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RESEARCH ARTICLE

Electrocardiogram markers of atrial and ventricular repolarization abnormalities and their association with symptom severity in antipsychotic-free patients with schizophrenia

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ABSTRACT

Objective: Increased risk for arrhythmias and the association between arrhythmogenic markers and symptom severity in antipsychotic-free patients with schizophrenia are understudied. We evaluated the changes in P-wave dispersion (PWD), corrected QT interval (QTc), QTc dispersion (QTcd), corrected JT interval (JTc), JTc dispersion (JTcd), T_{peak}-T_{end} (Tp-e), and Tp-e/QT ratio.

Method: Fifty-six patients with schizophrenia who were antipsychotic-free for at least 1 month and 56 age- and gender-matched healthy controls were included. Illness-related characteristics such as the Positive and Negative Syndrome Scale (PANSS) scores were recorded. Electrocardiography recordings were performed with standardized procedures for all participants, and risk markers of arrhythmia were calculated from the electrocardiograms.

Results: PWD ($p<0.001$), QTc ($p<0.001$), QTcd ($p=0.002$), JTc ($p<0.001$), and JTcd ($p<0.001$) values significantly increased in patients compared to the controls. Among the ECG markers, PWD was significantly and inversely correlated with the PANSS General subscale ($r=-0.27$, $p<0.05$), and JTc was correlated with age at illness onset ($r=0.41$, $p=0.001$).

Conclusion: Changes in ECG-derived markers of cardiac arrhythmia, which are acquired through an easy and cheap method, can be evaluated to predict and prevent serious cardiac conditions in antipsychotic-free schizophrenia patients.

Keywords: Autonomic nervous system, arrhythmia, cardiovascular diseases, electrocardiography, psychosis

INTRODUCTION

Schizophrenia is a complex syndrome with a highly heterogeneous combination of symptoms affecting nearly 1% of the world population and contributing substantially to the global burden of disease. Individuals with schizophrenia have a lifespan of as much as 20 years less than the general population. Moreover, the contribution of medical conditions such as cardiovascular diseases (CVDs) to reducing

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life expectancy is much greater than suicide, homicide, and accidents (1).

The mechanisms by which schizophrenia patients are susceptible to CVDs are complex and include lifestyle factors such as excessive smoking, unhealthy dietary choices, alcohol/substance use, sedentary behavior, and lack of physical activity, along with side effects from antipsychotic drugs and genetic factors. Moreover, physical illnesses diagnosed late or not receiving adequate care due to lack of access to good quality medical facilities may also contribute to the disorder (2). Although research into cardiovascular outcomes of schizophrenia has particularly focused on the comorbidity of metabolic syndrome and related diseases such as diabetes mellitus, the high incidence of cardiac morbidity and sudden cardiac death (SCD) suggest a direct link to cardiac arrhythmia in schizophrenia (2). In addition to coronary artery or myocardial diseases, cardiac electrophysiological abnormalities might substantially predispose patients to the development of ventricular arrhythmias and cardiac mortality. Antipsychotic drugs are largely implicated as the cardinal cause of ventricular arrhythmias and cardiac arrest; nonetheless, extensive autonomic nervous system (ANS) alterations related to cardiac electrical activity have been described in antipsychotic-free patients (3). These data suggest increased sympathetic modulation, decreased parasympathetic output, or both, indicating an impaired balance between sympathetic and parasympathetic nervous systems.

Electrocardiography (ECG) is a simple, easily available, and noninvasive medical procedure that can indicate the functionality of the sympathetic and parasympathetic branches of the ANS. ECG is a fundamental tool widely available in many different clinical settings and contributes greatly to diagnosing and predicting CVDs ranging from various arrhythmias to acute coronary syndrome. In previous studies, ECG markers of ANS abnormalities such as P-wave dispersion (PWD) and corrected QT (QTc) dispersion (QTcd) were shown to be associated with schizophrenia (4). QT interval indicates the ventricular repolarization time. QT interval is known to vary with the heart rate; therefore, an adequate rate correction (QTc) is necessary to compare measurements carried out at different time points and with varying heart rates. Prolongation of heart rate-corrected QT interval is a known risk factor for serious adverse events, including ventricular arrhythmias such as Torsades de Pointes and SCD (5). QTcd reflects the regional variation in ventricular repolarization. Possible ventricular arrhythmias and SCD are related to increased QTcd (6,7). Increased PWD, a marker of atrial fibrillation, is related to the prolongation of both intraatrial and interatrial conduction times as well as aberrant propagation of sinus impulses between the atria, leading to atrial arrhythmias (8).

