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Usefulness of Tp-Te interval and Tp-Te/QT ratio in the prediction of ventricular arrhythmias and mortality in acute STEMI patients undergoing fibrinolytic therapy

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ABSTRACT

Background and aim: Acute ST-elevation myocardial infarction (STEMI) is associated with fatal and non-fatal ventricular arrhythmic events (VAE). Although primary percutaneous intervention (PCI) is first-line treatment in STEMI, fibrinolytic therapy (FT) is still widely used in many countries. Tp-Te interval; Tp-Te/QT ratio and QT dispersion (QTd) are novel markers of ventricular repolarization (VR) and associate with VAE and mortality. Hereby, we assessed Tp-Te, QTd and Tp-Te/QT in acute STEMI patients undergoing FT and analyzed their relationship with post-FT VAE, and arrhythmic and overall deaths.

Methods: A total of 207 consecutive STEMI patients treated with FT were retrospectively evaluated. Patients were divided in Group 1 (non-VAE group) and Group 2 (VAE group). ECG, clinical and demographic data were noted. Relationship between the pre-FT electrocardiographic parameters of VR and post-FT VAE, arrhythmic and overall death was evaluated.

Results: Tp-Te, Tp-Te/QT and QTd were significantly higher in Group 2 compared to Group 1 ($p < 0.05$). Tp-Te, Tp-Te/QT, QTd, QTc and left ventricular ejection fraction (LVEF) predicted VAE. Tp-Te/QT and LVEF predicted arrhythmic death (1.05; 95% CI 1.01–1.08; $p = 0.031$ and 0.87; 95% CI 0.72–0.96; $p = 0.040$; respectively). In ROC analysis, cut-off for Tp-Te/QT to predict VAE was >0.305 with 87.5% sensitivity and 60.1% specificity (AUC: 0.90; 95% CI: 0.85–0.95; $p < 0.001$), and to predict arrhythmic death was >0.315 with 83.3% sensitivity and 62% specificity (AUC: 0.70; 95% CI: 0.60–0.81; $p = 0.018$).

Conclusion: Tp-Te, Tp-Te/QT, QTc, QTd and LVEF are independent predictors of post-FT VAE in acute STEMI. Tp-Te/QT ratio is associated with VA-related deaths.

Introduction

Cardiac arrhythmias are encountered frequently in the setting of acute coronary syndromes (ACS). Although seen more rarely today during an episode of ACS compared with old times thanks to the advent and wide availability of invasive coronary procedures, fatal arrhythmias like ventricular tachycardia (VT) and ventricular fibrillation (VF) are still regarded as the most dreaded complications of an ACS [1]. In this regard, timely management and early revascularization are of paramount importance during an episode of ACS.

Although primary percutaneous coronary intervention (PCI) is the treatment modality of choice in the management of an acute ST-elevation myocardial infarction (STEMI), a pharmaco-invasive strategy encompassing intravenous administration of fibrinolytic agents followed by referral to a PCI-center can be adopted in pre-hospital or hospital settings in non-PCI centers [2].

In electrocardiography (ECG), ventricular repolarization (VR) is represented by QT and QTc intervals, and their prolongations relate to a higher risk of ventricular arrhythmias (VA) in various disease conditions [3–5]. Furthermore, Tp-Te interval points out to the time interval between the peak of the T wave and its end. Ventricular repolarization starts soon after the onset of ventricular activation; thereby, the QT interval gives a general notion regarding overall repolarization status of the ventricles. On the other hand, Tp-Te interval reflects transmural dispersion of repolarization [6] and is associated with distinct action potential durations in epicardium, myocardium, and endocardium. In particular, ST-segment elevation during an ACS enhances the likelihood of cellular phase-2 reentry which also underlies the arrhythmogenic potential in Brugada syndrome and hence increases the arrhythmic potential through Tp-Te prolongation [7,8]. Moreover, evidence from various researches indicates that Tp-Te prolongation is closely related to VA potential [9–12]. Tp-Te/QT is another parameter representing ventricular arrhythmogenicity.

