ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

A Combination of Heart Rate-Corrected QT Interval and GRACE Risk Score Better Predict Early Mortality in Patients with Non-ST Segment Elevation Acute Coronary Syndrome

Kalp Hızı Düzeltilmiş QT Aralığı ve GRACE Risk Skorunun Bir Kombinasyonu ST-Segment Yüksekliği Olmayan Akut Koroner Sendromlu Hastalarda Erken Mortaliteyi Daha İyi Öngörür

ABSTRACT

Objective: This study aimed to evaluate whether the addition of heart rate-corrected QT interval prolongation to the Global Registry of Acute Coronary Events risk score improves the predictive value for early mortality in patients with non-ST segment elevation acute coronary syndrome.

Methods: We retrospectively screened our database for consecutive non-ST-segment elevation acute coronary syndrome patients between January 2017 and July 2019. The demographic and clinical parameters were acquired via chart review. All electrocardiograms were reviewed by 2 physicians. QT interval was measured using the tangent method. Early mortality was defined as all-cause death observed during the hospital stay or within 30 days after discharge.

Results: The final study population consisted of 283 patients, there were 17 early deaths. Ten of 59 patients with prolonged corrected QT intervals died (16.9%, $P < .001$). Both the Global Registry of Acute Coronary Events risk score (odds ratio: 1.032; 95% CI: 1.012-1.053; $P = .002$) and corrected QT interval (odds ratio: 1.026; 95% CI: 1.007-1.045; $P = 0.007$) independently predicted early mortality. The area under value was 0.769 (95% CI: 0.674-0.863, $P < .001$) for the corrected QT interval and 0.780 (95% CI:0.681-0.878; $P < .001$) for the Global Registry of Acute Coronary Events risk score alone. However, when the corrected QT interval and the Global Registry of Acute Coronary Events risk score were combined, it was found to be 0.808 (95% CI: 0.713-0.904, $P < .001$).

Conclusion: This study is the first to report that prolonged corrected QT and the Global Registry of Acute Coronary Events risk score independently predict early mortality and a combination of these 2 factors may improve the predictive value for early mortality in patients with ST-segment elevation acute coronary syndrome.

Keywords: Non-ST-segment elevation acute coronary syndrome, GRACE risk score, QTc interval

ÖZET

Amaç: Bu çalışma, kalp hızı düzeltilmiş QT aralığı (QTc) uzamasının GRACE risk skoruna eklenmesinin, ST-segment elevasyonu olmayan akut koroner sendromlu (NSTE-AKS) hastalarda erken mortalite için prediktif değeri iyileştirip iyileştirmediğini değerlendirmeyi amaçlamıştır.

Yöntemler: Ocak 2017 ile Temmuz 2019 arasında ardışık NSTE-AKS hastaları için veri tabanımızı geriye dönük olarak taradık. Demografik ve klinik parametreler çizelge incelemesi yoluyla elde edildi. Tüm elektrokardiyogramlar 2 doktor tarafından incelendi. QT aralığı tanjant yöntemi kullanılarak ölçüldü. Erken ölüm, hastanede kalış sırasında veya taburcu olduktan sonraki 30 gün içinde gözlenen tüm nedenlere bağlı ölüm olarak tanımlandı.

Bulgular: Çalışma popülasyonu 283 hastadan oluşuyordu, 17 erken ölüm vardı. QTc aralığı uzamış olan 59 hastanın onu öldü (%16.9, P < .001). Hem GRACE risk skoru (olasılık oranı: 1.032; %95 GA: 1.012 1.053; P = .002) hem de QTc aralığı (olasılık oranı: 1.026; %95 GA: 1.007-1.045; P = 0.007) bağımsız olarak erken mortaliteyi öngördü. Değerin altında kalan alan sadece QTc aralığı için 0.769 (%95 CI: 0.674-0.863, P < .001) ve sadece GRACE riski skoru için 0.780 (%95 CI:0.681-0.878; P < .001) idi. Ancak QTc aralığı ve GRACE risk skoru birleştirildiğinde 0.808 (%95 CI: 0.713-0.904, P < .001) bulundu.