Numerous other well-known as well as novel ECG markers, including T_{peak}-T_{end} (Tp-e), Tp-e/QT ratio, heart rate corrected JT interval (JTc), and JTc dispersion (JTcd), can potentially predict arrhythmic events in clinical practice (9). Tp-e reflects transmural dispersion of ventricular repolarization and was reported to be useful in predicting the risk of arrhythmia (10). The Tp-e/QT ratio was shown to predict cardiac arrhythmia; moreover, it does not need to be corrected by heart rate, giving it an advantage over the other markers (11). JT interval is a marker of ventricular repolarization and represents repolarization time with greater specificity than the QT interval. Due to this specificity, JTcd was considered a useful marker in patients with conduction abnormalities for predicting the risk of arrhythmia in ventricular repolarization heterogeneity with greater accuracy than QTcd (12). To date, JT interval-related ECG markers have not been studied in a patient sample diagnosed with schizophrenia.

Previous studies have not sufficiently examined the relationship between illness-related characteristics such as symptom severity and a broad range of ECG markers of ventricular repolarization among antipsychotic-free schizophrenia patients. In one of the few studies on this subject, Fujibayashi et al. (13) demonstrated that low general functioning was associated with impaired ANS parasympathetic nervous system activity in patients with schizophrenia. However, the literature still lacks addressing the direct relationship between the severity of symptoms specific to schizophrenia and cardiac electrophysiological abnormalities in this group. Therefore, evaluation of illness-related effects of schizophrenia on cardiac electrical activity is necessary, particularly with regard to impairment in ventricular conduction. Such an evaluation will also help understand the effects of symptom severity on cardiac morbidity and weigh the risk-benefit ratio of antipsychotics. In the current study, we aimed to evaluate risk markers of cardiac arrhythmia in patients diagnosed with schizophrenia in the natural course of the disorder. We also aimed to emphasize using easily measurable parameters that every clinician can

evaluate before starting antipsychotic treatment in schizophrenia patients to avoid possible arrhythmic events with a cumulative effect. Our null hypotheses included that patients with schizophrenia do not have an increased risk for cardiac arrhythmia, and there is no relationship between the clinical features of the disorder and risk markers of cardiac arrhythmia. We conducted this study to extrapolate the secondary hypotheses (H1) that the disorder per se and its clinical features are associated with an increase in the risk markers of cardiac arrhythmia.

METHOD

Study Participants

This study was designed in a cross-sectional nature and included patients with schizophrenia who met the disorder criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and were admitted to either the psychiatry outpatient or inpatient units at Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery (Istanbul, Turkey), between March 2022 and September 2022. Two senior psychiatrists independently diagnosed the patients on the basis of the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV). This tool is used to evaluate whether the diagnostic criteria of psychiatric disorders according to DSM-5 are met (14,15), along with an assessment of individual medical records. Only those patients who completely had ceased the use of their recommended oral antipsychotics for at least 1 month prior to the start of the study were screened. This criterion was based on previous clinical studies using an antipsychotic washout period, in which patients were considered "antipsychotic-free" if they had not taken any antipsychotic in the 2–4 weeks prior to the ECG recording (16–18). Inclusion criteria for all participants were as follows: being at the age of 18–65 years, the absence of any prior cardiac surgery or procedures such as implantation of a pacemaker, and lack of use for at least 1 month of vasoactive, antiarrhythmic, or other pharmacological agents that may influence the cardiac electrical activity. Exclusion criteria were set as follows: documented laboratory findings of renal or liver pathology, abnormal blood screening results such as electrolyte imbalance, documented substance, and alcohol use disorder, heavy smoking (>20 cigarettes per day), current or prior history of cardiac failure, the incidence of infarction of myocardium, cardiomyopathy, valvular heart disease or other established illnesses related to the structure or function of the heart, high blood pressure (>180/120 mmHg) and elevated heart rate (>120 bpm) at the time of the study, chronic systemic illnesses such as renal or hepatic failure, diabetes mellitus, and hypertension, pathological ECG findings including the presence of U waves, bundle branch block or other arrhythmias, and comorbid psychiatric or neurological disorders including accompanying psychotic symptoms (for the patient group only). No patient used a long-acting injectable antipsychotic for at least 6 months before the study. After applying the exclusion criteria, 56 (29 females, 27 males) out of 69 patients were included (Fig. 1).