There is little and conflicting data regarding the parameters of VR during pre- and post-reperfusion periods in the setting of STEMI

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[13–16]. Furthermore, most of the existing evidence revolves around the premise that pre-PCI Tp-Te interval and Tp-Te/QT ratio may indicate post-PCI arrhythmic complications or all-cause death [13,17,18]. However, there is no study to date that assessed the relationship of the parameters of VR with fatal and non-fatal VA occurrence as well as overall death before routine or rescue PCI in acute STEMI patients treated with fibrinolytic therapy (FT). We thereby aimed in the current study to evaluate Tp-Te/QT ratio, Tp-Te interval and QTd in acute STEMI patients undergoing FT and to analyze their association with post-FT VA occurrence, and arrhythmic and overall deaths.

Materials and methods

Study population

We retrospectively screened hospital registries of a total of 282 patients admitted with an acute STEMI to our hospital between 2015 February and 2017 June, in whom FT was administered within 6 h of symptom onset. Acute STEMI was defined as the presence of the pertinent criteria as follows: detection of rise and/or fall of cardiac troponins with at least one value above the 99th percentile of the upper reference limit and with at least one of the following features such as ischemia-related symptoms; new or presumably new ≥0.1 mV ST- segment elevation at the J-point in ≥2 contiguous leads with the cutoff point of ≥0.2 mV in the anterior leads V_2 and V_3; development of pathological Q waves in the electrocardiogram; imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality [19].

Exclusion criteria were as follows: contraindications to FT (n = 18), not providing an informed consent for FT (n = 2), lack of reperfusion within 90 min of fibrinolytic administration (n = 14), lack of adequate patient data (missing records over post-FT VA occurrence) (n = 2), left bundle branch block (n = 6), atrial fibrillation (n = 9); prior STEMI (n = 24). Remaining 207 patients (173 male, 34 female; mean age: 59.2 ± 10.2 years) eligible for FT were included in the study.

Clinical and demographic findings, and past medical history of the study patients were obtained through patient records. Tenecteplase was the fibrinolytic drug used in all patients. All patients had been treated compatibly with recommendations of the STEMI guideline [2]. Our study was performed according to the principals of the Helsinki Declaration, and we received approval from our institutional ethics committee.

A rapid and focused transthoracic echocardiographic examination of the patients was done using Vivid S5 (General Electric, Vingmed Ultrasound AS, Horten, Norway) bedside by an experienced cardiologist after admission of the patient to the coronary care unit and before administration of FT. Main focus of the rapid echocardiographic examination was on obtaining a quick insight about the general functioning of the heart and whether or not a contraindication to FT was present. Left ventricular ejection fraction was calculated using the modified Simpson's rule from the recorded echo images.

Electrocardiographic analysis, definitions, and study aims

In all patients, 12 lead ECG strips (Nihon Kohden, Tokyo, Japan) recorded at 25 mm/s paper speed with a sensitivity of 1 mV/10 mm just before the administration of FT were scanned and analyzed under x400% magnification in computer.

R-R and QT intervals were measured either from Lead 2 or Lead V5 [10]. Then, QT interval was corrected for heart rate using the Bazett's formula. QT dispersion (QTd) was calculated by abstracting the minimum QT from the maximum QT in 12 leads.

Tp-Te interval is commonly measured by 2 methods: tangent and tail methods [20,21]. The tangent method was utilized in the current study that refers to the time interval between the T-peak and the point of intersection of the tangent of the steepest down-slope of the T wave and the isoelectric line [20]. Previous studies used different leads for the determination of Tp-Te interval in the setting of STEMI or J-point elevation [7,10,13,17,18,22]. However, we preferred the longest measurement in all precordial leads, since the precordial leads appear to be much more specific for the measurement of Tp-Te as for reflecting the best the trans-mural dispersion of repolarization [7,10,22]. Finally, Tp-Te/QT was calculated. For every pertinent parameter, an average of three consecutive complexes was taken to end up with the ultimate value. ECG parameters were evaluated by 2 experienced cardiology specialists who were unaware of the study protocol. The interobserver and intraobserver coefficient of variation were 2.8 and 2.3%, respectively.

