

# Investigation of the Value of T peak to T end and QTc Intervals as Electrocardiographic Arrhythmia Susceptibility Markers in Acute Ischemic Stroke

## Elektrokardiyografik Aritmiye Yatkınlık Belirteçleri Olarak T tepe - T son ve QTc Aralıklarının Akut İskemik İnmedeki Değerinin Araştırılması

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### ABSTRACT

**Introduction:** Arrhythmias are one of the most common causes of mortality in patients with acute ischemic stroke (AIS). This study aimed to investigate the relationships of arrhythmia susceptibility markers (QT, QTc, Tpe, Tpe-D, Tpe/QT, and Tpe/QTc) with the localization and volume of the ischemic area, the National Institutes of Health Stroke Scale (NIHSS) scores, and troponin levels in AIS.

**Methods:** Patients diagnosed with AIS in the emergency department in the period from 01 November 2016 to 31 March 2019 were retrospectively reviewed. Patients admitted to the emergency department with no pathological ECG findings were included. The measurements of QT, QTc, Tpe, Tpe-D, Tpe/QTc, and Tpe/QT were performed under a digital microscope. The NIHSS scores, troponin values, and the ischemic area volume based on the diffusion-weighted magnetic resonance imaging findings at the time of admission were found.

**Results:** A total of 135 patients, comprising 70 AIS patients and 65

individuals as controls, were included in the study. The male/female ratio was 73/62 and the mean age was 68.51±10.80 years. All of the ECG parameters in the AIS group and the control group were statistically significantly different between the groups except Tpe-D ( $p=0.454$ ) (For QT, QTc, Tpe, Tpe/QTc, and Tpe/QT;  $p=0.003, 0.022, <0.001, 0.001, 0.001$ ; respectively). QT, QTc, Tpe, Tpe/QTc, and Tpe/QT values were not significantly different between the groups with a NIHSS score of  $\leq 5$  and  $>5$  ( $p=0.480, 0.688, 0.663, 0.512, 0.333$ , respectively).

**Conclusions:** Arrhythmia susceptibility markers including QT, QTc, Tpe, the values of Tpe-D, Tpe/QT, and Tpe/QTc are different in AIS patients compared to the individuals in the control group; therefore, these parameters can be included among the other parameters of close cardiac monitoring.

**Keywords:** Acute ischemic stroke severity, arrhythmia susceptibility, electrocardiography, infarct volume, T peak to T end

### ÖZ

**Amaç:** Aritmiler, akut iskemik inme (Aİİ) olgularında en sık mortalite sebeplerinden biridir. Çalışmada, Aİİ'de aritmiye yatkınlık belirteçlerinin (QT, QTc, Tpe, Tpe-D, Tpe/QT ve Tpe/QTc), iskemik alan lokalizasyonu ve volümü, The National Institutes of Health Stroke Scale (NIHSS) skoru ve troponin düzeyleri arasındaki ilişkinin araştırılması amaçlandı.

**Yöntem:** 01 Kasım 2016 ve 31 Mart 2019 tarihleri arasında acil servise Aİİ tanısı konulan hastalar retrospektif olarak incelendi. Kontrol grubu için acil servise başvurup EKG'lerinde patoloji tespit edilmeyen hastalar seçildi. Dijital mikroskop altında QT, QTc, Tpe, Tpe-D, Tpe/QTc, Tpe/QT ölçümleri yapıldı. Başvurudaki NIHSS skorları, troponin değerleri ve difüzyon ağırlıklı manyetik rezonans görüntülemeleri üzerinden iskemik alan hacmi hesaplandı.

**Bulgular:** Çalışmaya 70 Aİİ ve 65 kontrol grubu olmak üzere 135 hasta dahil edildi. Erkek/kadın oranı 73/62 ve yaş ortalaması 68,51±10,80

olarak bulundu. Aİİ grubu ile kontrol grubu EKG ölçümleri açısından karşılaştırıldığında Tpe-D ( $p=0,454$ ) hariç diğer tüm parametrelerde (QT, QTc, Tpe, Tpe/QTc, Tpe/QT) istatistiksel olarak anlamlı farklılık saptandı (sırasıyla;  $p=0,003, 0,022, <0,001, <0,001, <0,001$ ). QT, QTc, Tpe, Tpe/QTc, Tpe/QT ölçümleri için NIHSS skoru 5 üzeri ve altı olan gruplar arasında anlamlı farklılık tespit edilmedi (sırasıyla;  $p=0,480, 0,688, 0,663, 0,512, 0,333$ ).

