysteine levels, and oxidative stress may contribute to atherosclerotic risk in patients receiving long-term VPA treatment (Belcastro et al., 2013).

Moreover, VPA is a potent histone deacetylase (HDAC) enzyme inhibitor. HDAC inhibition promotes histone acetylation, leading to chromatin relaxation and facilitating transcriptional activation. Recent findings highlight the critical role of histone acetylation in the pathogenesis of type 2 DM diabetes mellitus (Jianping, 2013). In our working group, the high FHRS in the patient groups using VPA instead of lithium suggested that VPA may have contributed to the increased risk of CHD compared to lithium.

The highest risk for prolongation of heart rate-corrected QT interval (QTc) was seen with ziprasidone and sertindole. The highest risk of weight gain was seen with clozapine and olanzapine (Haddad & Sharma, 2007). In

Table 4. Correlation analyzes of clinical variables, FHRS, ECG parameters and cholesterol values

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. SBP	1																
	393																
2. DBP	,513**	1															
	,000																
	392	392															
3. Pulse	,052	-,022	1														
	,300	,658															
	393	392	393														
4. HDL	,113*	,042	-,033	1													
	,025	,409	,515														
	393	392	393	393													
5. TC	,082	,100*	,124*	,189**	1												
	,105	,048	,014	,000													
	393	392	393	393	393												
6. QT	,004	,048	-,858**	-,012	-,038	1											
	,930	,342	,000	,808	,451												
	393	392	393	393	393	393											
7. QTc	,102*	,057	,073	-,070	,137**	,434**	1										
	,044	,264	,148	,167	,007	,000											
	393	392	393	393	393	393	393										
8. TPe	,024	,064	-,599**	-,072	-,063	,721**	,329**	1									
	,629	,207	,000	,157	,215	,000	,000										
	393	392	393	393	393	393	393	393									
9. TPe/QT	,034	,023	,370**	-,084	-,033	-,399**	-,153**	,345**	1								
	,497	,644	,000	,097	,509	,000	,002	,000									
	393	392	393	393	393	393	393	393	393								
10. TPe/QTc	-,025	,039	-,663**	-,036	-,136**	,530**	-,171**	,874**	,438**	1							
	,618	,440	,000	,474	,007	,000	,001	,000	,000								
	393	392	393	393	393	393	393	393	393	393							
11. FHRS	,291**	,124*	,093	-,194**	,301**	,105*	,383**	,109*	-,050	-,108*	1,000						
	,000	,014	,065	,000	,000	,038	,000	,031	,318	,032	.						
	393	392	393	393	393	393	393	393	393	393	393						
12. NMD	,189**	,064	,046	,109*	,111*	,012	,098	-,100*	-,174**	-,173**	,281**	1,000					
	,000	,206	,363	,031	,028	,810	,053	,048	,001	,001	,000	.					
	393	392	393	393	393	393	393	393	393	393	393	393					
13. NPD	-,021	-,015	,141**	-,124*	,039	-,028	,208**	-,040	-,017	-,145**	,044	,150**	1				
	,674	,771	,005	,014	,447	,574	,000	,426	,741	,004	,385	,003					
	393	392	393	393	393	393	393	393	393	393	393	393	393				
14. NAP	-,020	,004	,061	-,079	,033	,062	,229**	,018	-,060	-,095	,023	,003	,657**	1			
	,694	,940	,231	,119	,516	,223	,000	,716	,232	,061	,654	,950	,000				
	393	392	393	393	393	393	393	393	393	393	393	393	393	393			
15. Age	,231**	,095	-,036	,253**	,097	,173**	,313**	,096	-,108*	-,056	,536**	,194**	-,033	,004	1		
	,000	,060	,481	,000	,056	,001	,000	,057	,033	,270	,000	,000	,514	,944			
	393	392	393	393	393	393	393	393	393	393	393	393	393	393	393		
16. DD	,106*	-,001	-,012	,087	,027	,093	,179**	,067	-,037	-,019	,241**	,078	,180**	,197**	,488**	1	
	,036	,990	,820	,085	,593	,066	,000	,186	,470	,704	,000	,122	,000	,000	,000		
	393	392	393	393	393	393	393	393	393	393	393	393	393	393	393	393	
17. NPH	,019	-,014	,058	-,127*	-,080	,006	,140**	,020	,018	-,049	,096	,039	,300**	,247**	,150**	,477**	1
	,706	,788	,255	,012	,111	,901	,006	,688	,727	,335	,058	,443	,000	,000	,003	,000	
	393	392	393	393	393	393	393	393	393	393	393	393	393	393	393	393	393