Fatal VAs were defined as ventricular fibrillation (VF) or ventricular tachycardia (VT) leading to cardiac arrest. Non-sustained and sustained VTs were defined as episodes of VT with a heart rate of at least 120 beats/min that last for at least three beats and persist less than and >30 s, respectively [23]. VT, either sustained or non-sustained, that resolves spontaneously without hemodynamic compromise were defined as non-fatal VA.

Patients with >50% ST resolution in sum of the relevant ST-segment elevation together with symptomatic relief were considered to have attained successful reperfusion [2].

Our aim was to assess the predictive role of the parameters of VR in the development of fatal and/or non-fatal VA events within 90 min after the administration of FT. We also sought to analyze the same relationship with VA-related death and overall death within the same period.

Table 1
Demographic, clinical and electrocardiographic characteristics of the study population.

	No ventricular arrhythmic events (Group 1) (n - 159)	Ventricular arrhythmic events (Group 2) (n - 48)	P
Age, years	58.9 ± 11.2	59.7 ± 9.8	0.656
Gender, male, n (%)	134 (84)	39 (81)	0.128
Height, cm	167.3 ± 10.8	168.5 ± 9.4	0.567
Weight, kg	78.6 ± 12.2	79.6 ± 13.8	0.139
BMI, kg/m^2	28.3 ± 4.8	29.2 ± 4.5	0.156
Anterior STEMI, n (%)	87 (54)	36 (75)	**0.037**
Non-anterior STEMI, n (%)	72 (46)	12 (25)	**0.032**
Sum of ST-segment elevations at baseline, mm	12.3 ± 10.1	14.2 ± 8.4	0.064
TC, mg/dL	179.1 ± 37.5	180.0 ± 34.6	0.274
HDL-C, mg/dL	51.0 ± 12.3	49.3 ± 18.5	0.776
LDL-C, mg/dL	132.9 ± 34.3	124.3 ± 28.2	0.407
TG, mg/dL	155.2 ± 75.4	201.3 ± 56.9	0.336
Glucose, mg/dL	141.1 ± 14.2	133.7 ± 10.4	0.318
BUN, mg/dL	30.6 ± 10.3	32.5 ± 10.4	0.476
Serum creatinine, mg/dL	0.78 ± 0.07	0.81 ± 0.09	0.775
Systolic BP, mm Hg	141.3 ± 26.9	137.3 ± 32.1	0.424
Diastolic BP, mm Hg	86.14 ± 14.8	77.6 ± 17.6	**0.03**
Heart rate, beats per minute	80.9 ± 14.4	78.3 ± 17.1	0.412
LVEF, %	46.05 ± 6.9	39.2 ± 5.8	<**0.001**
Tp-Te, ms	121.2 ± 10.1	133.3 ± 11.6	<**0.001**
Tp-Te/QT ratio	0.293 ± 0.02	0.340 ± 0.03	<**0.001**
QTc, ms	426.4 ± 23.6	436.0 ± 24.1	0.059
QT, ms	398.1 ± 20.3	401.0 ± 24.2	0.232
QT dispersion, ms	36.1 ± 3.3	46.0 ± 12.9	<**0.001**
Post-FT non-arrhythmic cardiac death, n (%)	12 (7.5)	2 (4.1)	**0.032**
Post-FT arrhythmic death, n (%)	–	10 (21)	
Post-FT overall death, n (%)	12 (7.5)	12 (25)	**0.025**
Time from symptom onset to FT, min	140.1 ± 142.3	146.3 ± 157.2	**0.442**

BMI, body-mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; BUN, blood urea nitrogen; BP, blood pressure; LVEF, left ventricular ejection fraction; FT, fibrinolytic therapy; Post-FT, post-fibrinolytic therapy.

We divided the study population into 2 subgroups as the group without fatal/non-fatal VA (Group 1; n = 159) and the group with fatal/non-fatal VA (Group 2; n = 48).