**Sonuç:** Aritmiye yatkınlık belirteçleri olan QT, QTc, Tpe, Tpe-D, Tpe/QT ve Tpe/QTc değerleri, Aİİ olgularında kontrol grubuna göre farklılık göstermektedir ve bu parametreler yakın kardiyak monitörizasyonda göz önünde bulundurulabilir.

**Anahtar Kelimeler:** Akut iskemik inme şiddeti, aritmiye yatkınlık belirteçleri, elektrokardiyografi, infarct volümü, T tepe-T son

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## INTRODUCTION

Acute ischemic stroke (AIS) is a major cause of mortality and morbidity caused by sudden discontinuation of blood flow to the cerebral arteries due to thrombotic or embolic occlusion, resulting in deterioration of neurological functions (1). Controllable and treatable cardiovascular diseases (CVD); such as hypertension, atrial fibrillation (AF), and ischemic heart disease, are the cornerstones of the etiology and treatment of AIS (2). Although CVDs can be identified by electrocardiographic (ECG) findings including pre-existing ST interval and T and U wave changes and conduction anomalies; the prognostic value of these findings in AIS continues being investigated (3).

Besides each type of CVD being a risk factor for the development of AIS, the involvement of sympathetic and parasympathetic autonomic systems in AIS can result in cardiovascular changes (4). The medulla oblongata is accepted as the cardioregulatory center, serving as the main control center of cardiac functions in the body. The nuclei in the medulla oblongata regulate the heart rate, myocardial contractility, and the dilatation and constriction of peripheral vessels. There are studies in the literature demonstrating that parasympathetic system activation due to the involvement of the anterior hypothalamus causes bradycardia; whereas, the involvement of the posterior hypothalamus causes tachycardia and extrasystoles (5, 6). The responses of the sympathetic and parasympathetic autonomic system resulting from AIS, intracranial hemorrhage, and other central nervous system pathologies can be manifested as arrhythmias and repolarization changes in ECG (7, 8). The QT interval and the T-wave are the reflections of ventricular repolarization in ECG. Measured QT interval and the corrected QT interval (QTc) values are known to be indicative of cardiac arrhythmogenicity (9). Tpeak to Tend interval (Tpe) and Tp dispersion (Tpe-D) are used as the indices of arrhythmia susceptibility (10). Furthermore, the Tpe/QT ratio is reported to predict a cardiac arrhythmia risk (11). There is a need for electrophysiological studies investigating these ECG parameters as the indicators of the potential of AIS in creating arrhythmia susceptibility in the cardiovascular system.

Detection of elevated cardiac troponin (cTn) levels in patients with AIS; in whom an acute coronary syndrome diagnosis is excluded, is described as neurogenic stunned myocardium (12-14). Although myocardial involvement is associated with a sudden elevation of catecholamine levels in patients with acute ischemia mostly involving the insular cortex; the cardiac effects of AIS have not been fully elucidated yet (2, 15). Reported in the literature, the cardiac conduction system involvement and myocardial injuries developing due to AIS but not being accounted for any pathophysiological mechanisms point out a large clinical field to be investigated scientifically.

The aim of this study was to investigate the relationship of the arrhythmia susceptibility markers derived from the calculated parameters on the ECG recordings of AIS patients to the location and volume of the ischemic area, the severity of acute ischemic stroke [The National Institutes of Health Stroke Scale (NIHSS) scores], and cTn levels as a marker of cardiac injury.

## METHODS

### Study Design and Patient Selection

The approval of the University of Health Sciences Gulhane Non-Interventional Research Ethics Committee was obtained to conduct this retrospective study (Decision no: 19/205).

A retrospective patient information review was performed on the Gulhane Training and Research Hospital's electronic patient management system (FONET®, Information Technology Incorporation, Turkey). The

patients; who applied to the emergency department in the first 24 hours after the onset of neurological symptoms and who were admitted due to a diagnosis of AIS in the period from 01 November 2016 and 31 March 2019, were retrieved and their medical records were reviewed. The patients; who applied to the emergency department due to a variety of reasons in the same time interval defined above; who underwent ECGs, and who were discharged from the emergency department with no pathological findings in the ECG were included in the control group.