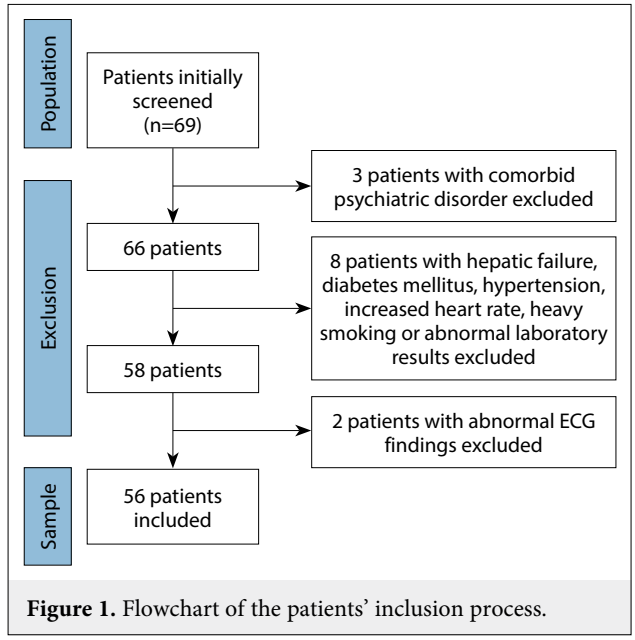


Figure 1. Flowchart of the patients' inclusion process.

The comparison group consisted of age- and sex-matched healthy subjects (n=56, 29 females and 27 males) undergoing routine employee medical examinations or pre-employment health check-ups at the outpatient clinic and matched for smoking status. These controls had no current or prior diagnosis of psychiatric disorders, including substance or alcohol use, which was confirmed with SCID-5-CV. All participants were normal in a physical examination and routine recent blood tests. The study was approved by the Scientific Research Ethics Committee of the University of Health Sciences Hamidiye [IRB: 11.03.2022—22/159] and was conducted according to the principles stated in the Helsinki Declaration. Following a thorough explanation of the study procedure, all participants or (where necessary) their legal representatives/guardians provided written informed consent for participation in the study.

Table 1: Description of ECG markers and other characteristics of the study sample

	Patients (n=56)	Controls (n=56)	t/Z	p
Gender (F/M)	29/27	29/27		1.000
Age†	36.09±10.81	33.46±6.27	1.572	0.119
BMI (kg/m^2)‡	26.61±3.05	24.96±4.61	-1.262	0.214
Heart rate (per minute)†	85.59±15.39	73.57±13.47	4.396	<**0.001**
P dispersion (ms)‡	38.46±18.78	27.28±18.11	-3.572	<**0.001**
QTc (ms)‡	419.11±39.32	387.75±28.08	-4.759	<**0.001**
QTc dispersion (ms)‡	52.32±33.25	34.14±24.4	-3.157	**0.002**
JTc (ms)‡	326.07±43.26	294.86±23.47	-4.098	<**0.001**
JTc dispersion (ms)‡	52.5±31.29	31.87±23.59	-3.771	<**0.001**
Tp-e (ms)‡	72.64±22.27	66.57±14.07	-1.483	0.138
Tp-e/QTc ratio‡	0.20±0.06	0.19±0.04	-0.213	0.832
Age at illness onset	27.66±9.43			
Duration of illness (years)	8.46±7.65			
PANSS positive	30.44±7.91			
PANSS negative	22.71±6.81			
PANSS general	41.91±7.36			
PANSS total	95.14±14.96			

F: Female; M: Male; BMI: Body mass index; †t: Independent samples t-test; ‡Z: Mann–Whitney U test; QTc: Corrected QT interval; Tp-e: T-peak to T-end interval; JTc: Corrected JT interval; PANSS: Positive and Negative Syndrome Scale. P<0.05 statistically significant (bold values).

