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# QTc interval and QTc dispersion as indicators of short-term outcomes in acute ischemic stroke patients

**Shivam Sethi[1], Rajeev Mohan Kaushik[2*], Yashpal Singh[3], Reshma Kaushik[4]**

[1]Senior Resident, Department of General Medicine, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, P.O. Jolly Grant-248016, Dehradun, Uttarakhand, India

[2] Professor, Department of General Medicine, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, P.O. Jolly Grant-248016, Dehradun, Uttarakhand, India

[3]Professor and Head, Department of Neurology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, P.O. Jolly Grant-248016, Dehradun, Uttarakhand, India

[4]Professor and Head, Department of General Medicine, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, P.O. Jolly Grant-248016, Dehradun, Uttarakhand, India

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**Abstract**

Introduction: Interaction between the central nervous system and the cardiovascular system in acute cerebrovascular events can lead to electrocardiographic changes like ST segment deviation, QT interval prolongation, and T wave changes and affect the outcome. This study was done to assess and compare corrected QT (QTc) interval and corrected QT dispersion (QTcd) as prognostic markers for short-term outcomes of acute ischemic stroke. Patients and methods: Ninety-six patients with acute ischemic stroke were included in the study. QTc interval and QTcd were determined for all patients using an electrocardiogram recorded at the time of admission. The patients were assessed for their outcome during hospitalization and at 3 months. The predictive values of QTc interval and QTcd regarding 3-month mortality were assessed and compared using receiver operating characteristic curves.

**Results:** Prolonged QTc interval was observed in 14.6% of patients with acute ischemic stroke while prolonged QTcd was observed in 16.7% of patients. For predicting the short-term outcome of acute ischemic stroke, the C-statistic of the QTc interval was 0.702 (p=0.006, 95% CI 0.555 - 0.848) and was statistically significant. The C-statistic of the QTcd was 0.680 (p=0.014, 95% CI 0.544 - 0.815) and was statistically significant. The difference between the C-statistics of QTc interval and QTcd was not statistically significant (p=0.752).

**Conclusions:** Both QTc interval and QTcd were good predictors of short-term outcomes of acute ischemic stroke. QTc interval was slightly better than QTcd for predicting the short-term outcome of acute ischemic stroke but the difference was not significant.

**Keywords:** Acute ischemic stroke, QTc interval, QTc dispersion, Prognostic marker, Short-term outcome

## Introduction

Cerebral stroke is a worldwide health problem leading to morbidity, mortality, and disability in developed as well as developing countries. It has been an important cause of death among adults with 5.78 million deaths all over the world, equivalent to 10.2% of all deaths in 2016. Although stroke cases are fewer in India when compared with developed countries, they are likely to increase in India with an increase in life expectancy.[1]

The incidence of ischemic stroke is higher but hemorrhagic stroke is responsible for higher mortality and disability-adjusted life-years (DALYs) lost. The ischemic stroke occurs following the blockage of cerebral arteries, caused by a thrombus or an embolism which is followed by a reduced blood flow resulting in tissue death in the diseased region.[2]

The risk of death in stroke cases is highest during the first week after the event. The mortality rates of acute ischemic stroke at 7 and 28 days are 12.2% and 19% respectively. Deaths occur mainly due to the direct effects of brain damage in the early days of the stroke.[3]

Interaction between the central nervous system and the cardiovascular system in acute cerebrovascular events has been evident from several past studies. Various electrocardiographic (ECG) changes have been reported in patients with stroke including ST segment deviation, QT interval prolongation, and T wave changes. Such abnormalities in ECG frequently occur 12 to 48 hours after the disease onset and are usually transient as they last for not more than 1 week.[2,4] This work was planned to assess the corrected QT (QTc) interval and corrected QT dispersion (QTcd) as prognostic markers of acute ischemic stroke and to compare them as predictors of short-term outcomes in patients with acute ischemic stroke.

## Methods

The study was observational longitudinal research carried out at the Department of General Medicine, Himalayan Institute of Medical Sciences, Dehradun, India, from July 2021 to June 2022. It was conducted following informed written consent from participants and received ethical approval from the institutional review board.

The sample size was found to be 95 patients taking the prevalence of QT interval prolongation in patients with ischemic stroke as 43.8% based upon a previous study[5] and a 10% margin of error at 95% confidence level.