The exclusion criteria were being younger than 18 years old or having the following findings in the ECG including atrial fibrillation, left bundle branch block (LBBB), right bundle branch block (RBBB), pacemaker rhythm, tachycardia (>100 bpm), bradycardia (<60 bpm), and ischemic changes. The ischemia criteria in ECG were ST-segment depression or elevation, T-wave inversions, the emergence of the U-wave, and presence of ST-elevation in aVR. Those criteria were determined to include new ST-segment elevation ( $\geq 1$  mm) or depression (>0.5 mm) and T-wave inversion ( $\geq 2$  mm) provided that these changes were observed in two consecutive leads. Furthermore; patients receiving antiarrhythmic drugs or drugs with a potential to cause parasympathomimetic, parasympatholytic, sympathomimetic, and sympatholytic side effects, and patients with electrolyte imbalance were excluded from the study.

The patients' age, gender, and comorbid diseases, and the findings at the time of admission to the emergency department including the ECG recordings, NIHSS scores to determine the stroke severity, cTn values, and anatomic location and volume of the ischemic area derived from diffusion-weighted magnetic resonance imaging (DWI) were found and recorded. Patients were divided into two groups based on the severity of AIS; one group including the patients with mild AIS (NIHSS <5) and the other including patients with moderate-severe (NIHSS  $\geq 5$ ) AIS.

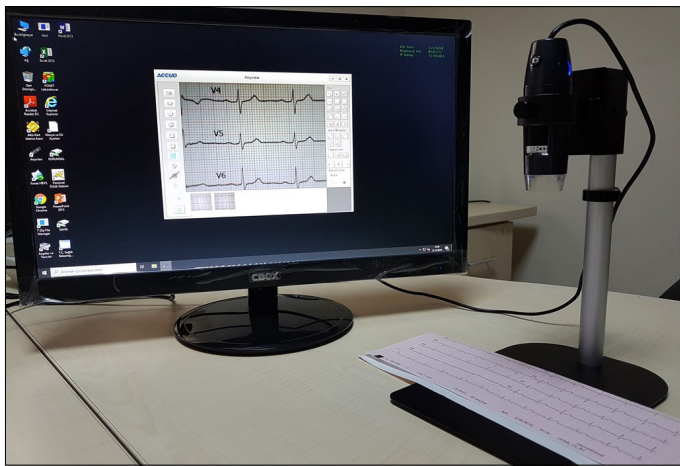
### Assessment of ECG

ECG was recorded at 10 mm/mV amplitude and at a pace of 25 mm/sec. ECG recordings were carried out using a Cardiovit AT-102 Plus device (Schiller AG, Baar, Switzerland) and MAC 2000 ECG Analysis System (General Electric, WI, USA). The ECG parameters (QT interval, RR interval, Tpe, and Tpe-D) were measured using an Accud digital microscope DM200 (Accud Co., Ltd., China) (Figure 1, 2). The ECG intervals were measured in mm and, when needed, the interval values were converted to interval times ( $\times 40$  ms). The QT interval (msn) was defined as the time from the beginning of the Q wave to the end of the T wave in DII derivation. The RR interval was defined as the time between two consecutive R-wave peaks (16). T-peak depicted the peak of the T-wave. T-end was found at the intersection of the isoelectric line and the tangent to the downslope of the T wave provided that the T-wave was completely distinct from the following U-wave or no U-wave followed. When U-waves follow T-waves, the lowest point between the U-wave and the T-wave depicted T-end (17). When the T-wave was negative or biphasic, the tangent was drawn to the lower point of the T-wave (11).