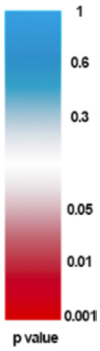
Procedure, Electrocardiogram Recording, and Measurement

Background information, including age and duration of illness, was collected from all patients. Next, the severity of symptoms related to schizophrenia was assessed for the patient group with the Positive and Negative Syndrome Scale (PANSS) (19,20). ECG recordings were obtained using standardized procedures after 10 min of acclimatization of the patients with regular breathing in the supine position in a quiet room. ECG recordings were carried out with a standard 12-lead surface tracing at a paper speed of 50 mm/s and amplitude of 20 mV/mm. To exclude any possible effect of diurnal variations, we obtained all recordings in the morning between 9:00 and 10:00 a.m. An experienced cardiologist, blinded to the subjects' clinical information, initially evaluated the ECG records and supervised the Measurement of the ECG parameters. To minimize errors, we measured ECG parameters from the readings with calipers using a magnifying glass. The initial heart rate (per minute) was recorded for each patient. The duration of the P and QT waves was measured manually.

The onset of either a positive or negative P wave was defined as the first visible upward positive or downward negative movement of the trace between the baseline and the offset of the P waves, defined as the junction between the end of the P wave deflection and the isoelectric line. In each lead, three consecutive beats at minimum were evaluated. The durations of P_{max} and P_{min} in each of the 12-lead surface electrocardiograms were considered. PWD was calculated by subtracting P_{min} from P_{max}. The QT interval was defined as the duration from the onset of the QRS complex to the end of the T wave, also referred to as the return to the T–P isoelectric baseline. QT_{max} and QT_{min} durations were determined as the longest and shortest measurable durations of the QT wave, respectively, in any lead. The mean of three consecutive beat complexes was considered the R–R interval. Bazett's (21) formula [$QTc=QT/\sqrt{RR}$] was used to correct the QT intervals for the patients' heart rates. The difference between QTcmax and QTcmin was considered as the QTcd. The JT interval was measured from the onset of the J point to the end of the T wave. Bazett's formula was used to calculate JTc. JTcd was determined as the difference between all leads' minimal and maximal JTc values. The interval between the end of the repolarization (T_{end}) and the electrocardiographic T wave peak (T_{peak}), corresponding to the transmural dispersion, was considered as Tp-e. The Tp-e/QTc ratio was calculated from these data. Except for the heart rate, all ECG parameters were calculated in milliseconds.

Table 2: Correlations between clinical features and ECG markers in antipsychotic-free patients with schizophrenia

r	PWD	QTc	QTcd	JTc	JTcd	Tp-e	Tp-e/QTc
Age at illness onset	0.13	0.23	-0.04	0.41	-0.13	0.01	-0.16
Duration of illness	0.01	-0.13	-0.23	-0.11	-0.23	-0.01	0.05
PANSS Positive	-22	-0.01	0.02	-0.21	0.10	-0.06	0.05
PANSS Negative	0.19	-0.03	-0.07	-0.05	-0.12	-0.04	-0.17
PANSS General	-0.27	-0.04	-0.09	-0.13	-0.05	-0.19	-0.16
PANSS Total	-0.25	-0.03	-0.07	-0.19	-0.02	-0.15	-0.13



r: Pearson's correlation coefficient; HR: Heart rate; PWD: P-wave dispersion; QTc: Corrected QT interval; QTcd: QTc dispersion; JTc: Corrected JT interval; JTcd: JTc dispersion; Tp-e: T-peak to T-end interval; PANSS: Positive and Negative Syndrome Scale.

Statistical Analysis

Statistical Package for Social Sciences software for Mac OS, Version 25.0 (Armonk, NY: IBM Corp.) was used to analyze the study data. The Shapiro–Wilk test was used to determine the normality of the distribution of the numeric data before performing further analyses. Accordingly, the independent samples t-test was used as a parametric test for continuous variables, and the Mann–Whitney U test was used as the nonparametric test. Pearson's correlation coefficient was used to determine the relationship between illness-related characteristics and ECG parameters in the patient group. A value of $p<0.05$ was accepted as significant.