Patients >18 years of age with acute ischemic stroke were included in the study. All patients with hemorrhagic stroke were excluded.

Acute ischemic stroke is characterized by sudden neurological impairment due to localized brain ischemia, confirmed by imaging that shows acute infarction.[6] Central Nervous System (CNS) infarction refers to the death of brain, spinal cord, or retinal cells due to ischemia. This is determined by: 1. Pathological, imaging, or other objective evidence of focal ischemic injury in a specific vascular area affecting the brain, spinal cord, or retina; or 2. Clinical evidence of such an injury, indicated by symptoms lasting 24 hours or more, or until death, with other causes ruled out.[7] The diagnosis of ischemic cerebral stroke was made on the basis of detailed history, clinical examination and confirmatory neuroimaging findings. The demographic data including age, sex, residence, and socioeconomic status were collected. History of smoking and alcohol intake was also collected from all the patients. The investigations performed included a complete hemogram, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), kidney function tests, liver function tests, fasting blood sugar (FBS)/ post-prandial blood sugar (PPBS-2 hrs) / random blood sugar (RBS),

glycosylated hemoglobin (HbA1C) (in known case of diabetes), serum lipid profile and ECG. The imaging studies included chest X-ray (PA view), 2D echocardiography, and computed tomography (CT) brain/ magnetic resonance imaging (MRI) brain.

The stroke severity was evaluated using the National Institute of Health (NIH) Stroke Scale.[8] The type of ischemic stroke was categorized according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[9] The QT interval was measured from the ECG taken at admission, and the QTc interval was calculated using Bazett's formula: QTc = QT / √ (R-R interval in seconds).

Grading of QTc interval prolongation was done as per The National Cancer Institute Common Terminology of Clinical Adverse Events v5[10] as follows:

Grade 1**:** QTc interval 450 - 480 ms

Grade 2**:** QTc interval 481 - 500 ms

Grade 3**:** QTc interval ≥ 501 ms; > 60 ms change from baseline

Grade 4**:** Torsade de pointes; signs/symptoms of serious arrhythmia

Grade 5: Death

QT dispersion (QTd) was calculated from the admission electrocardiogram as the difference between maximum and minimum QT intervals in the peripheral and precordial leads. QTcd was derived after correcting QTd for rate.

The patients were assessed for their outcome during hospitalization and at 3 months. The predictive values of QTc interval and QTcd regarding 3-month mortality were assessed and compared.

**Statistical Analysis:** Data analysis was performed using SPSS software (version 23). The student's t-test was employed for comparing quantitative data, while Fisher's exact test or Chi-square test was used for comparing qualitative variables. The concordance (c) statistic, equivalent to the area under the receiver operating characteristic (ROC) curve (AUC), assessed the prognostic value of the QTc interval and QTcd. Delong's test was used to compare the C-statistics of QTc interval and QTcd. A p-value of less than 0.05 was considered statistically significant.

**Results**

The study was conducted on 96 patients with acute ischemic stroke. Most of the patients who had an ischemic stroke were males (63.5%) with > 60 years of age (71.8%). As per TOAST classification, the majority of the patients (36%) had cardioembolic stroke as shown in Table 1.

**Table 1: Demographic and clinical characteristics of patients with acute ischemic stroke**

| Variable | Categories | Number of Patients | Percentage |
|---|---|---|---|
| Age | ≤ 60 years | 27 | 28.2 |
| | > 60 years | 69 | 71.8 |
| Gender | Male | 61 | 63.5 |
| | Female | 35 | 36.5 |
| Residence | Rural | 30 | 31.2 |
| | Urban | 66 | 68.8 |
| Socio-economic | Upper class | 28 | 29.2 |

| | | | |
|---|---|---|---|
| status | Middle class | 49 | 51 |
| | Lower class | 19 | 19.8 |
| Smoking | Yes | 21 | 21.9 |
| | No | 75 | 78.1 |
| Duration of smoking | < 20 years | 20 | 20.8 |
| | > 20 years | 76 | 79.2 |
| Habituated to alcohol | Yes | 19 | 19.8 |
| | No | 77 | 80.2 |
| Stroke subtype | Large artery atherosclerosis | 13 | 13.6 |
| | Cardio-embolic | 35 | 36.5 |
| | Small vessel occlusion | 19 | 19.8 |
| | Undetermined etiology | 23 | 23.9 |
| | Other determined etiology | 6 | 6.2 |

Table 2 displays the laboratory results and imaging findings for patients with acute ischemic stroke. In 2D ECHO, 13.5% of patients had valvular heart disease and in X-ray chest, 41.7% of the patients were found to have cardiomegaly.