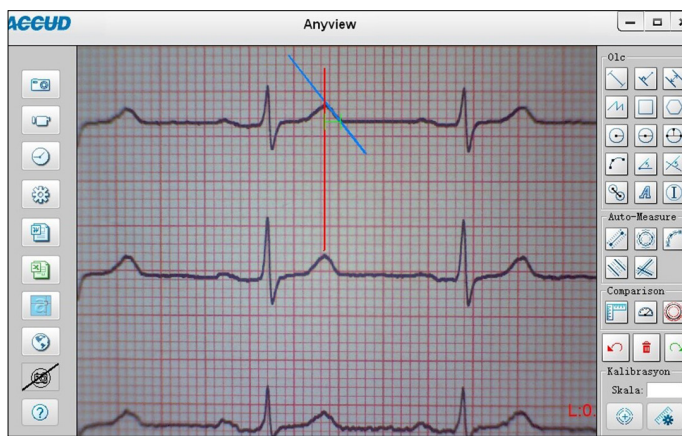
The QTc value was calculated using the QT time in Bazett's formula ( $QTc = QT/RR$ ). Tpe interval was calculated on lead V6. When it was not possible to measure it, the lead V5 was used for the calculation (18). Tpe-D was found by subtracting the minimum Tpe value from the maximum Tpe value in 12-derivation ECG. The Tpe/QT and Tpe/QTc ratios were calculated.

### Calculation of the Infarct Volume

The volume of the infarct was calculated using the classical formula,  $sABC/2$ ; commonly used in radiology practice. The  $sABC/2$  formula requires the length of three pre-defined distances in the radiological image. The lengths of these distances were traced by hand by the radiologist. After identifying the widest parts of the infarct and their



**Figure 1.** The ECG measurements were performed with a digital microscope (Accud digital microscope DM200, Accud Co. Ltd., China).



**Figure 2.** Tpe interval measurement; vertical line crossing the peak of the T wave (red line), tangential line from the downsloping T wave (blue line), Tpe interval (green dimension extension line).

diameters perpendicular to each other, defined as the anteroposterior (A) and transverse (B) diameters; the lengths of these diameters were measured on the axial image as the two longest diameters of the area of the infarct. Then, the length of the craniocaudal axis (C) was measured. Also, the number of the slices from the start to the end of the infarct area was found and this number was multiplied by 3 mm, which depicted the slice thickness. All lengths were measured in millimeters and all volumes were recorded in milliliters.

Troponin I (0–14 ng/mL) and high-sensitivity troponin I (0–17.5 pg/mL) were tested using the Beckman Coulter Access 2 Immunoassay System device (CA, USA).

**Power analysis:** A sample size of 120 patients comprising 60 individuals in each group was calculated at an alpha value of 0.05, 80% power, an enrollment ratio of 1, QTc of 407.2±23.30 msec for group 1 (control group), and QTc of 419.1 msec for group 2 (AIS patients) (19).

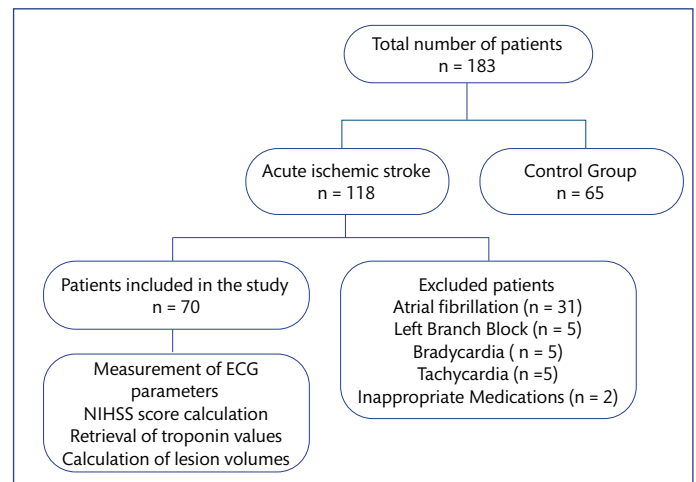
### Statistical Analysis

Statistical analyses were performed using the SPSS 18.0 software. The categorical variables were summarized in frequencies and percentages. The continuous variables were summarized in mean and standard deviation. The Chi-square test was used for comparing the categorical data. The Kolmogorov-Smirnov test was used for determining whether the data were distributed normally. The Student's t-test was used for the pairwise comparison of groups with normal distribution; whereas, the

Mann-Whitney U test was used for the pairwise comparison of groups with non-normal distribution. The correlation between the continuous variables was analyzed with the Spearman test. The statistical significance was evaluated at a *p*-value of 0.05.

