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A Novel Electrocardiographic Marker for Predicting Total Mortality in Ischemic Stroke: Frontal QRS-T Angle

İskemik İnmede Toplam Mortaliteyi Tahmin Etmeye Yönelik Yeni Bir Elektrokardiyografik Belirteç: Frontal QRS-T Açısı

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: This study aimed to investigate the relationship between mortality and the frontal QRS-T angle (FQRS-TA), obtained by calculating the absolute difference between the QRS and T waves electrocardiographically (ECG), in patients diagnosed with ischemic stroke (IS).

Methods: This research is a retrospective and cross-sectional study. The diagnosis of IS was confirmed through brain imaging and physical examination. Patients with sinus rhythm were included in the study. The FQRS-TA was measured by calculating the absolute difference between the QRS-axis and the T-axis, as automatically measured on the ECG. Patients were divided into two groups: those who died within five years and those who survived, and the groups were compared.

Results: A total of 322 patients with IS were included in the study, of whom 290 survived, and 32 died. Age, creatinine level, PR interval, QRS duration, corrected QT (cQT) value, and FQRS-TA value were found to be higher in the deceased group. Cox regression analyses were performed to examine the association between predictors of stroke-related mortality. Age [hazard ratio (HR): 1.091, 95% (1.045-1.140), $P < 0.001$], high-density lipoprotein (HDL) [HR: 0.914, 95% (0.875-0.955), $P < 0.001$], and FQRS-TA [odds ratio (OR): 1.011, 95% (1.003-1.019), $P = 0.007$] were associated with mortality. A FQRS-TA of 68 degrees or higher was associated with cumulative mortality in the Kaplan-Meier survival analysis (log rank [Mantel-Cox] test: $P = 0.001$).

Conclusion: In this study, increased FQRS-TA was found to be associated with mortality in patients with IS. ECG parameters are simple and time-efficient measurements that can provide important prognostic information. To the best of our knowledge, this research is the first study to examine the relationship between FQRS-TA and mortality in patients with IS.

Keywords: Electrocardiography, frontal QRS-T angle, mortality, stroke

ÖZET

Amaç: Bu çalışmada, iskemik inme (İİ) tanısı almış hastalarda, elektrokardiyografi (EKG) ile QRS ve T dalgalarının mutlak farkı hesaplanarak elde edilen frontal QRS-T açısı (FQRS-TA) ile mortalite arasındaki ilişkinin araştırılması amaçlanmıştır.

Yöntem: Araştırma retrospektif ve kesitsel bir çalışmadır. İS tanısı beyin görüntüleri ve fizik muayene ile doğrulandı. Çalışmaya sinüs ritmi olan hastalar dahil edildi. Frontal QRS-T açısı (FQRS-TA), EKG'de otomatik olarak ölçülen QRS ekseni ile T ekseni arasındaki mutlak fark hesaplanarak ölçüldü. Hastalar 5 yıl içinde ölenler ve hayatta kalanlar olmak üzere iki gruba ayrılarak karşılaştırıldı.

Bulgular: Çalışmaya 290'ı hayatta kalan, 32'si ölen toplam 322 İS dahil edildi. Yaş, kreatinin düzeyi, PR aralığı, QRS süresi, cQT değeri ve FQRS-TA değeri ölüm grubunda daha yüksek bulundu. İnmeye bağlı mortalitenin öngördürücüleri arasındaki ilişkiyi incelemek amacıyla Cox regresyon analizleri yapıldı. Yaş [HR: 1,091, %95 (1,045-1,140), $P < 0,001$], HDL [HR: 0,914, %95 (0,875-0,955), $P < 0,001$] ve FQRS-TA [OR: 1,011, %95 (1,003)). -1,019) $P = 0,007$] mortalite ile ilişkiliydi. Kaplan-Meier hayatta kalma analizinde 68 derece veya üzeri bir FQRS-TA kümülatif mortalite ile ilişkilendirildi (log sıralaması [Mantel-Cox]: $P = 0,001$).

Sonuç: Çalışmamızda İS hastalarında FQRS-TA artışının mortalite ile ilişkili olduğunu bulduk. EKG parametreleri basit ve zaman almayan ölçümlerdir ve hastanın prognozu hakkında önemli bilgiler sağlayabilir. Şu ana kadarki bilgilerimize göre bu araştırma FQRS-TA ve İS hastalarında mortaliteyi araştıran ilk çalışmadır.