RESULTS

Descriptive characteristics and ECG parameters of the study groups are presented in Table 1. The mean age of the patient group was 36.09±10.81 years and 33.46±6.27 years for the control group. The difference in age and gender of the two study groups did not show any significant difference. The heart rate per minute was higher in the patient group (85.59±15.39 for patients and 73.57±13.47 for controls; t=4.396, <0.001). The patient group showed significantly higher PWD (Z=-3.572, $p<0.001$), QTc (Z=-4.759, $p<0.001$), QTcd (Z=-3.157, $p=0.002$), JTc (Z=-4.098, $p<0.001$) and JTcd (Z=-3.771, $p<0.001$) values compared to the controls. A trend for an increase in the Tp-e value and Tp-e/QTc ratio was observed, but differences did not reach statistical significance ($p>0.05$). Age at illness onset was 27.66±9.43 years, and the mean duration of illness was 8.46±7.65 years in the schizophrenia group. Mean PANSS Positive, Negative, General, and Total scores of the patients were 30.44±7.91, 22.71±6.81, 41.91±7.36, and 95.14±14.96, respectively.

We next evaluated the association between the ECG parameters and illness-related factors, including age at onset, duration, and PANSS scores in the patient group (Table 2). The PWD ratio was significantly and inversely correlated with the PANSS General subscale ($r=-0.27$, $p<0.05$), and age at illness onset was correlated with JTc ($r=0.41$, $p=0.001$). The other correlations did not reach statistical significance (r=-025 to 0.23).

DISCUSSION

The current study was designed to evaluate any alterations in QT and JT intervals along with their dispersions and their rate-corrected values in drug-free schizophrenia patients. In addition, the association between ECG markers and illness-related factors, such as symptom severity related to schizophrenia, was determined. To our knowledge, this is the first study to examine JT interval-derived arrhythmogenic markers in schizophrenia patients. We found that compared to healthy control samples, PWD, QTc, QTcd, JTc, and JTcd were significantly higher in schizophrenia patients who were not under antipsychotic treatment for at least 1 month.

Prolongation of the QT interval may indicate a lack of homogeneity in myocardial repolarization or a uniform increase in the action potential. Complex repolarization patterns, particularly a certain degree of fusion of the T and U waves, are associated with increased QTcd, which may characterize numerous proarrhythmic conditions better than QT or QTc interval (22). The latter parameters are more sensitive to intrinsic and extrinsic factors, such as characteristics of the myocardium and its changes, inherited QT syndromes, cell death, biochemical alterations, and disturbances in neurohormonal regulation (23). Accordingly, compared to QTc prolongation, increased dispersion of QTc was suggested as a better

predictor of susceptibility to ventricular tachyarrhythmias, suggesting that loss in the homogeneity of repolarization was more closely related to the risk of arrhythmia than the prolongation of repolarization itself (24).

Abnormalities in ECG have been previously reported in patients with schizophrenia (25). The traditional QT interval is commonly investigated in schizophrenia. An increased duration of QT and QTc, which are associated with ventricular arrhythmias and SCD (26), was found to be more prevalent in schizophrenia patients compared to healthy controls (27). However, most of the studies examining QT-derived markers were carried out in patients on antipsychotics (28), which are pharmacological agents that are known to prolong the QT interval due to their effects on myocardial potassium and sodium ion channels (29). On the other hand, longer QT intervals in schizophrenia patients not receiving antipsychotic treatment compared to healthy controls have been reported (30). In patients with active psychotic symptoms, the parasympathetic activity and cardiovagal tone were reported to be significantly decreased without any significant changes in the sympathetic activity (31). Our finding that markers of ventricular repolarization are increased in patients compared to healthy subjects is consistent with the previous findings.

In a previous study conducted by Hatta et al. (17), the mean QTc interval of psychiatric emergency patients was longer than that of clinically stable psychiatric outpatients; however, they have not found an association between QTc and acute agitation symptom severity evaluated by the Brief Psychiatric Rating Scale. Emul et al. (18) failed to demonstrate any association between baseline PWD, QTc, and QTcd values and positive, negative, and general symptoms in a sample of antipsychotic-free patients with schizophrenia. Tekin et al. (32) reported that QT and QTc were not correlated with PANSS domains. Congruently, we did not find a significant association between ventricular repolarization markers and the severity of symptom domains, which may suggest that prolonged ventricular repolarization may be manifested as a particular biological feature of schizophrenia regardless of the use of medication or other clinical factors.