Statistical analysis

The statistical analysis was performed using PASW Statistics (Version 18.0 for Windows, SPSS Inc., Chicago, USA). Quantitative data were assessed for normality by using Kolmogorov- Smirnov and Shapiro-Wilk tests. Baseline characteristics of patients were given in numbers and percentages for dichotomous variables, and mean ± SD for continuous variables. Differences between continuous variables were compared by Student *t*-test. Categorical variables were compared among the groups by chi-square test. Univariate Multivariate logistic regression analysis was implemented in order to determine the risk factors predicting VAs, post-FT overall and arrhythmic deaths. Finally, receiver-operating characteristics (ROC) curve analysis was implemented in order for specifying cut-off values of Tp-Te/QT to predict post-FT VA events, arrhythmic deaths and overall deaths. A *P* value was regarded as statistically significant, should it be <0.05.

Results

Baseline demographic and clinical characteristics

Baseline demographic, and ECG findings of the study population were presented in Table 1. Age, gender and BMI distributions were similar between Group 1 and 2 (p > 0.05). No significant difference was evident between the groups regarding serum glucose, lipid parameters and kidney functions (p > 0.05). Despite similar mean systolic blood pressure (BP) between the groups, mean diastolic BP was significantly lower in Groups 2 (p = 0.03). Mean heart rate was similar between the groups (p > 0.05). Mean LVEF was lower in Group 2, compared with Group 1 (39.2 ± 5.8% vs 46. 5 ± 6.9%, respectively; p < 0.001).

Table 2
Univariate and multivariate regression analysis for predicting post-FT ventricular arrhythmic events.

	Univariate Odds ratio	P	Multivariate Odds ratio	P
Tp-Te	1.09 (95% CI 1.02–1.15)	< 0.001	1.05 (95% CI 1.03–1.07)	0.015
Tp-Te/QT ratio	1.12 (95% CI 1.05–1.18)	< 0.001	1.08 (95% CI 1.05–1.11)	0.001
QTc	1.02 (95% CI 1.01–1.04)	0.013	1.01(95% CI 1.00–1.03)	0.032
QT	0.86 (95% CI 0.70–1.02)	0.514		
QT dispersion	1.04 (95% CI 1.02–1.07)	< 0.001	1.03 (95% CI 1.02–1.06)	0.010
LVEF	0.83 (95% CI 0.68–0.91)	0.041	0.88 (95% CI 0.69–0.94)	0.030

Post-FT, post-fibrinolytic therapy; LVEF, left ventricular ejection fraction.

Anterior STEMI was more prevalent in Group 2 compared with Group 1 (75% vs 54%, respectively; p = 0.037). Mean QTc and QT intervals did not significantly differ between the groups; however, QTd was significantly higher in Group 2 compared with Group 1 (46.0 ± 12.9 ms vs 36.1 ± 3.3 ms, respectively; p < 0.001). Mean Tp-Te interval was significantly prolonged (133.3 ± 11.6 ms vs 121.2 ± 10.1 ms, respectively; p < 0.001), and Tp-Te/QT ratio was significantly greater (0.340 ± 0.03 vs 0.293 ± 0.02, respectively; p < 0.001) in Group 2 compared with Group 1 (Table 1, Fig. 1).

Post-FT ventricular arrhythmic events and overall mortality

Of all 207 STEMI patients included, VA events were encountered in 48 (23.1%). Mortality occurred in 12 (25%) of the patients in Group 2, while 12 patients (7.5%) died in Group 1 (Table 1). The reasons for mortality in Group 2 were intractable and fatal VAs leading to cardiac arrest (n = 10) and progressive cardiac failure (n = 2); however, those in Group 1 were intracranial hemorrhage (n = 2), asystole (n = 3), and progressive cardiac failure (n = 7). Electrocardiographic reperfusion was achieved in patients in whom mortality did not occur within