Anahtar Kelimeler: Elektrokardiyografi, frontal QRS-T açısı, mortalite, inme

Songül Usalp

Bayram Bağırtan

Department of Cardiology, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, İstanbul, Türkiye

Corresponding author:
Songül Usalp
✉ dr.songulusalp@hotmail.com

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Ischemic stroke (IS) is one of the significant and undesirable complications of cardiovascular diseases[1,2]. It can range from transient ischemic attack to severe brain damage. The five-year cumulative mortality rate of IS varies between 1% and 7%.[2] Diabetes mellitus (DM), hypertension (HT), smoking, and atherosclerotic cardiovascular diseases are the leading causes of IS. Factors contributing to ischemic stroke mortality are still under investigation. In stroke patients, increased atherosclerosis and cardiac fibrosis due to advanced age may contribute to mortality by causing changes in the cardiac conduction axis. The simplest method to detect changes in cardiac electrical impulses is through electrocardiographic (ECG) evaluation. In recent years, one of the ECG parameters that has gained attention and has been associated with mortality is the frontal QRS-T angle (FQRS-TA).

The FQRS-TA represents the difference between the linear vector angles of ventricular depolarization and repolarization[3]. Two methods are used to measure this difference. In practice, frontal plane QRS-TA values are frequently used because they are easier to calculate.[3,4] However, there is no definitive cut-off value for FQRS-TA associated with increased mortality. The heterogeneity of the patient groups included in the study may partly explain the variability in findings. Studies have demonstrated that an increase in the FQRS-TA is associated with increased mortality in conditions such as hypertension, coronary artery disease, and diabetic cardiovascular autonomic neuropathy.[3,4] It has also been reported that the frontal QRS-T angle can predict both arrhythmias and mortality.[3,4]

To the best of our knowledge, previous studies have not explored the relationship between FQRS-TA and mortality in patients with IS. In this study, clinical and electrocardiographic mortality determinants were investigated in patients previously diagnosed with ischemic stroke over an average follow-up period of five years. We aimed to examine the relationship between arrhythmia parameters, such as FQRS-TA, and mortality in patients with ischemic stroke.

Materials and Methods

This research is a retrospective and cross-sectional study. Patients admitted to our central hospital between 2017 and 2018, who were previously diagnosed or newly diagnosed with IS,[2] had an approximate follow-up period of five years, were hospitalized, and were thoroughly evaluated by a cardiologist, were included in the study. The average follow-up period for the patients was approximately 1,812 days. Approval for the study was obtained from the Istanbul Health Sciences University Sancaktepe City Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2021/197, Date: 29.09.2021), and the study adhered to the principles of the Declaration of Helsinki.

ABBREVIATIONS

AV	Atrioventricular
CT	Computed tomography
DM	Diabetes mellitus
ECG	Electrocardiography
FQRS-TA	Frontal QRS-T angle
IS	Ischemic stroke
MRI	Magnetic resonance imaging

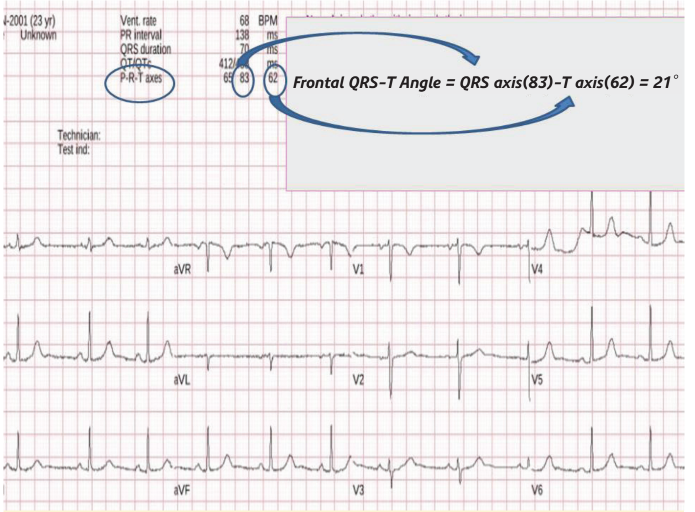

Figure 1. Illustration of electrocardiographic measurements for calculating the frontal QRS-T angle.