ORIGINAL ARTICLE
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Received: September 7, 2021
Accepted: April 4, 2022

Cite this article as: Demirtaş İnci S, Tekindal MA, Altınsoy M, et al. A combination of heart rate-corrected QT interval and GRACE risk score better predict early mortality in patients with non-ST segment elevation acute coronary syndrome. *Turk Kardiyol Dern Ars.* 2022;50(5):340-347.

DOI:10.5543/tkda.2022.21198

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Sonuç: Bu çalışma, QTc aralığı uzama ve GRACE risk skorunun bağımsız olarak erken mortaliteyi öngördüğünü ve bu 2 faktörün bir kombinasyonunun NSTE-AKS'lu hastalarda erken mortalite için prediktif değeri iyileştirebileceğini bildiren ilk çalışmadır.

Anahtar Kelimeler: ST-segment elevasyonu olmayan akut koroner sendrom, GRACE risk skoru, QTc aralığı

The patients without ST-segment elevation (NSTE) during their admission on electrocardiogram (ECG) constitute the majority of people presenting with acute coronary syndrome (ACS). The clinical profile of these patients is extremely heterogeneous, and the incidence of severe complications varies considerably according to their baseline risk class. Therefore, rapid and accurate risk stratification is essential for the early identification of the high-risk patients.[1-3] The Global Acute Coronary Event Registry (GRACE) risk score has been shown to be a potential predictor of major adverse cardiac events in the patients with ACS in general, as well as the patients with NSTE-ACS.[4,5]

Electrocardiogram is an attractive tool for risk assessment in patients with ACS, because of its easy and safe application, widespread availability, and low cost.[6] Especially, the heart rate-corrected QT interval (QTc), which represents the time it takes for global ventricular depolarization and repolarization,[7] has been reported to be an independent predictor of arrhythmic death after acute myocardial infarction (MI) when prolonged to a certain degree.[8] Moreover, it has been suggested as an indicator of more severe coronary involvement or extensive ischemia in patients with NSTE-ACS.[9] Therefore, the purpose of this study was to evaluate whether the addition of prolonged QTc to GRACE risk score improves the predictive value for early mortality in patients with NSTE-ACS.

Methods

We retrospectively screened our hospital database for consecutive NSTE-ACS patients who are admitted to our emergency department between January 2017 and July 2019. Approval for this study was obtained from the Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Approval Date: January 11, 2021; Approval Number: 102/19). The need for a written informed consent form from each participant was waived due to the retrospective nature of the study.

The ST-segment elevation cut-offs on ECG were defined according to the fourth universal definition of MI consensus,[10] and only patients not exceeding these cut-offs were included in the study. The Non-ST-segment elevation acute coronary syndrome myocardial infarction (NSTEMI) was defined as acutely rising troponin levels with at least one value above the 99th percentile upper reference limit in combination with at least one of the following: (1) symptoms compatible with Acute Coronary Syndrome (ACS), (2) dynamic ST-T wave changes indicating ischemia or newly developed pathological Q waves, or (3) a culprit lesion on the coronary angiogram. Unstable angina (USAP) was defined as the abovementioned parameters without an increase in troponin levels exceeding the 99th percentile upper reference limit. Non-ST segment elevation acute coronary syndrome comprised of NSTE-MI and USAP.[11] The exclusion criteria were the presence of atrial fibrillation, atrial flutter, paced rhythm, pre-excitation, high-grade atrioventricular block, the presence of implantable defibrillators, the use of type Ia or III antiarrhythmic drugs, incomplete demographic and clinical parameters in records. The patients with missing or technically inadequate ECGs for QT interval assessment were also excluded.