## RESULTS

A total of 118 patients diagnosed with AIS were found and 48 of them were excluded from the study. A total of 135 patients (70 AIS patients and 65 patients for the control group) were included in the study (Figure 3). In the AIS group, 61.4% (*n*=43) of the patients were male and 38.6% (*n*=27) were female, and the mean age was 69.06±11.50 years. The comorbid diseases in the AIS group were hypertension in 24 patients (34.28%), diabetes mellitus in 21 (30.00%), coronary artery disease in 7 (10.00%), cardiac failure in 3 (4.28%), and chronic obstructive pulmonary disease in 3 (4.28%) patients. Because the lesions were micro-infarcts in 33 patients in the AIS group, the volume of the infarct area could not be measured. The median volume was 1.91 (Q1:0.41, Q3:29.68) in 37 patients; whose lesions could be measured. Acute myocardial injury (M-inj) was detected in 15 patients (31.91%) in the AIS group based on cTn values. Regarding the severity of the ischemic stroke, 44 patients (65.67%) were allocated to the mild (NIHSS <5) and 23 patients (34.33%) were allocated to the moderate-severe (NIHSS ≥5) AIS groups.



**Figure 3.** Study flowchart.

Apart from Tpe-D (*p*=0.454), the values of all ECG parameters measured (QT, QTc, Tpe, Tpe/QTc, Tpe/QT) were statistically significantly different between AIS and control groups (*p*=0.003, 0.022, <0.001, 0.001, 0.001; respectively) (Table 1).

A comparison of the left-sided lesion patients to the right-sided patients within the AIS group revealed no differences in the values of the ECG parameters between the groups (*p*=0.318, 0.646, 0.790, 0.770, 0.794, 0.696; respectively) (Table 2). The cTn values at admission were not different according to whether the lesion was on the left or right (*p*=0.367; Student's t-test). There were no differences in the NIHSS scores in the patients having right hemisphere lesions compared to the patients with lesions in the left hemisphere (*p*=0.097; Mann-Whitney U test).

There were no significant differences in the measured values of QT, QTc, Tpe, Tpe-D, Tpe/QTc, and Tpe/QT between the cortical and subcortical lesion patients in the AIS group (*p*=0.542, 0.483, 0.242, 0.136, 0.387, 0.187; respectively). The cTn values of the patients at admission were not different by the lesion being cortical or subcortical (*p*=0.100) (Table 3).

Among the ECG parameters measured; there was a significant difference in the Tpe-D values between those who scored ≥5 and those who scored

**Table 1.** Comparison of the demographic data and ECG measurements between the acute ischemic stroke group and the control group.

Parameter	AIS group Mean ± SD	Control Group Mean ± SD	p
Age (year)	69.86±11.50	67.06±9.88	0.131*
Sex (male/female)	43/27	30/35	0.075**
QT (ms)	392.74±38.96	375.52±26.31	0.003*
QTc (ms)	441.57±36.60	429.20±24.57	0.022*
Tpe (ms)	79.56±15.00	60.65±13.57	<0.001*
Tpe-D (ms)	26.65±10.96	24.95±14.91	0.454*
Tpe/QTc	0.18±0.03	0.14±0.03	<0.001*
Tpe/QT	0.20±0.04	0.16±0.03	<0.001***

Student's t-test\*

Chi-square test\*\*

Mann-Whitney U test\*\*\*

AIS, acute ischemic stroke; QTc, corrected QT interval; SD, standard deviation; Tpe, T peak to T end interval; Tpe-D, T peak to T end dispersion.

**Table 2.** Comparison of the ECG measurements, troponin levels, and infarct volumes according to whether the lesions were in the right or left hemisphere.