For the diagnosis of IS, patients underwent brain computed tomography (CT) and brain magnetic resonance imaging (MRI). The diagnosis of IS was confirmed based on brain imaging findings. Other causes of stroke, including brain hemorrhage, were excluded through imaging methods. Additionally, carotid artery ultrasonography and carotid artery CT angiography were performed on all patients. The diagnosis of acute IS was made following international guideline recommendations.[2] At the initial admission, patients underwent ECG, echocardiography, 24-hour rhythm Holter recordings, and blood tests, all of which were completed within 48 hours. The ECG was recorded in 12 leads with the patient in the supine position (Firstmed, ECG-1200G). Only patients with sinus rhythm were included in the study. The FQRS-TA was measured by calculating the absolute difference between the QRS-axis and the T-axis, as automatically measured on the ECG (Figure 1).[5]

The PR interval was measured as the time from the beginning of the P wave to the beginning of the QRS complex, reflecting conduction through the atrioventricular (AV) node. QRS duration was defined as the time from the beginning of the Q wave to the end of the S wave. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, and the corrected QT interval (cQT) was calculated by adjusting the QT interval according to heart rate.

Echocardiographic evaluations were performed with the patient in the left lateral decubitus position. Images and measurements were obtained using a commercial echocardiography device (Toshiba, Aplio i900, Canon Medical Systems USA, Inc.). The patient's ejection fraction and heart valve insufficiency were assessed during echocardiography. The ejection fraction was calculated using the Simpson method.[6]

Routine blood tests, including assessments of serum glucose, cholesterol, renal and hepatic function, and thyroid hormones, were performed after an 8-hour fasting period.

Those with advanced heart failure, ischemic heart disease, age under 18 years, hereditary or acquired coagulopathy conditions, atrial or ventricular arrhythmias, advanced heart valve disease and/or those undergoing surgery, severe liver or kidney failure, malignancy, intracranial hemorrhage, epilepsy, or carotid artery stenosis exceeding 50% were excluded from the study.

Patients with IS were divided into two groups: those who died within a five-year follow-up period and those who survived, and these groups were compared.

Statistical Analysis

All statistical analyses and calculations were performed using the SPSS statistical package, version 20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied to assess whether the data followed a normal distribution. FQRS-TA values that did not follow a normal distribution were analyzed using the Mann-Whitney U Test (median [min-max]). Categorical variables were expressed as frequencies and percentages (analyzed using Pearson's chi-square test), and continuous variables were presented as mean ± standard deviation (analyzed using Student's t-test).

Univariable and multivariable logistic regression analyses were performed to identify independent risk factors in stroke patients. Receiver operating characteristic (ROC) curve analyses were used to determine the predictive value of FQRS-TA, identified as an independent risk factor, for distinguishing between deceased and surviving patients.

The follow-up period was defined as the interval from the date of initial diagnosis to the date of the last recorded patient evaluation.

To determine the five-year follow-up relationship between the predictive value of the FQRS-TA and mortality, Cox regression analyses were performed, with hazard ratios (HR) and confidence interval (CI) values reported in both univariate and multivariate analyses. Kaplan-Meier survival analyses stratified by FQRS-TA were used to estimate the cumulative risk of death over approximately five years of follow-up.

In all analyses, *P*-values below 0.05 were considered statistically significant.

Results

A total of 322 individuals were included in the study, of whom 290 survived and 32 died due to ischemic stroke.

In the deceased group, the following variables were significantly higher: age (63.7 ± 12.5 vs. 74.7 ± 8.5 years, *P* < 0.001), serum creatinine level (0.9 ± 0.3 vs. 1.1 ± 0.4, *P* = 0.026), PR interval (157.4 ± 27.2 vs. 174.3 ± 38.3, P = 0.003), QRS duration (97.0 ± 21.8 vs. 108.7 ± 14.4, *P* = 0.006), cQT value (442.3 ± 44.1 vs. 468.6 ± 33.7, *P* = 0.002), and FQRS-TA value (57 [52-62] vs. 93 [76-111], *P* < 0.001) (Table 1).

Table 1. Comparison of Ischemic Stroke Survival and Deceased Groups in Terms of Demographic, Clinical, and Electrocardiographic Characteristics