**Table 2: Laboratory and imaging results for patients with acute ischemic stroke at admission**

| Variable | Mean | Range |
|---|---|---|
| Hemoglobin (gm/dl) | 14.2 ± 4.1 | 6.5 -16.4 |
| WBC count (thousand/mm$^3$) | 13.6 ± 3.6 | 4.1 - 24.8 |
| Platelet count (thousand/mm$^3$) | 190.4 ± 40.5 | 103 - 460 |
| MCV (fl) | 83.4 ± 20.6 | 58.8 - 109 |
| MCH (pg) | 29.7 ± 7.3 | 14.4 - 38.1 |
| MCHC (g/dl) | 38.9 ± 9.3 | 24 - 62.4 |
| Hematocrit (%) | 46.1 ± 20.4 | 9 - 117.9 |
| ESR (mm/h) | 18.8 ± 7.1 | 2 - 59 |
| HbA1C (%) | 7.7 ± 1.2 | 5.1 - 16 |
| RBS (mg/dl) | 140.5 ± 30.7 | 117 - 430 |
| FBS (mg/dl) | 124.5 ± 28.2 | 88 - 287 |
| PPBS (mg/dl) | 200.4 ± 45.6 | 110 - 578 |
| Serum creatinine (mg/dl) | 2.04 ± 0.8 | 0.21 - 10.1 |
| BUN (mg/dl) | 25.3 ± 5.6 | 6.4 - 57.1 |
| Serum Na (meq/L) | 135.6 ± 8.6 | 121.7 - 152 |
| Serum K (meq/L) | 4.1 ± 0.6 | 1.27 - 6.16 |

| | | |
|---|---|---|
| Serum total bilirubin (mg/dl) | 0.63 ± 0.07 | 0.3 - 2.04 |
| Serum direct bilirubin (mg/dl) | 0.29 ± 0.08 | 0.06 - 0.71 |
| Serum indirect bilirubin (mg/dl) | 0.98 ± 0.04 | 0.02 - 1.71 |
| Serum AST (U/L) | 80.8 ± 20.3 | 14 - 165 |
| Serum ALT (U/L) | 100.7 ± 45.6 | 6 - 275 |
| Serum ALP (U/L) | 100.4 ± 40.7 | 50 - 157 |
| Serum total protein (g/dL) | 7.1 ± 0.6 | 5.5 - 8.14 |
| Serum albumin (g/dL) | 2.9 ± 0.53 | 1.89 - 4.46 |
| Serum globulin (g/dL) | 2.1 ± 0.6 | 1.7 - 5.15 |
| A/G ratio | 1.98 ± 0.5 | 0.53 - 2.84 |
| PT (seconds) | 9.8 ± 8.8 | 1.15 - 18.6 |
| Serum triglyceride (mg/dL) | 200 ± 80 | 100 - 470 |
| Serum HDL (mg/dL) | 36.8 ± 8.1 | 24 - 55 |
| Serum LDL (mg/dL) | 110 ± 20 | 75 - 140 |
| Serum VLDL (mg/dL) | 40 ± 10.1 | 30.5 - 78.2 |
| Serum total cholesterol (mg/dL) | 180 ± 52.3 | 70 - 280 |
| | | |
| **Category** | **Number of patients** | **Percentage** |
| **Chest X-ray** | | |
| Normal | 56 | 58.3 |
| Cardiomegaly | 40 | 41.7 |
| **Territory involved in brain imaging** | | |
| Anterior cerebral artery | 9 | 9.4 |
| Middle cerebral artery | 74 | 77.1 |
| Posterior cerebral artery | 1 | 1 |
| Anterior and middle cerebral artery | 3 | 3.1 |
| Middle and posterior cerebral artery | 9 | 9.4 |
| **2D Echocardiography** | | |
| Normal study | 64 | 66.7 |
| Valvular heart disease | 13 | 13.5 |

| | | |
|---|---|---|
| Diastolic dysfunction with left ventricular hypertrophy | 10 | 10.4 |
| CAD with reduced LVEF | 9 | 9.4 |