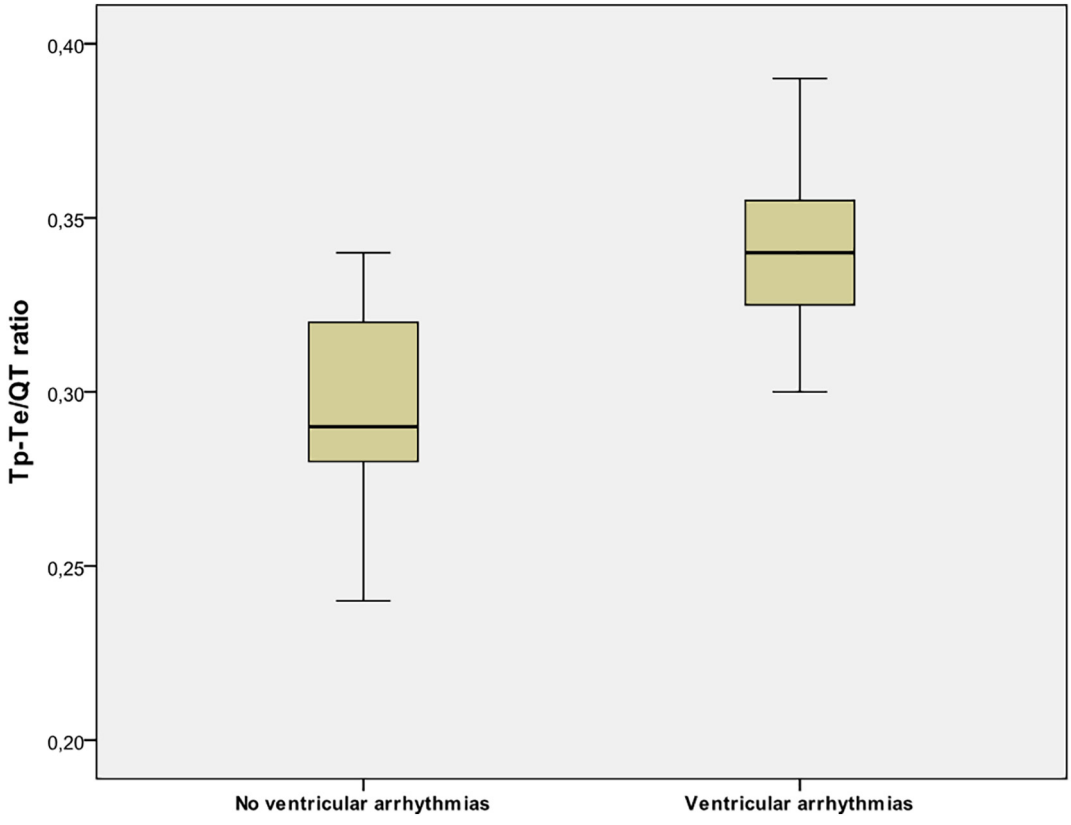

Fig. 1. Comparison of Tp-Te/QT ratio between the groups.

Table 3
Univariate and multivariate regression analysis for predicting post-FT ventricular arrhythmic death.

	Univariate Odds ratio	P	Multivariate Odds ratio	P
Tp-Te	1.02 (95% CI 0.97–1.05)	0.303		
Tp-Te/QT ratio	1.07 (95% CI 1.03–1.10)	0.018	1.05 (95% CI 1.01–1.08)	0.031
QTc	1.01(95% CI 0.89–1.02)	0.124		
QT	0.93 (95% CI 0.89–1.04)	0.519		
QT dispersion	0.91 (95% CI 0.81–0.97)	0.415		
LVEF	0.71 (95% CI 0.64–0.92)	0.021	0.87 (95% CI 0.72–0.96)	0.040

Post-FT, post-fibrinolytic therapy; LVEF, left ventricular ejection fraction.

90 min after the onset of FT. Moreover, all the surviving patients were referred for PCI 90 min after FT.

Regression and ROC curve analyses

Tp-Te interval, Tp-Te/QT ratio, QTc interval, QTd and LVEF emerged as predictors of post-fibrinolytic fatal/non-fatal VA events in univariate logistic regression analysis. Furthermore, these parameters remained significant and independent predictors of the VA events in multivariate logistic regression analysis (1.05; 95% CI: 1.03–1.07, and 1.08; 95% CI: 1.05–1.11, and 1.01; 95% CI: 1.00–1.03, and 1.03; 95% CI: 1.02–1.06, and 0.88; 95% CI: 0.69–0.94; respectively, $p < 0.05$ for all) (Table 2).