Variables	Survival Group (n = 290)	Deceased Group (n = 32)	*P*
Age, years	63.7 ± 12.5	74.7 ± 8.5	**<0.001**
Sex, male	183 (63.1)	15 (46.8)	0.246
Hypertension, n,%	199 (68.6)	20 (62.5)	0.263
Diabetes mellitus, n,%	137 (47.2)	11 (34.8)	0.467
Smoking, n,%	67 (23.1)	6 (18.6)	0.567
Heart failure, n,%	18 (6.2)	3 (9.3)	0.058
Ejection fraction, %	58.8 ± 4.9	55 ± 4.2	0.643
Carotid artery disease, n,%	20 (5.9)	8 (4.3)	0.075
Glucose, mg/dL	135.8 ± 58.3	138.5 ± 78.3	0.850
HgbA1c,%	7.1 ± 2.1	6.5 ± 1.7	0.917
Creatinine, mg/dL	0.9 ± 0.3	1.1 ± 0.4	**0.026**
eGFR, mL/min/1.73 m^2	81.7 ± 20.2	69.1 ± 21.0	**0.002**
Total cholesterol, mg/dL	181.2 ± 43.8	179.1 ± 70.2	0.856
Low-density lipoprotein, mg/dL	109.2 ± 36.2	115.1 ± 50.6	0.446
High-density lipoprotein, mg/dL	42.6 ± 13.9	33.5 ± 7.5	**0.001**
Triglycerides, mg/dL	162.1 ± 81.6	151.1 ± 112.1	0.508
Thyroid-stimulating hormone, mIU/L	2.2 ± 1.3	2.4 ± 1.4	0.346
Electrocardiographic features			
Heart rate, bpm	76.1 ± 13.7	79.4 ± 12.2	0.226
P wave duration, ms	107.6 ± 13.7	109.9 ± 22.0	0.599
PR interval, ms	157.4 ± 27.2	174.3 ± 38.3	**0.003**
QRS duration, ms	97.0 ± 21.8	108.7 ± 14.4	**0.006**
QT interval, ms	399.8 ± 43.2	468.5 ± 33.5	0.085
cQTinterval, ms	442.3 ± 44.1	468.6 ± 33.7	**0.002**
Frontal QRS-T Angle*	57 (52-62)	93 (76-111)	**<0.001**

eGFR, Estimated Glomerular Filtration Rate; HgbA1c, Hemoglobin A1c. *Mann-Whitney U Test (median [min-max]).

Table 2. Univariable and Multivariable Logistic Regression Analyses for Ischemic Stroke-Independent Risk Factors

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age, years	1.078 (1.044-1.114)	**<0.001**	**1.086 (1.054-1.116)**	**<0.001**
Creatinine	1.868 (0.943-3.699)	0.073	0.660 (0.138-3.149)	0.602
eGFR	0.976 (0.960-0.994)	**0.008**	1.010 (0.968-1.053)	0.659
HDL	0.916 (0.874-0.959)	**<0.001**	0.866 (0.813-0.924)	**<0.001**
PR interval	1.020 (1.008-1.032)	**0.001**	1.019 (1.003-1.036)	**0.023**
QRS duration	1.021 (1.008-1.035)	**0.002**	1.020 (0.996-1.045)	0.103
cQT interval	1.017 (1.007-1.022)	**0.001**	1.016 (1.000-1.032)	0.053
Frontal QRS-T A	1.015 (1.008-1.022)	**<0.001**	1.017 (1.007-1.027)	**0.001**

eGFR, Estimated Glomerular Filtration Rate; HDL, High-Density Lipoprotein; OR, Odds Ratio; CI, Confidence Interval.

Table 3. Assessment of Predictive Parameters for Mortality in Ischemic Stroke Using Cox Regression Analysis

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age, years	1.072 (1.040-1.104)	**<0.001**	1.091 (1.045-1.140)	**<0.001**
HDL	0.932 (0.894-0.972)	**0.001**	0.914 (0.875-0.955)	**<0.001**
PR interval	1.016 (1.005-1.027)	**0.005**	1.094 (0.993-1.015)	0.482
Frontal QRS-T A	1.012 (1.005-1.018)	**<0.001**	1.011 (1.003-1.019)	**0.007**

HDL, High-Density Lipoprotein; HR, Hazard Ratio; CI, Confidence Interval.