We would like to especially draw attention to JTc and JTcd, which were found to be increased in schizophrenia patients compared to the healthy controls. JT interval abnormalities seem to be more reliable arrhythmogenic markers in patients with ventricular conduction defects, such as bundle branch block. The superiority of the JT interval over QT measurements for the duration of repolarization has already been reported, particularly in patients with ventricular conduction defects (33). As it is affected by the heart rate, Beach and colleagues have suggested a cautious approach to the interpretation of changes in the JT interval (34). Therefore, we evaluated this marker using its heart rate corrected form (JTc). Previous studies have suggested that JTcd is a useful marker that can predict ventricular arrhythmia better than QTcd, as JTcd is less affected by the heterogeneity in ventricular depolarization and ventricular repolarization (12). Thus, our findings imply that JTcd may be used as a specific ECG marker of ventricular arrhythmia in antipsychotic-free schizophrenia patients. Future studies should focus on the reproducibility of JT interval measurements in schizophrenia patients without overt conduction defects who will be started on antipsychotic medication and bring this parameter into routine clinical use.The negative symptoms of schizophrenia are closely associated with parameters such as psychological distress, sedentary behavior, lack of activity, or social withdrawal. Severe negative symptoms can increase the risk of CVD and cardiac death (35). A longer duration of illness is associated with higher disability and more severe negative symptoms and was also found to be associated with pathological ECG changes, such as frontal QRS-T in schizophrenia (32). However, we found that the duration of the illness and the presence of negative symptoms were not related to arrhythmogenic markers. Indeed, lifestyle changes such as regular physical exercise might be an ideal supplementary treatment that can be suggested to patients to overcome negative symptoms of the disorder, address any lack of motivation, and improve ANS abnormalities (36).

We found that higher age at illness onset was significantly associated with increased PWD. However, other markers of abnormalities in conduction were not related to the age of illness onset in schizophrenia. A previous study has reported that patients with a later onset of illness had a significantly lower cardiovagal tone (31). In contrast, other studies have argued that death due to cardiac events were not associated with the age of onset (37). These studies indicate the existence of subtypes of schizophrenia with heterogeneous pathophysiology, which reflect the distinctive patterns of autonomic activity.

The current study has several limitations. Illness-related confounders such as lifestyle features, patterns of physical activity, and variations in the diet, which may affect ECG parameters, were not excluded. The study had a relatively small sample size for the patient and the healthy control groups. Due to the study's cross-sectional design, we could not obtain follow-up data for the patients on subsequent arrhythmias and cardiac events. The study findings were not supported by biomarkers such as heart rate variability that also indicate ANS disturbances. Although there was a significant difference in heart rates between patients and controls, we excluded patients with a heart rate >120 bpm. We nevertheless attempted to minimize the effect of heart rate on ventricular repolarization markers by correcting them by heart rate. However, an increased heart rate, which may be related to a clinical exacerbation of schizophrenia, may influence uncorrected markers of cardiac arrhythmia. We included only those patients who were not on active antipsychotic treatment; however, we relied on patient statements and medical records to confirm this, as therapeutic drug monitoring for antipsychotics is limited. Antipsychotic drugs, some of which have a prolonged influence on the ECG parameters, may have previously been used by the patients. We also could not rule out the individuals who received PRN (pro re nata) medication at admission. We ruled out participants with medical and psychiatric comorbidities and documented abnormal laboratory findings; however, subjects with undiagnosed medical conditions that can affect ECG parameters may have been inadvertently included. The echocardiographic data of the patients were not available to determine the presence of any structural heart disease. We could not rule out all possible etiologies of ventricular arrhythmias. Manual measurement of electrophysiological parameters off an ECG tracing is inevitably related to some variation.

CONCLUSION

Predicting risk factors for cardiac arrhythmias may be essential to recognize and preventing cardiovascular morbidity and mortality in patients diagnosed with schizophrenia, regardless of the severity of the symptoms presented. To our knowledge, the current study is the first to examine a broad panel of cardiac arrhythmia risk markers as well as their association with illness-related factors. ECG is essential for assessing cardiovascular risk and may be particularly valuable as it is readily available, noninvasive, and inexpensive. Easy monitoring of QTcd, JTc, and JTcd, besides traditional markers such as QTc, from ECG readings may be a practical form of cardiovascular risk assessment and can help to decide the treatment for schizophrenia patients.. Future studies with larger samples of drug-naive and drug-free patients may help to translate electrocardiographic changes into the pathophysiology of ANS abnormalities in schizophrenia.