As for post-FT VA-related death, only Tp-Te/QT interval and LVEF independently predicted fatal VA-related deaths in univariate and multivariate logistic regression analysis (1.05; 95% CI: 1.01–1,08; $p = 0.031$ and 0.87; 95% CI: 0.72–0.96; $p = 0.040$; respectively) (Table 3).

Although Tp-Te, Tp-Te/QT and LVEF significantly predicted post-FT overall deaths in univariate regression model, only LVEF remained a significant predictor of overall death in multivariate logistic regression analysis (0.74; 95% CI:0.62–0.94; $p < 0.001$) (Table 4).

In ROC analysis of Tp-Te/QT ratio, the optimal cut-off value to predict post-FT VA events was >0.305 with 87.5% sensitivity and 60.1% specificity (AUC: 0.90; 95% CI: 0.85–0.95; $p < 0.001$) (Fig. 2), whereas the optimal cut-off to predict post-FT VA-related death was >0.315 with 83.3% sensitivity and 62% specificity (AUC: 0.70; 95% CI: 0.60–0.81; $p = 0.018$) (Fig. 3). There wasn't any significant cut-off value for the other parameters of VR.

Discussion

This study shows that Tp-Te interval, Tp-Te/QT ratio, QTc interval, QTd and LVEF are independent and significant predictors of fatal and non-fatal VA occurrence within 90 min of the post-FT period. In addition, Tp-Te/QT ratio and LVEF independently predict VA-related deaths, and only LVEF significantly predicts overall death within the same time period. To our knowledge, this study is the first to evaluate the predictive role of the parameters of VR in the development of VA events and VA-related deaths after the onset of FT.

Although primary PCI is the treatment of choice in the management of acute STEMI, pharmaco-invasive approach comprising FT followed by PCI within 2–24 h has still been applied in many centers worldwide owing to geographic hindrances and non-homogeneous distribution of PCI-centers in many countries [24]. Hence, introduction of easy-to-use and cost-effective prognostic markers to the physicians' practice is of paramount importance especially for non-PCI centers.

Acute STEMI is associated with a congeries of electrochemical changes within the heart that give rise to marked intercellular alterations in membrane potentials between the infarcted zones and the zones of normal perfusion, and hence the propensity for VA events. These alterations, in turn, are responsible for heterogeneity in VR and roughly correspond in surface ECG to the changes in Tp-Te/QT, Tp-Te, QTd and QT [6,8,10,13,25]. Sustained VAs may be generated in around 20% of patients with STEMI undergoing FT and have been suggested to point out a poorer prognosis [26–30].

Previous studies conducted on the effect of revascularization on QTd after FT demonstrated conflicting results. In a recent study by Oni Heris et al. [15], QTd was reported not to have changed after FT. Although they concluded that FT did not escalate the risk of VA over time, they did not seek to correlate their findings with post-FT VA events and relied solely on QTd as a risk factor VA. Similarly, Mehta et al. [31] found that QTd did not change significantly after FT. However, Nikiforos et al. [16] reported a decrease in QTd following successful FT. Similar conflicting results also emerged in studies on Tp-Te interval. Haarmark et al. [13] measured Tp-Te interval just before and after PCI in STEMI patients and found that Tp-Te interval did not change significantly after revascularization. However, another study [14] demonstrated a shortening of Tp-Te interval over the first 4 h after PCI. Because of these conflicting results on QTd and Tp-Te in pre- and post-revascularization periods, we only used the parameters of VR in ECGs recorded immediately before fibrinolytic administration and sought to correlate VA events not only with QTd but also with more novel parameters such as Tp-Te interval and Tp-Te/QT ratio. We also found that pre-FT Tp-Te interval, QTc interval, QTd, and Tp-Te/QT ratio predicted VA events within 90 min after FT.