The demographic and clinical parameters were acquired via chart review. The GRACE risk score was calculated using 8 parameters, including age, serum creatinine level, heart rate, systolic blood pressure, Killip class, cardiac arrest at presentation, increased levels of cardiac markers, and ST-segment depression on the ECG. The GRACE risk scores of <108, 108-140, and >140 were accepted as low-, medium-, and high risk, respectively.[12]

All ECGs were reviewed by 2 physicians to detect technical errors, poor image quality of the recordings, the presence of atrial fibrillation, or ventricular pacing. The QT, QTc, and QRS time intervals were evaluated on ECG by the same physicians. The QT interval was measured using the tangent method[6] and was corrected according to heart rate using Bazett's formula. A prolonged QTc interval was defined as 450 ms or above.[13]

The primary endpoint was all-cause death observed during the hospital stay or within 30 days after discharge.

Statistical Analysis

The sample size calculated taking into consideration minimal clinically important differences in no QTc prolonged and QTc prolonged was n=58 for each training group using a power of 0.8 and α level of 0.05. The data were evaluated using the statistical program Statistical Package for the Social Sciences version 25 for Windows (IBM Corp., Armonk, NY, USA). The variables were evaluated after checking the prerequisites for normality and homogeneity of variance with Shapiro–Wilk and Levene test. The variables were expressed as mean ± standard deviation and percentage values, as appropriate. For the analysis of the data, a Student's *t*-test was used to compare the means of 2 groups, while the Mann–Whitney *U* test was used if the abovementioned prerequisites were not met. Chi-square and Fisher's exact tests were used to compare categorical data. The relationship between 2 continuous variables was evaluated using Pearson's correlation coefficient and Spearman's correlation coefficient. Multivariate logistic regression was used to test the significance

ABBREVIATIONS

ACS	Acute coronary syndrome
CAD	Coronary artery disease
ECG	Electrocardiogram
EF	Ejection fraction
GRACE	Global Registry of Acute Coronary Events
MI	Myocardial infarction
NSTE-ACS	Non-ST Segment Elevation Acute Coronary Syndrome
QTc	Heart rate-corrected QT interval
USAP	Unstable angina

Table 1. Demographics of Patients in Groups Based on the Prolongation of QTc Intervals

Variables	No QTc Prolonged (n=224)	QTc Prolonged (n=59)	*P*
Demographic features			
Age, (years)	60.41 ± 13.1	65.93 ± 13.75	.005
BMI, (kg/m^2)	27.78 ± 4.70	28.42 ± 5.45	.630
Gender, men, n (%)	155 (69.19)	44 (73.3)	.539
HT, n (%)	121 (54.0)	35 (60)	.461
DM¸ n (%)	67 (29.9)	22 (36.6)	.346
Smoker, n (%)	107 (47.7)	18 (31.6)	.009
Previous CAD, n (%)	84 (36.1)	29 (48.3)	.136
HR (beats/min)	75.73 ± 13.62	77.75 ± 14.40	.323
SBP, (mm HG)	136.97 ± 26.96	136.66 ± 26.44	.938
EF, (%)	52.20 ± 9.18	51.00 ± 9.34	.397
Killip, n (%)			.172
I	217 (80)	57 (95)	
II	1 (0.3)	0	
III	1 (0.3)	1 (3.3)	
IV	0	1 (1.6)	
NSTEMI, n (%)	98.25 ± 13.26	107.88 ± 22.45	.001
GRACE risk score	110.82 ± 30.10	131.00 ± 30.79	.001
Laboratory			
Glucose,(mg/dL)	133.43 ± 62.12	135.71 ± 57.49	.799
Creatinine,(mg/dL)	1.22 ± 0.93	1.53 ± 1.57	0.063
Sodium, (mEq/L)	137.11 ± 2.78	136.98 ± 3.25	.766
Potassium, (mEq/L)	4.12 ± 0.44	4.15 ± 0.68	.626
Calcium, (mEq/L)	9.13 ± 0.59	9.11 ± 0.70	.812
LDL-Cholesterol,(mg/dL)	124.95 ± 35.89	123.67 ± 30.97	.804
Hemoglobin, (g/dL)	14.05 ± 2.09	13.25 ± 2.08	.010
Peak troponin T, (ng/mL)	6.84 ± 15.15	8.79 ± 13.07	.385
CAG, n (%)	208 (92.8)	55 (91.6)	
None or minimal CAD, n (%)	39 (17.4)	10 (16.6)	.535
One-vessel, n (%)	60 (26.7)	14 (23.3)	.535
Two-vessel, n (%)	61 (27.2)	15 (25)	.835
Left main and/or 3-vessel, n (%)	60 (26.7)	18 (30)	.935
Stenting the related artery, (ADA/CxA/RCA) (%)	(53/50/31)	(18/8/9)	.641
Surgery decision, n (%)	35 (15.6)	9 (15)	.535
ECG			
ST segment depression, n (%)	97 (42)	34 (58)	.027
QRS duration, (ms)	184 (82.1)	55 (91.6)	.029
QTc interval, (ms)	409.26 ± 23.89	467.63 ± 14.52	.001