WBC – White Blood Cell; MCV – Mean Corpuscular Volume; MCH – Mean Corpuscular Hemoglobin; MCHC – Mean Corpuscular Hemoglobin Concentration; ESR – Erythrocyte Sedimentation Rate; HbA1c – Glycosylated Hemoglobin; FBS – Fasting Blood Sugar; PPBS – Post-Prandial Blood Sugar; RBS – Random Blood Sugar; BUN – Blood Urea Nitrogen; Na – Sodium; K – Potassium; AST – Aspartate Aminotransferase; ALT – Alanine Aminotransferase; ALP – Alkaline Phosphatase; A/G – Albumin/Globulin Ratio; PT – Prothrombin Time; HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; VLDL – Very Low-Density Lipoprotein; CAD – Coronary Artery Disease; LVEF – Left Ventricular Ejection Fraction

In ECG at admission, the mean PR interval was 130.2±30.8 ms, mean QRS interval 100.6±20.5 ms, mean QTc interval 440.6±35.4 ms, mean QTd 59.5±21.6 ms and mean QTcd 63±14.2 ms. (Table 3).

**Table 3: ECG findings at the time of admission**

| Variable | Mean ± SD | Range |
|---|---|---|
| PR interval (ms) | 130.2 ± 30.8 | 0 – 190 |
| QRS interval (ms) | 100.6 ± 20.5 | 58 – 120 |
| QT interval (ms) | 420.7 ± 70.8 | 276 – 510 |
| QTc interval (ms) | 440.6 ± 35.4 | 401 – 530 |
| QTd (ms) | 59.5 ± 21.6 | 25 – 110 |
| QTcd (ms) | 63 ± 14.2 | 30 – 118 |

QTc, Corrected QT; QTd, QT dispersion; QTcd, Corrected QT dispersion

The most common abnormality in ECG at the time of admission was ST-T changes (in 69.98% of patients) followed by prolonged QT interval (in 14.6% of patients). The other ECG changes observed were arrhythmia (8.3%), bundle branch block (4.2%), and left axis deviation (3.1%) or low voltage (3.1%).

Of 96 patients, 88.5% survived while 11.5% of patients died. A prolonged QTc interval was observed in 14 patients (14.6%). It was found to be significantly associated with the final outcome of the patients as the majority of the patients who died had prolonged QTc intervals. No statistically significant association was observed between the QTc interval prolongation and the subtype or severity of stroke. Out of the 14 patients who had prolonged QTc interval, 3 patients (21.4%) had Grade I/II/III QTc interval prolongation while 11 patients (78.6%) had Grade IV/V QTc interval prolongation. A statistically significant association was present between the grade of QTc interval prolongation and final outcome. (Table 4)

**Table 4: Association of QTc interval and its grading with subtype, severity and final outcome of acute ischemic stroke**

| Variable | Prolonged QTc interval n (%) | QTc interval within normal limits n (%) | p value | Grade I/II/III n (%) | Grade IV/V (Life threatening/Death) n (%) | p value |
|---|---|---|---|---|---|---|
| **Subtype** | | | | | | |
| Large artery atherosclerosis (n=13) | 3 (23.1) | 10 (76.9) | 0.763 | 1 (33.3) | 2 (66.7) | 0.713 |
| Cardio embolic (n=35) | 6 (17.1) | 29 (82.9) | | 2 (33.3%) | 4 (66.7) | |
| Small vessels occlusion (n=19) | 2 (10.5) | 17 (89.5) | | 0 (0) | 2 (100) | |
| Undetermined (n=23) | 2 (8.7) | 21 (91.3) | | 0 (0) | 2 (100) | |
| Other determined etiology (n=6) | 1 (16.7) | 5 (83.3) | | 0 (0) | 1 (100) | |
| **Severity** | | | | | | |
| Mild and moderate (n=76) | 10 (13.2) | 66 (86.8) | 0.44 | 3 (30) | 7 (70) | 0.506 |
| Severe (n=20) | 4 (20) | 16 (80) | | 0 (0) | 4 (100) | |
| **Final outcome at the time of admission** | | | | | | |
| Survived (n=85) | 5 (5.9) | 80 (94.1) | <0.0001 | 3 (100) | 0 (0) | 0.003 |
| Mortality (n=11) | 9 (81.8) | 2 (18.2) | | 0 (0) | 11 (100) | |