It was suggested in previous studies that Tp-Te/QT ratio predicted more accurately the VA events than sole Tp-Te interval, as it proves to be more stable and is not influenced from variations in body weight and heart rate in a particular subject [17,32]. Additionally, it is much more revealing as to the status of VR when compared with sole QT and Tp-Te intervals [32]. Zhao et al. [17] conducted a study on 338 STEMI treated with PCI and found that only pre-PCI Tp-Te/QT was independently associated with in- and out-of-hospital overall death and major adverse cardiac events (MACE). In their study, the cut-off value for Tp-Te/QT in the prediction of MACE and death was ≥0.29. Note that their findings are derived from STEMI patients treated with primary PCI. Our study, on the other hand, was conducted on STEMI patients treated with FT. In this regard, our study further extends the current literature such that we suggested new cut-off values of Tp-Te/QT >0.305 and > 0.315 in the prediction of VA events and VA-related death, respectively.

Study limitations

Our study had better be assessed with some limitations. This study is a single center and enrolled a relatively small population. We did not seek to correlate the parameters of VR with longer-term VA events

Table 4
Univariate and multivariate logistic regression analysis for predicting post-FT overall death.

	Univariate Odds ratio	P	Multivariate Odds ratio	P
Tp-Te	1.02 (95% CI 1.01–1.06)	0.045		
Tp-Te/QT ratio	1.07 (95% CI 1.03–1.10)	0.004		
QTc	1.01(95% CI 0.97–1.03)	0.124		
QT	0.88 (95% CI 0.81–0.94)	0.421		
QT dispersion	0.95 (95% CI 0.91–1.04)	0.343		
LVEF	0.69 (95% CI 0.53–0.92)	< 0.001	0.74 (95% CI 0.62–0.94)	< 0.001

Post-FT, post-fibrinolytic therapy; LVEF, left ventricular ejection fraction.

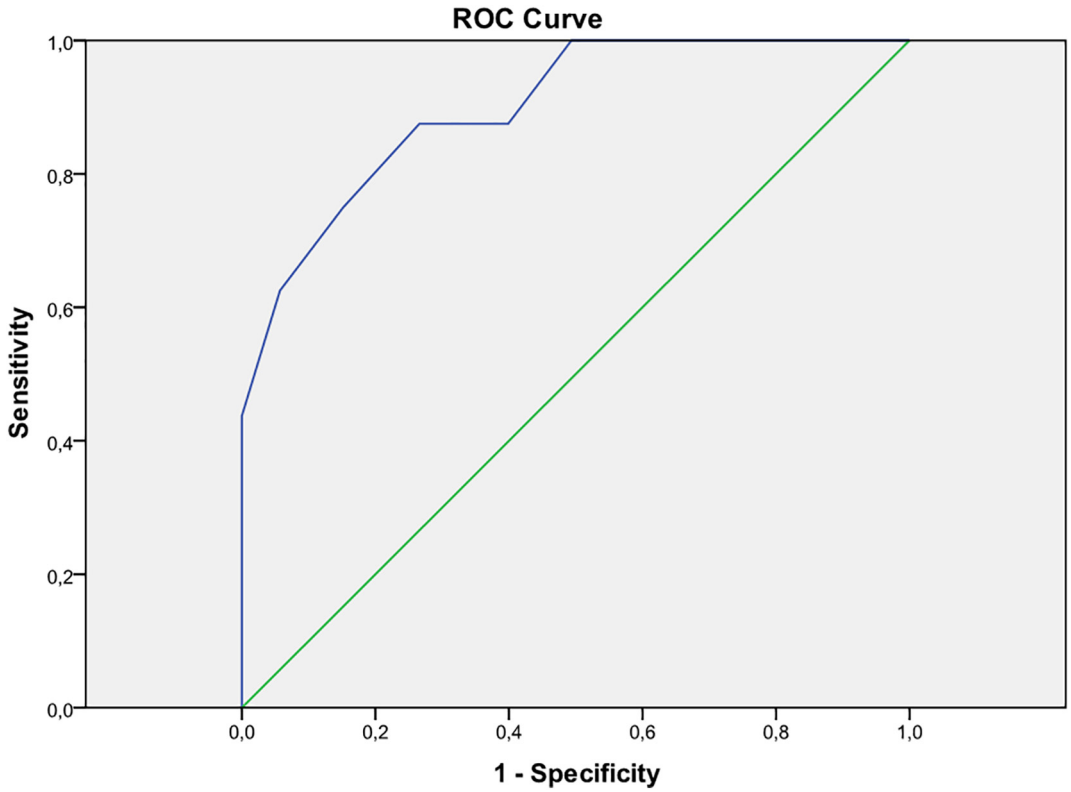

Fig. 2. ROC curve for the relationship between Tp-Te/QT ratio and the ventricular arrhythmic events.

and arrhythmic death after routine PCI following FT. We did not include a healthy control group for the comparison of VR parameters. In this regard, our findings need to be confirmed by future large-scale studies.