Parameter	Right Hemisphere Group Mean ± SD (n)	Left Hemisphere Group Mean ± SD (n)	p
Age (year)	73.84±11.46 (19)	67.63±11.08 (24)	0.079*
QT (ms)	385.21±40.56 (19)	397.20±37.06 (24)	0.318*
QTc (ms)	442.57±42.61 (19)	437.45±29.79 (24)	0.646*
Tpe (ms)	78.14±15.83 (19)	76.87±15.18 (24)	0.790*
Tpe-D (ms)	27.58±13.55 (19)	26.55±9.63 (24)	0.770*
Tpe/QTc	0.18±0.04 (19)	0.17±0.03 (24)	0.794*
Tpe/QT	0.20±0.05 (19)	0.19±0.04 (24)	0.696**
Troponin I (positive/negative)	4/10	5/14	0.595***
NIHSS (mild/moderate-severe)	9/9	16/7	0.171***
Infarct volume (mL)	42.74±49.37 (16)	7.64±14.02 (19)	0.010**

**Table 3.** Comparison of the ECG measurements, troponin levels, and infarct volumes according to whether the lesions were cortical or subcortical.

Parameter	Cortical Mean ± SD (n)	Subcortical Mean ± SD (n)	p
Age (year)	71.56±7.63 (18)	70.63±13.80 (27)	0.797*
QT (ms)	390.77±41.75 (18)	398.51±41.12 (27)	0.542*
QTc (ms)	446.50±37.68 (18)	438.66±35.49 (27)	0.483*
Tpe (ms)	80.55±13.13 (18)	75.05±16.49 (27)	0.242*
Tpe-D (ms)	31.06±12.96 (18)	25.81±10.17 (27)	0.136*
Tpe/QTc	0.18±0.04 (18)	0.17±0.04 (27)	0.387*
Tpe/QT	0.20±0.04 (18)	0.18±0.04 (27)	0.187**
Troponin I (positive/negative)	6/9	3/17	0.100***
NIHSS (mild/moderate-severe)	9/7	18/8	0.300***
Infarct volume (mL)	64.28±42.84 (12)	2.59±4.81 (25)	0.001**

<5 in NIHSS in the AIS group ( $p=0.032$ ). The values of QT, QTc, Tpe, Tpe/QTc, and Tpe/QT were not statistically significantly different between those who scored  $\geq 5$  and those who scored <5 in NIHSS in the AIS group ( $p=0.480, 0.688, 0.663, 0.512, 0.333$ ; respectively) (Table 4).

The correlation coefficients between the values of QTc, Tpe, Tpe-D, Tpe/QT, and Tpe/QTc and the cTn level at admission in the AIS group were 0.212, 0.028, 0.192, -0.004, and -0.002, respectively. The correlation coefficients between infarct volumes and the values of QTc, Tpe, Tpe-D, Tpe/QT, and Tpe/QTc were 0.154, 0.101, 0.071, 0.114, and 0.062, respectively (Table 5).

**Table 4.** Comparison of the ECG measurements and infarct volumes according to the severity of acute ischemic stroke.

Parameter	Mild Stroke (NIHSS Score <5) Mean ± SD (n)	Moderate and Severe Stroke (NIHSS Score $\geq 5$ ) Mean ± SD (n)	p
Age (year)	68.37±10.85 (43)	75.05±10.52 (22)	0.021*
QT (ms)	389.84±35.67 (43)	396.91±43.90 (22)	0.480*
QTc (ms)	441.88±36.46 (43)	438.04±37.97 (22)	0.688*
Tpe (ms)	78.85±16.13 (43)	81.45±13.53 (22)	0.512*
Tpe-D (ms)	28.92±12.04 (43)	22.80±7.94 (22)	0.032*
Tpe/QTc	0.17±0.03 (43)	0.18±0.04 (22)	0.333*
Tpe/QT	0.20±0.04 (43)	0.21±0.04 (22)	0.663**
Infarct volume (mL)	14.99±27.01 (24)	36.64±50.71 (13)	0.176**
Troponin I (positive/negative)	8/20	7/9	0.340***

\*Student's t-test.

\*\*Mann-Whitney U test.

\*\*\*Chi-Square test.

NIHSS, The National Institutes of Health Stroke Scale; QTc, corrected QT interval; SD, standard deviation; Tpe, T peak to T end interval; Tpe-D, T peak to T end dispersion.