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; CAG, coronary angiography; CAD, coronary artery disease; SBP, systolic blood pressure; HR, heart rate; EF, ejection fraction; ADA, anterior descending artery; CxA, circumflex artery; RCA, right coronary artery; NSTEMI, non-ST segment elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events; ECG, electrocardiography.

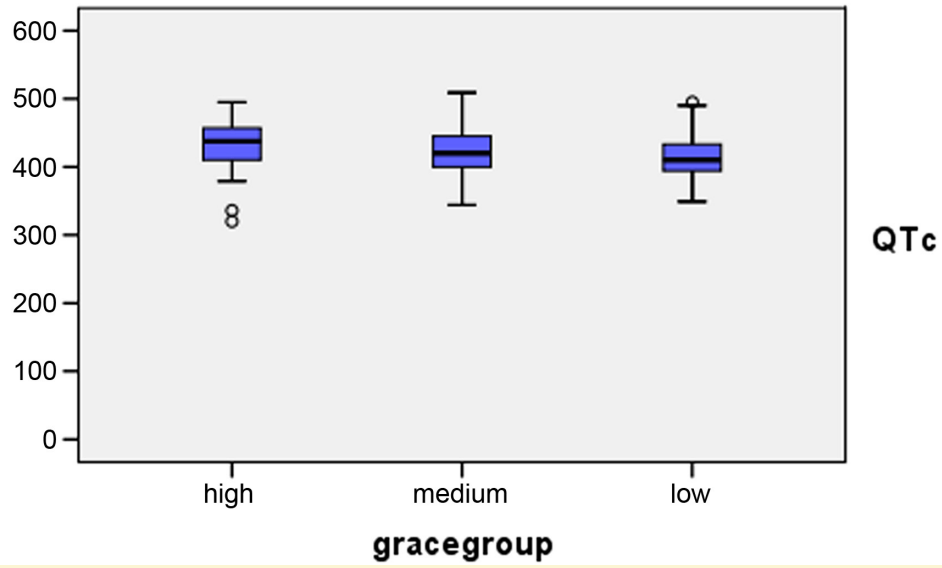


Figure 1. Association of QTc interval with GRACE risk score (high, moderate, and low) groups, $P < .0001$. QTc, corrected QT interval; grace, Global Acute Coronary Event Registry.

Table 2. Comparison of the Basic Characteristics of Patients with and without Mortality