*p<0,05 **p<0,001 SBP: Systolic Blood PreSDure, DBP: Diastolic Blood PreSDure, TC: Total Cholesterol, FHRS: Framingham Hearth Risk Scoring, NMD: Number of Medical Drugs, NPD: Number of Psychotropic Drugs, NAP: Number of Antipsychotics, DD: Disease Duration, NPH: Number of Psychiatric Hospitalizations

another study, QTc prolongation was found to be higher in the group using AP+AD compared to the two groups using antipsychotics and antidepressants together (Sala et al., 2005). In a similar study, it was observed that the QTc interval was longer in the group that added 2nd generation AP to the 1st generation AP treatment and between the two groups treated by switching from the 1st generation to the 2nd generation (Sciascio et al., 2011). When we look at the QTc duration, which shows the risk of ventricular arrhythmia in the ECG parameters in our study group, it has been observed that it is longer in female patients, in patients who use additional medical drugs, in patients with DM, and in patients with high cholesterol levels. In our study, QTc was not found to be directly related to antipsychotic, antidepressant, or MS drugs. However, as the number of antipsychotics, duration of illness, hospitalization, and patient age increased, the QTc duration was prolonged, and the FHRS increased.

Additionally, in BAD and schizophrenic patients, the chronicity of the disease and the use of multiple drugs have shown that the risk of cardiac arrhythmia may increase as time progresses. Another study found that second-generation antipsychotic drugs are less likely to prolong the QTc interval than first-generation antipsychotic drugs (Ozeki et al., 2010). However, our study observed no difference in ECG parameters between typical and atypical antipsychotic users.

The TPe interval is a relatively new ECG parameter that shows ventricular repolarization. It has been associated with ventricular arrhythmias and sudden death, even in patients with normal QTc. However, because QT and TPE intervals vary with body weight and heart rate, these indexes are less sensitive in predicting arrhythmogenesis (Panikkath et al., 2011; Erikssen et al., 2012). In a meta-analysis, prolonged TPe intervals were found to be associated with a 1.14-fold increase in the risk of malignant ventricular arrhythmias or sudden cardiac death (Tse et al., 2017). In our study, TPe and OT times were positively correlated with the FHRS. In other words, TPe and QT prolongation, which show that the incidence of ventricular arrhythmias increases, also increase the CHD score. TPe/QT ratios have also recently been used as a new electrocardiographic marker for ventricular repolarization and have been reported to be associated with malignant ventricular arrhythmias (Antzelevitch & Oliva, 2006).

In this context, the TPe/QTc ratio is preferable to a single assessment of Tpe or QT intervals because this ratio remains constant regardless of dynamic changes in heart rate (Gupta et al., 2008; Erikssen et al., 2012). In our study, TPe/QTc ratios, one of the ventricular arrhythmia markers, were higher in male patients than female patients and lower in patients with a higher FHRS, a medical illness, and a higher number of psychotropics. Second-generation antipsychotics have been linked to weight gain, lipid disorders, and glucose dysregulation, all of which contribute to the development of metabolic syndrome (Howes et al., 2004). There were significant differences in metabolic side effects among antipsychotics, especially olanzapine and clozapine, which exhibited the worst profiles. At the same time, aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone were found to exhibit benign profiles. Baseline weight, male sex, and nonwhite ethnicity were evaluated as predictors of susceptibility to antipsychotic-induced metabolic change. Improvements in total symptom severity were associated with weight increases, higher BMI, TC, and cholesterol concentrations, and decreases in HDL cholesterol concentrations (Pillinger et al., 2020).

In our working group, a positive correlation was found for a pulse, DPS, OTc, FHRS, and the number of medical drugs in patients with high cholesterol levels. HDL, the cholesterol that protects against cardiac pain, was negatively correlated with the number of psychotropics and psychiatric hospitalizations. Our study has some limitations. The patients were included in the study during their hospitalization; each patient used more than one drug; they were not excluded from substance or alcohol use, and their medical illnesses were not excluded. However, evaluating all patients with the FHRS score and comparing them according to their risk of cardiac arrhythmia is significant in the study. Similar studies with more homogeneous groups, such as those with similar disease duration, drug use, no medical disease, and no alcohol or substance abuse, may yield more effective results.

CONCLUSION

When we evaluated the cardiac risk indexes of SCZ and BAD patients, we found that the FHRS was higher in smokers, female patients, and those with other medical diseases such as diabetes. In addition, we found that QTc rates, markers of cardiac arrhythmia, were associated with FHRS, the number of APs used, patient age, disease duration, and the number of hospitalizations. In addition, a positive correlation was found between QTc rates in women, patients with diabetes, and those using additional medical drugs. TPe and QT rates increased in the same direction as FHRS. According to the results of our study, the FHRS showing a 10-year cardiac index is higher in SCZ and BAD female patients, especially with the use of additional medical drugs, DM, and smokers. The parameters indicate that the risk of cardiac arrhythmia increases with the number of antipsychotics, disease

duration, hospitalizations, and age. We think evaluating electrocardiographic repolarization parameters in this group of patients will help predict the risk of ventricular arrhythmia. Moreover, by evaluating the cardiac risk in psychiatric diseases, the follow-up and treatment of this group of patients should be arranged according to these risk factors.

Ethical Considerations

Does this study include human subjects? NO

Conflict of interest

No conflict of interest

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