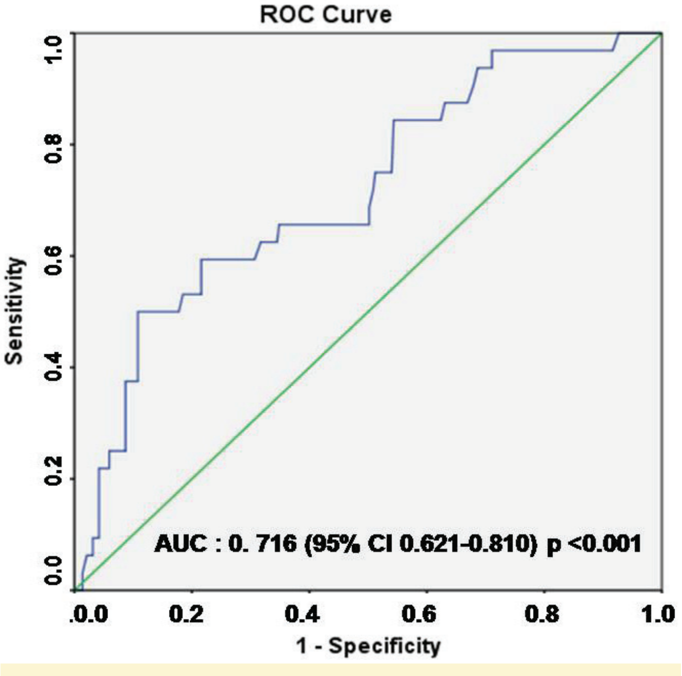

Figure 2. Receiver operating characteristic curve for predicting ischemic stroke survival. The predictive optimal cut-off value for the frontal QRS-T angle was determined to be 67.5 degrees, with a sensitivity of 70.4% and specificity of 67.8%. The area under the curve was 0.716 (95% CI: 0.621-0.810, P < 0.001).

In contrast, estimated glomerular filtration rate (eGFR) (81.7 ± 20.2 vs. 69.1 ± 21.0, *P* = 0.002) and high-density cholesterol (HDL) levels (42.6 ± 13.9 vs. 33.5 ± 7.5, *P* < 0.001) were higher in the surviving patients (Table 1).

Multivariable regression analyses identified the following as independent risk factors between surviving and deceased patients: age [OR: 1.086, 95% (1.054-1.116), *P* < 0.001], HDL [OR: 0.866, 95% (0.813-0.924), *P* < 0.001], PR interval [OR: 1.019, 95% (1.003-1.036), *P* = 0.023], and FQRS-TA [OR: 1.017, 95% (1.007-1.027), *P* < 0.001] (Table 2).

ROC curves for detecting survival in patients with IS showed that the predictive optimal cut-off for the FQRS-TA was 67.5 degrees, with a sensitivity of 70.4%, a specificity of 67.8%, and an area under the curve of 0.716 (95% CI: 0.621-0.810, *P* < 0.001) (Figure 2).

Cox regression analyses were performed to examine predictors of stroke-related mortality. Age [HR: 1.091, 95% (1.045-1.140), *P* < 0.001], HDL [HR: 0.914, 95% (0.875-0.955), *P* < 0.001], and FQRS-TA [OR: 1.011, 95% (1.003-1.019), *P* = 0.007] were associated with increased mortality (Table 3). A FQRS-TA value of 68 degrees or higher was associated with cumulative mortality in Kaplan-Meier survival analysis (log rank [Mantel-Cox] test: *P* = 0.001) (Table 4, Figure 3).

Table 4. Kaplan-Meier Survival Analysis Stratified by Frontal QRS-T Angle and Ischemic Stroke Mortality Over a 5-Year Follow-up

	Mean Survival Time		Median Survival Time	
	95% Confidence Interval		95% Confidence Interval	
	Estimate	Lower - Upper Bound	Estimate	Lower - Upper Bound
Frontal QRS-T Angle <68	55.687	53.846-57.511		
Frontal QRS-T Angle ≥68	43.683	38.410-48.056	48.000	40.526-55.474
Overall	50.845	47.452-54.237	58	

Overall comparison: Log-Rank (Mantel-Cox), *P* = 0.001.

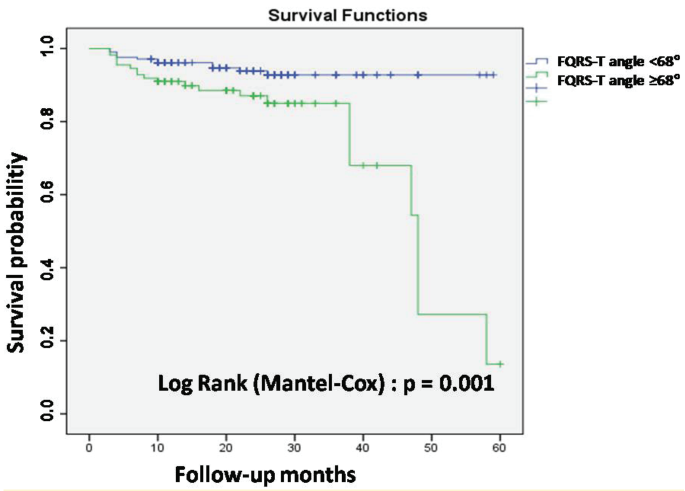

Figure 3. Kaplan-Meier survival analysis stratified by the frontal QRS-T angle.