Prolonged QTcd was observed in 16 (16.7%) of the patients with acute ischemic stroke at the time of admission. A prolonged QTcd showed a significant association with the severity of the stroke and final outcome of the patients. There was no significant association between QTcd and the subtype

of acute ischemic stroke. (Table 5)

**Table 5: Relationship between QTcd and the subtype, severity, and outcomes of acute ischemic stroke**

| Variable | Prolonged QTcd n (%) | QTcd within normal limits n (%) | p value |
|---|---|---|---|
| **Subtype** | | | |
| Large artery atherosclerosis (n=13) | 3 (23.1) | 10 (76.9) | 0.853 |
| Cardio embolic (n=35) | 7 (20) | 28 (80) | |
| Small vessels occlusion (n=19) | 3 (15.8) | 16 (84.2) | |
| Undetermined (n=23) | 2 (8.7) | 21 (91.3) | |
| Other determined etiology (n=6) | 1 (16.7) | 5 (83.3) | |
| **Severity** | | | |
| Mild and moderate (n=76) | 9 (11.8) | 67 (88.2) | 0.033 |
| Severe (n=20) | 7 (35) | 13 (65) | |
| **Final outcome at the time of admission** | | | |
| Survived (n=85) | 11 (12.9) | 74 (87.1) | 0.022 |
| Mortality (n=11) | 5 (45.5) | 6 (54.5) | |

QTc interval and QTcd were also used to predict 3-month mortality in patients with acute ischemic stroke. The accuracy of QTc interval and QTcd to predict 3-month mortality due to acute ischemic stroke was 70.2% and 68% respectively which was found to be statistically significant. The cut-off values of QTc interval and QTcd were 440 ms and 61 ms respectively in predicting the 3-month mortality. The C-statistics for QTc interval and QTcd were 0.702 (p = 0.006) and 0.680 (p = 0.014) respectively and both were statistically significant (Table 4). However, the difference between the C-statistics of QTc interval and QTcd to predict the short-term outcome of acute ischemic stroke was not statistically significant (p=0.752). (Fig. 1).

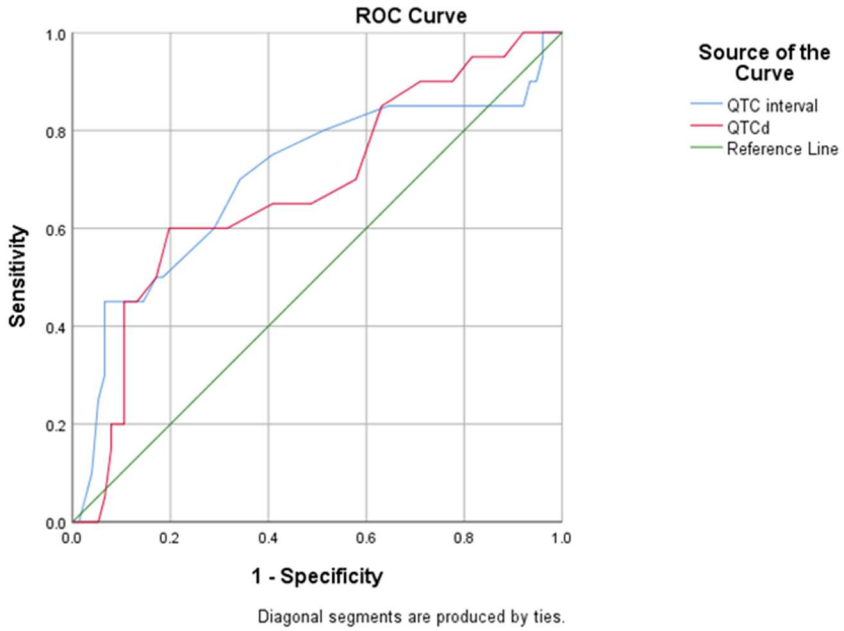


**Fig. 1. ROC curves illustrating the predictive values of QTc interval and QTcd for 3-month mortality in acute ischemic stroke.**

## Discussion

This study aimed to evaluate the QTc interval and QTcd as prognostic markers in acute ischemic stroke. Both QTc interval and QTcd were significantly associated with treatment outcomes and proved to be reliable indicators for predicting 3-month mortality in patients with acute ischemic stroke.