Conclusion

Tp-Te interval, Tp-Te/QT ratio, QTc interval, QTd and LVEF are independent and significant predictors of VA events within 90 min after FT

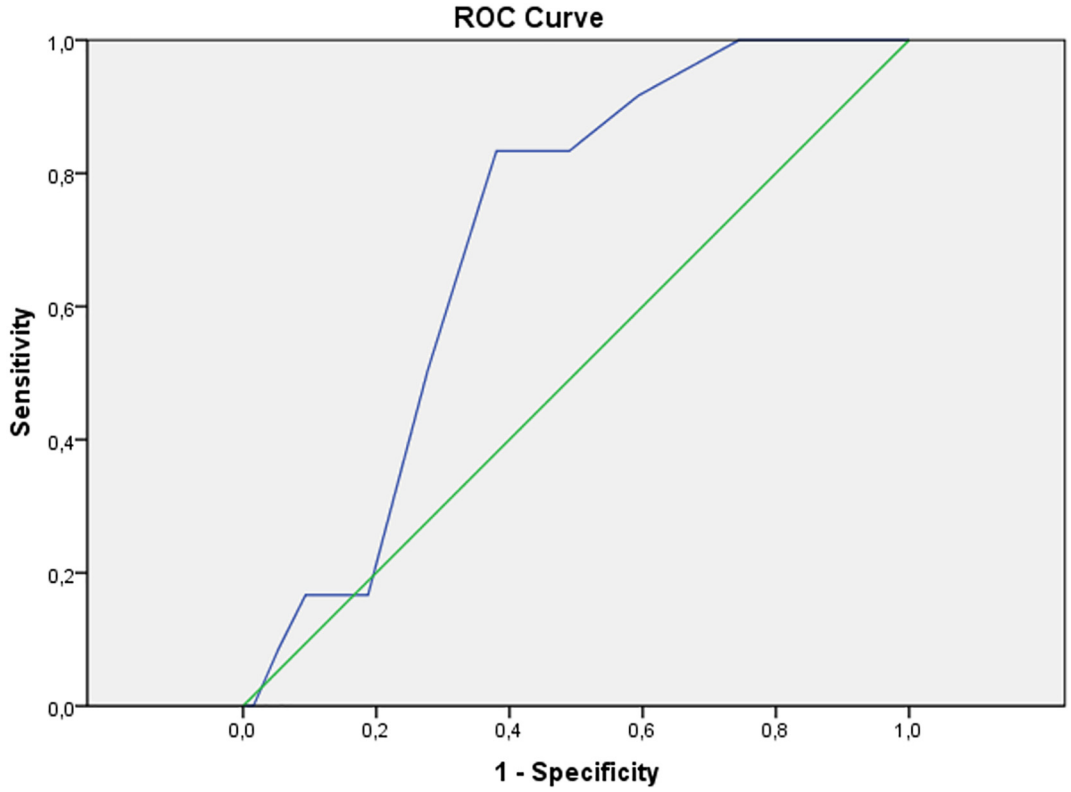

Fig. 3. ROC curve for the relationship between Tp-Te/QT ratio and the ventricular arrhythmia-related death.

in acute STEMI. Furthermore, Tp-Te/QT ratio is independently associated with VA-related death. This simple ECG parameter may prove very useful in the risk stratification of STEMI patients deemed appropriate for FT.

Author's contribution

SC.Ö, study concept, design, data collection; E.S, data collection, design, drafting the manuscript.

Declaration of Competing Interests

None to declare.

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