**Table 5.** Correlation analysis results between the ECG measurements, troponin levels, infarct volume, and the severity of acute ischemic stroke.

	n	Correlation Coefficient*	p*
<b>Troponin value</b>			
QTc	47	0.212	0.152
Tpe	47	0.028	0.854
Tpe-D	47	0.192	0.196
Tpe/QT	47	-0.004	0.978
Tpe/QTc	47	-0.002	0.989
<b>Infarct volume</b>			
QTc	37	0.154	0.364
Tpe	37	0.101	0.554
Tpe-D	37	0.071	0.674
Tpe/QT	37	0.114	0.500
Tpe/QTc	37	0.062	0.715
<b>NIHSS Score</b>			
QTc	67	-0.081	0.517
Tpe	67	0.181	0.144
Tpe-D	67	-0.091	0.462
Tpe/QT	67	0.142	0.253
Tpe/QTc	67	0.222	0.071

\*Spearman's rho correlation analysis

n, frequency; NIHSS, The National Institutes of Health Stroke Scale; QTc, corrected QT interval; SD, standard deviation; Tpe, T peak to T end interval; Tpe-D, T peak to T end dispersion.

## DISCUSSION

Repolarization and ischemia-like ECG changes observed in the acute phase of ischemic stroke may evoke clinical dilemmas in the diagnosis, follow-up, and treatment of the patients. ECG changes can reflect a direct outcome of the acute phase of stroke regardless of a CVD or they may coincide with AF or AIS developing after acute coronary syndrome (20). The results of our study are of primary importance because they demonstrate the non-cardiac manifestations of acute-phase AIS in ECG of the patients without findings of M-inj and rhythm and conduction disturbances. Although studies are available in the literature investigating ECG changes in AIS patients; this is the first study examining the Tpe, Tpe-D, Tpe/QTc, and Tpe/QT values. The results of our study showed a significant increase in the values of the arrhythmia susceptibility markers; including QT, QTc, Tpe, Tpe/QT, and Tpe/QTc in the AIS group compared to the control group. ECG changes are common in AIS patients and QTc prolongation is one of the most common ECG findings (3). Kaya et al. investigated the prognostic value of ECG changes in AIS patients and reported that QTc prolongation was the most common ECG abnormality in the first 24 hours (7). They reported no significant differences in QTc parameter findings by the right and left hemisphere ischemic lesions and the cortical and subcortical ischemic lesions. Although QTc was found to be longer in AIS patients in our study, the lack of any differences in QTc between the right and left hemisphere lesions is similar to the results of Kaya et al. study. However, there are also studies in the literature reporting that QTc is longer in the lesions of the right hemisphere compared to the left (21, 22). We considered that this difference occurred due to the inclusion of acute hemorrhagic stroke patients into respective studies and the precise microscopic measurements performed in these studies. There are no studies investigating the value of QT and QTc parameters in the literature by performing a subgroup analysis according to AIS severity and ischemic area volume. We consider that the lack of relationship of these ECG parameters to the ischemic area volume or NIHSS scores in our study provides a unique set of results.

Tpe is the measure of the transmural dispersion of the left ventricular repolarization (23, 24). The relationship between Tpe and ventricular arrhythmias is explained with the predisposition of the subendocardial M-cells (Mason-Pfizer mid-myocardial Moe cells) to ventricular arrhythmia due to the high rate of late sodium-calcium exchange current and the weakness of slowly-activating delayed rectifier currents in these cells (25). M-inj may develop resulting from the imbalance between the sympathetic and parasympathetic systems and catecholamine discharge in AIS (26). For these reasons, a long Tpe depicts a developing susceptibility to ventricular arrhythmia. It has been reported that Tpe can be used as a predictor of sudden cardiac death in patients with normal or unmeasurable QTc intervals (25). The higher Tpe values in the AIS group compared to the control group in our study support the need for close cardiac monitoring in AIS patients. The Tpe/QT ratio indicates the risk of arrhythmogenicity for long QT syndrome (27). In this study, a significant increase was detected in the Tpe/QT and Tpe/QTc values in the AIS group compared to the control group. Based on these findings, it was considered that the increase in the Tpe parameter was higher compared to the increase in QT and QTc in AIS patients. To the best of our knowledge, this is the first study; which investigated the measured values of Tpe, Tpe/QT, and Tpe/QTc in AIS patients, comparing the findings with the control group. In this respect, it was concluded that the Tpe parameter might be a more valuable marker for arrhythmia susceptibility in AIS patients.