The maximum number of patients (71.8%) belonged to the age group of more than 60 years which was in accordance with the finding of Banerjee et al[11] that the mean age of onset of stroke in India is 63 years. However, Ojha et al[12] in their study on the incidence of stroke in adults in the population of western India reported that 50% of cases of acute ischemic stroke occurred in patients of <46 years of age. Rathmann et al[13] observed that age was the most common non-modifiable risk factor for the development of stroke. In our study, 20.8% of patients were smokers and 19.8% of patients were consuming alcohol which was higher than the findings of Nayak et al[14] that 7.7% of patients were smokers and 10.8% of patients were habituated to alcohol. Whereas, in a study conducted by Shah et al[15], it was found that 39.7% and 41.2% of acute ischemic stroke patients had a history of smoking and alcohol intake respectively.

A study by Mittal et al[16] reported that 75% of the admitted acute ischemic patients survived while 25% of patients died in the hospital. However, Shah et al[15] reported a mortality of 20.5% in patients with acute ischemic stroke in their study. The mortality of 11.5% observed among our patients with acute ischemic stroke was relatively less than the mortality observed in these studies. Goel et al[17] reported severe stroke in 34.6% of patients with acute ischemic stroke as per NIH Stroke Scale which was higher than our findings that only 20.8% of the acute ischemic stroke patients had a severe stroke.

In our study, the most frequent ECG finding in patients with acute ischemic stroke was ischemic ST-T segment changes (70%), followed by QT prolongation (15%). Some patients exhibited two or more ECG changes concurrently. These findings align with those of Tandur et al. and Kandala et al.[18], who

also observed ST segment depression as the most common change, followed by prolonged QTc interval, T wave inversion, and tachycardia. However, other studies identified QTc interval prolongation as the most prevalent ECG change in acute ischemic stroke patients.[20, 21]
QTcd was significantly higher in our patients with severe acute ischemic stroke. Similarly, in a study by Kaya et al[20], the severity of stroke was higher as measured with NIH Stroke Scale in patients with ECG changes. Lazar et al[22] also found a significant association between QTd and the severity of stroke. We did not observe a significant association between the subtype of stroke and QTc interval, grade of QTc interval, and QTcd which is similar to the findings of Afsar et al[23], Lazar et al[24] and Chugh et al.[25]
We found that an increase in QTc interval and QTcd was associated with an increase in mortality at 3 months in acute ischemic stroke patients. The AUC for the QTc interval and QTcd were 0.702 and 0.680 respectively. Based on AUC in the ROC curves, QTc interval, and QTcd were found to be good predictors for the short-term outcome of acute ischemic stroke which was similar to the findings of Asadi et al[26] and Stead et al.[27] The US Third National Health and Nutrition Examination Survey suggested that a prolonged (QTc) interval can predict all-cause mortality in the general population.[28] Likewise, in the studies done by Huang et al[29], Bicakci et al[30], and Afsar et al[23], QTd was found to be a prognostic factor of acute ischemic stroke. In contrast, a study by Tang et al[31] revealed that there was no significant relationship between the QTd and the outcome of acute ischemic stroke. Also, a prospective cohort study by Lederman et al[32] provided no evidence that QTd is related to high mortality rates and poor functional outcomes on hospital discharge among acute ischemic stroke patients. In our study, there was no significant difference in the accuracy of these markers for predicting the prognosis of acute ischemic stroke at 3 months following the event.

## Conclusion

QTc interval prolongation was observed in a significant number of patients with acute ischemic stroke. Both prolonged QTc interval and QTcd were reliable indicators of increased 3-month mortality following acute ischemic stroke. Although the QTc interval was slightly more effective than QTcd in predicting short-term outcomes, the difference was not statistically significant. Consequently, both QTc interval and QTcd can serve as simple, quick, inexpensive, and valuable tools for predicting short-term outcomes in acute ischemic stroke patients.

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