Contribution Categories		Author Initials
Category 1	Concept/Design	Y.H.B., S.S.K.B.
	Literature review	H.G., B.B.D., S.S.K.B.
	Data analysis/Interpretation	Y.H.B., S.S.K.B.
Category 2	Drafting manuscript	Y.H.B.
	Critical revision of manuscript	S.S.K.B., F.O.
Category 3	Final approval and accountability	Y.H.B., H.G., B.B.D., S.S.K.B., F.O.
Other	Supervision	Y.H.B., S.S.K.B., F.O.

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Ethical Approval: The University of Health Sciences Hamidiye Scientific Research Ethics Committee granted approval for this study (date: 11.03.2022, number: 22/159).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Marder SR, Cannon TD. Schizophrenia. N Engl J Med 2019; 318:1753-1761. [CrossRef]
2. Emul M, Kalelioglu T. Etiology of cardiovascular disease in patients with schizophrenia: Current perspectives. Neuropsychiatr Dis Treat 2015; 112493-2503. [CrossRef]
3. Bär KJ. Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relatives - a small review. Front Neurol 2015; 6:139. [CrossRef]
4. Ozsoy F, Zorlu C, Kaya S. Electrocardiographic evaluation of the ventricular arrhythmia risk in patients diagnosed with schizophrenia. Alpha Psychiatry 2021; 22:85-89.
5. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon

V. Risk factors for QTc-prolongation: Systematic review of the evidence. Int J Clin Pharm 2017; 39:16-25. [CrossRef]

6. Saadeh AM, Evans SJ, James MA, Jones JV. QTc dispersion and complex ventricular arrhythmias in untreated newly presenting hypertensive patients. J Hum Hypertens 1999; 13:665-669.
7. Ozturk HM, Erdogan M, Alsancak Y, Yarlioglues M, Duran M, Boztas MH, et al. Electrocardiographic alterations in patients consuming synthetic cannabinoids. J Psychopharmacol 2018; 32:296-301. [CrossRef]
8. Okutucu S, Aytemir K, Oto A. P-wave dispersion: What we know till now? JRSM Cardiovasc Dis 2016; 5:204800401663944.
9. Castro-Torres Y, Carmona-Puerta R, Katholi RE. Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. World J Clin Cases 2015; 3:705-720.
10. Kirlioglu Balcioglu SS, Balcioglu YH, Oncu F. Electrocardiographic markers of arrhythmogenic risk in synthetic cannabinoids users. Cannabis Cannabinoid Res 2022 Apr 29. doi: 10.1089/can.2021.0193. [Epub ahead of print].
11. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006; 47:1828-1834. [CrossRef]
12. Russo V, Rago A, Pannone B, Papa AA, Di Meo F, Mayer MC, et al. Dispersion of repolarization and beta-thalassemia major: The prognostic role of QT and JT dispersion for identifying the high-risk patients for sudden death. Eur J Haematol 2011; 86:324-331. [CrossRef]
13. Fujibayashi M, Matsumoto T, Kishida I, Kimura T, Ishii C, Ishii N, et al. Autonomic nervous system activity and psychiatric severity in schizophrenia. Psychiatry Clin Neurosci 2009; 63:538-545. [CrossRef]
14. First MB. Structured Clinical Interview for the DSM (SCID). The Encyclopedia of Clinical Psychology. Hoboken, New Jersey: John Wiley & Sons Ltd, 2015, 1-6. [CrossRef]
15. Elbir M, Alp Topbas O, Bayad S, Kocabas T, Zulkif Topak O, Cetin S, et al. Adaptation and reliability of the structured clinical interview for DSM-5-disorders - clinician version (SCID-5/CV) to the Turkish language. Turk Psikiyatr Derg 2019; 30:51-56. [Turkish] [CrossRef]
16. Warner JP, Barnes TRE, Henry JA. Electrocardiographic changes in patients receiving neuroleptic medication. Acta Psychiatr Scand 1996; 93:311-333. [CrossRef]
17. Hatta K, Takahashi T, Nakamura H, Yamashiro H, Yonezawa Y. Prolonged QT interval in acute psychotic patients. Psychiatry Res 2000; 94:279-285. [CrossRef]
18. Emul M, Dalkiran M, Coskun O, Yavuz R, Tosun M, Duran A, et al. P wave and QT changes among inpatients with schizophrenia after parenteral ziprasidone administration. Pharmacol Res 2009; 60:369-372. [CrossRef]
19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261-276. [CrossRef]
20. Kostakoglu E, Batur S, Tiryaki A, Gogus A. Reliability and validity of the Turkish version of the positive and negative syndrome scale. Turkish J Psychol 1999; 14:23-34.
21. Bazett HC. An analysis of time relations of electrocardiograms. Heart 1920; 7:353-370.
22. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994; 343:327-329. [CrossRef]
23. Alonso MAG, Lima V de AC de C, Carreira MAM de Q, Lugon JR. Reproducibility and reliability Of QTc and QTcd measurements and their relationships with left ventricular hypertrophy in hemodialysis patients. Arq Bras Cardiol 2017; 109:222-230. [CrossRef]
24. Perkiömaki JS, Koistinen MJ, Yli-mayry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. J Am Coll Cardiol 1995; 26:174-179.
25. Polcwiartek C, Atwater BD, Kragholm K, Friedman DJ, Barcella CA, Attar R, et al. Association between ECG abnormalities and fatal cardiovascular disease among patients with and without severe mental illness. J Am Heart Assoc 2021; 10:1-11.
26. Koponen H, Alaräisänen A, Saari K, Pelkonen O, Huikuri H, Raatikainen MJP, et al. Schizophrenia and sudden cardiac death - A review. Nord J Psychiatry 2008; 62:342-345. [CrossRef]
27. Ali Z, Ismail M, Nazar Z, Khan F, Khan Q, Noor S. Prevalence of QTc interval prolongation and its associated risk factors among psychiatric patients: A prospective observational study. BMC Psychiatry 2020; 20:277. [CrossRef]
28. Okayasu H, Shinozaki T, Takano Y, Sugawara N, Fujii K, Yasui-Furukori N, et al. Effects of antipsychotics on arrhythmogenic parameters in schizophrenia patients: Beyond corrected QT interval. Neuropsychiatr Dis Treat 2021; 17:239-249. [CrossRef]
29. Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing QT interval prolongation and its associated risks with antipsychotics. CNS Drugs 2011; 25:473-490. [CrossRef]
30. Fujii K, Ozeki Y, Okayasu H, Takano Y, Shinozaki T, Hori H, et al. QT is longer in drug-free patients with schizophrenia compared with age-matched healthy subjects. PLoS One 2014; 9:e98555. [CrossRef]
31. Malaspina D, Bruder G, Dalack GW, Storer S, Van Kammen M, Amador X, et al. Diminished cardiac vagal tone in schizophrenia: Associations to brain laterality and age of onset. Biol Psychiatry 1997; 41:612-617. [CrossRef]
32. Tekin A, Tanriverdi Z, Kapici Y, Guc B, Karamustafalioglu O. Comparison of frontal QRS-T angle in patients with schizophrenia and healthy volunteers. J Psychiatr Res 2022; 149:76-82. [CrossRef]
33. Salik J, Muskin PR. Consideration of the JT interval rather than the QT interval. Psychosomatics 2013; 54:502. [CrossRef]

34. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, torsades de pointes, and psychotropic medications: A 5-year update. Psychosomatics 2018; 59:105-122. [CrossRef]

35. Al-Seddik G, Hachem D, Haddad C, Hallit S, Salameh P, Nabout R, et al. Cardiovascular events in hospitalised patients with schizophrenia: A survival analysis. Int J Psychiatry Clin Pract 2019; 23:106-113. [CrossRef]

36. Ostermann S, Herbsleb M, Schulz S, Donath L, Berger S, Eisenträger D, et al. Exercise reveals the interrelation of physical fitness, inflammatory response, psychopathology, and autonomic function in patients with schizophrenia. Schizophr Bull 2013; 39:1139-1149. [CrossRef]

37. Hou PY, Hung GCL, Jhong JR, Tsai SY, Chen CC, Kuo CJ. Risk factors for sudden cardiac death among patients with schizophrenia. Schizophr Res 2015; 168:395-401. [CrossRef]