Kaya et al. reported that the increase in cTn values was the highest in cerebellar infarcts compared to cerebral and brain stem lesions and that the cTn levels were significantly higher in the right cerebral hemisphere lesions compared to the left cerebral hemisphere infarcts (7). However, our study did not find a statistical difference in the cTn levels between the subgroups of patients with right cerebral hemisphere lesions and the left

cerebral hemisphere lesions in the AIS group. In order to be able to argue that M-inj is present in the absence of coronary ischemia findings in the ECG, at least the cTn levels higher than the upper level of the laboratory reference values should be evaluated. A dilemma is created when the laboratory values in the normal range are included in the comparison of cTn levels between the subgroups or between the patient and control groups. Therefore, in our study, the cTn levels were evaluated as positive or negative based on the upper limit of the laboratory reference interval. The patients with cTn levels higher than the upper limit of the laboratory reference interval were evaluated as M-inj positive. Thereby, the patients with M-inj were clearly defined.

AIS itself is a stressor that increases the catecholamine levels. Elevated cTn levels in AIS remain controversial but underlying cardiac disturbances including AF, LBBB, RBBB, and conduction and rhythm disturbances accompanying AIS impair coronary artery perfusion leading to M-inj (28). Compared to the control group; the high values of arrhythmia susceptibility markers; including QT, QTc, Tpe, Tpe-D, Tpe/QTc, and Tpe/QT observed in the AIS patients with no diagnosis of AF, LBBB, RBBB, bradycardia, tachycardia, and ischemic ECG changes, elucidate the manifestations of AIS in the electrical activity of the cardiovascular system solely. We consider that the lack of difference in the cTn levels in the subgroup analysis might be due to the excluded ECG findings. Therefore, our study is of importance for the evaluation of AIS patients for cardiac arrhythmogenicity as it identified significant changes in the arrhythmia susceptibility markers between subgroups of patients with no M-inj.

Millis et al. found different NIHSS scores between the patients with left hemisphere lesions and with right hemisphere lesions (29). In our study, a statistically significant difference was not found in the NIHSS scores when the patient group having right hemisphere lesions was compared to the patient group with left hemisphere lesions and when the patient group with cortical lesions was compared to the patient group with subcortical lesions. Ozturk et al reported that the Tpe value was lower in AIS patients with low NIHSS scores, concluding that Tpe values can be a marker for stroke severity. (30).

In our study, it was found that the Tpe values did not differ by the NIHSS scores between the subgroups and that NIHSS scores did not correlate with the Tpe values; however, it was found out that the Tpe-D values were different between the subgroups made according to the NIHSS scores. Although there was not a difference between the AIS and control groups in Tpe-D that reflected the dispersion of Tpe, the observation of Tpe-D narrowing in the 12-lead ECG of the high score NIHSS patients suggest that Tpe should be evaluated in combination with Tpe-D rather than being evaluated alone in AIS patients.

The correlation analysis of the lesion volume and ECG parameters of the study in AIS patients did not reveal any statistically significant correlations. This is an important conclusion since it demonstrates that arrhythmia susceptibility is independent of the lesion diameter; and therefore, there may be a risk of arrhythmia even in small lesions.

### Study Limitations

The ECGs examined in this study represent a cross-sectional evaluation of acute-phase AIS patients in the emergency department. Long-term projection of the study data cannot be assessed due to the lack of follow-up ECGs of the patients after their admission to the hospital. The other limitation of the study is its single-center and retrospective design.

## CONCLUSION

Cardiologists, neurologists, and emergency department physicians focus on the cardiac rhythm, heart rate, conduction disturbances, ST-elevation,

ST-depression, QT prolongation, pathological Q waves, hyperacute T-waves, and T-wave negativity when they evaluate the heart with ECG. However, arrhythmia susceptibility markers in AIS include QT, QTc, Tpe, Tpe-D, Tpe/QT, and Tpe/QTc values; which can appropriately contribute to clinical practice and future electrophysiological studies. These markers may contribute to lowering the mortality and morbidity rates of AIS patients because they are arrhythmia markers regardless of the myocardial injury.

**Ethics Committee Approval:** The approval of the University of Health Sciences Gulhane Non-Interventional Research Ethics Committee was obtained to conduct this retrospective study (Decision no: 19/205).

**Peer-review:** Externally peer-reviewed.

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