Discussion

In our study, we found a significant relationship between age, low HDL levels, FQRS-TA values, and mortality in patients with IS during a five-year follow-up period. It is well-established that age and low HDL levels are associated with mortality and morbidity in various cardiovascular diseases. Although studies have linked FQRS-TA with mortality, to the best of our knowledge, no prior research has specifically examined this relationship in patients with IS.

Whang et al.[7] demonstrated that elevated and abnormal spatial and FQRS-TA values are associated with adverse cardiovascular events and all-cause mortality. Previous studies have shown that an increased burden of atherosclerosis correlated with higher FQRS-TA values.[8] Since IS is a complication of atherosclerosis in the brain, it is reasonable to hypothesize that the increased atherosclerotic load in these patients is related to elevated FQRS-TA values. Atherosclerosis and fibrosis, which increase with age, also affect the cardiac conduction system. Disruptions in this system can lead to an increased FQRS-TA and arrhythmias. In our study, patients who died were older, had lower HDL levels, exhibited a more pronounced atherosclerotic process, and had higher FQRS-TA values compared to those who survived.

Stroke is associated with various conditions, including systemic inflammation and autonomic dysfunction. In acute stroke, changes in the central and autonomic nervous systems and secreted neurohormones may lead to metabolic variations and arrhythmias in cardiac cells.[9,10] Various pathological electrocardiographic changes, such as increased QT interval, U waves, ST segment depression or elevation, and negative or biphasic T waves, may occur following IS. Autonomic system alterations after stroke may also increase the FQRS-TA by inducing changes in the cardiac conduction system.[9]

In a study conducted by Jogu et al.,[11] the average FQRS-TA in patients over 65 years of age with cardiovascular and stroke risk factors was found to be 40.1° ± 35.6°. The study also observed that atrial fibrillation (AF) developed in 30% of the patients during a follow-up period of 12.1 years, with every 10-degree increase in FQRS-TA being associated with a 3% increased risk. In our study, the mean FQRS-TA value was 57° (range: 52-62°) in the survival group and 93° (range: 77-111°) in the deceased group. These FQRS-TA values in our study were markedly different from those reported in previous studies.

There is no definitive value for the FQRS-TA associated with mortality.[4] These values may vary based on factors such as age, accompanying diseases, medications, and the characteristics of the patient population being studied.[12,13] For instance, in a study of patients with acute coronary syndrome, two-year mortality was low in those with an FQRS-TA <38 and high in those with an FQRS-TA >104.[14] In research conducted by Gündüz et al.,[15] an FQRS-TA ≥90 was associated with mortality in patients with Coronavirus Disease 2019 (COVID-19). In patients who underwent cardiac resynchronization therapy (CRT) implantation for heart failure, an FQRS-TA below 135° was linked to an improved response.[16] Furthermore, in a general population study of individuals over 30 years of age followed for six years, an FQRS-TA ³100° was associated with both sudden cardiac death and all-cause mortality.[17]

Conclusion

In our study, we found that an increased FQRS-TA angle was associated with all-cause mortality and unfavorable outcomes in patients with IS. To the best of our knowledge, this research is the first to examine the relationship between FQRS-TA and mortality in stroke patients. Future larger-scale studies are needed to further clarify this relationship.

Limitations

The most significant limitations of this study were its retrospective and single-center design and the inability to calculate the spatial QRS-TA. The fact that the FQRS-TA did not follow a normal distribution may have contributed to differences in our findings compared to those of other studies. Additionally, some patients with ischemic stroke may have undiagnosed concomitant coronary artery disease without being aware of it. In this study, patients with ischemic heart disease and heart failure were excluded based on their anamnesis. As this was a retrospective study, it was not possible to investigate patients for ischemic heart disease. The number of patients included in the study was limited, as many did not return for follow-up. Furthermore, since no similar studies have been conducted previously, sufficient comparisons could not be made to evaluate the strength of the study.

Ethics Committee Approval: Ethics committee approval was obtained from Istanbul Health Sciences University Sancaktepe City Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2021/197, Date: 29.09.2021).

Informed Consent: Written informed consent was waived due to the retrospective natüre of the study.

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