Variables	Mortality (+) (n=17)	Mortality (–) (n=266)	*P*
Age, years	75.18 ± 8.71	60.60 ± 13.12	**.001**
Men, n (%)	10 (58)	188 (70)	.286
HT, n (%)	14 (82)	142 (53)	**.041**
DM, n (%)	9 (52)	79 (29)	.062
Smoker, n (%)	3 (17)	122 (45)	.048
Previous CAD, n (%)	12 (70)	101 (37)	**.019**
HR, (beats/min)	82.12 ± 14.39	75.77 ± 13.71	0.066
SBP, (mm HG)	143.94 ± 25.58	136.44 ± 26.92	.265
EF, (%)	47.07 ± 9.75	52.28 ± 9.10	**.039**
Hb, (g/dL)	12.37 ± 1.88	14.00 ± 2.07	**002**
Glucose, (mg/dL)	147.76 ± 52.13	133.07 ± 61.70	.338
Creatinine, (mg/dL)	1.90 ± 1.52	1.25 ± 1.05	**0.019**
Troponin T, (ng/mL)	4.81 ± 7.51	2.66 ± 6.99	.224
GRACE risk score	144.41 ± 27.01	113.24 ± 30.67	**.001**
QRS duration, (ms)	111.81 ± 24. 49	100.07 ± 15.11	**.025**
QTc interval, (ms)	454.59 ± 27.20	419.55 ± 31.65	**.001**
None or minimal CAD, n (%)	2 (11)	44 (18)	.436
One-vessel, n (%)	3 (17)	73 (27)	13
Two-vessel, n (%)	5 (29)	70 (26)	.846
Left main and/or 3-vessel, n (%)	7 (41)	79 (29)	.863
Stenting the related artery, (ADA, RCA, CxA), (%)	(17/ 23/5)	(25/13/21)	.341
Surgery decision, n (%)	2 (11)	25 (9)	
NSTEMI, n (%)	16 (94)	222 (83)	.109

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HR, heart rate; SBP, systolic blood pressure; EF, ejection fraction; Hb, hemoglobin; ADA, anterior descending artery; CxA, circumflex artery; RCA, right coronary artery; NSTEMI, non-ST segment elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events.

Table 3. Different Variables Affecting In-Hospital Mortality Based on the Multivariate Logistic Regression Analysis

		95% CI OR		
Variables	**OR**	**Lower**	**Upper**	***P***
GRACE risk score	1.032	1.012	1.053	**.002**
QTc interval	1.026	1.007	1.045	**.007**

OR, odds ratio; GRACE, Global Registry of Acute Coronary Events.

of the data on mortality. Adjusted values of odd proportions (OR) and 95% CI were calculated. The performance of a test can be defined by the diagnostic ability of the test or by its ability to accurately divide events into subgroups (healthy/patient, etc.). The cut-off points of the parameters were evaluated by receiver-operating characteristic (ROC) analysis. The area under the curve value, sensitivity, and selectivity values were calculated. The discriminatory power of the GRACE risk score, QTc interval, and their combination were evaluated by ROC analysis. A cut-off for combined GRACE risk score and QTc was defined by the determination of the Youden index. A *P* value below .05 is considered to be statistically significant.

Results

In the screening period, we identified 328 patients fulfilling the inclusion criteria. Forty-five patients were excluded from the analysis based on the exclusion criteria, namely for high-grade atrioventricular block (n=8), technically inadequate ECG (n=11), using antiarrhythmic (amiodarone or ranolazine) (n=12), and inability to calculate the GRACE risk score (n=14). In 20 patients, coronary angiogram reports could not be retrieved, but these patients remained in the final study population. The final study population consisted of 283 patients. Of these, 238 (84.0%) were diagnosed with NSTEMI, and 45 (15.9%) were diagnosed with USAP.

The mean age was 61.5 ± 13.4 years and 199 (70.3%) of the patients were male. A total of 157 (55.4%) patients were hypertensive, 89 (31.4%) patients were diabetic, 126 (44.5%) patients were smokers, a history of coronary artery disease (CAD) was present in 113 (39.9%) patients, and an ejection fraction (EF) <50% was in 95 (33.5%) patients. A prolonged QTc interval was present in 59 (20.8%) patients.

The baseline characteristics of the patient groups with or without prolonged QTc interval are presented in Table 1. Briefly, age, smoking, GRACE risk score, QRS duration and ST-segment depression on ECG, and the proportion of NSTEMI were higher in the group with prolonged QTc interval compared to the group without prolonged QTc inverval. There were 30 patients with a QRS duration greater than 120 ms, of which 18 had QTc interval prolongation.

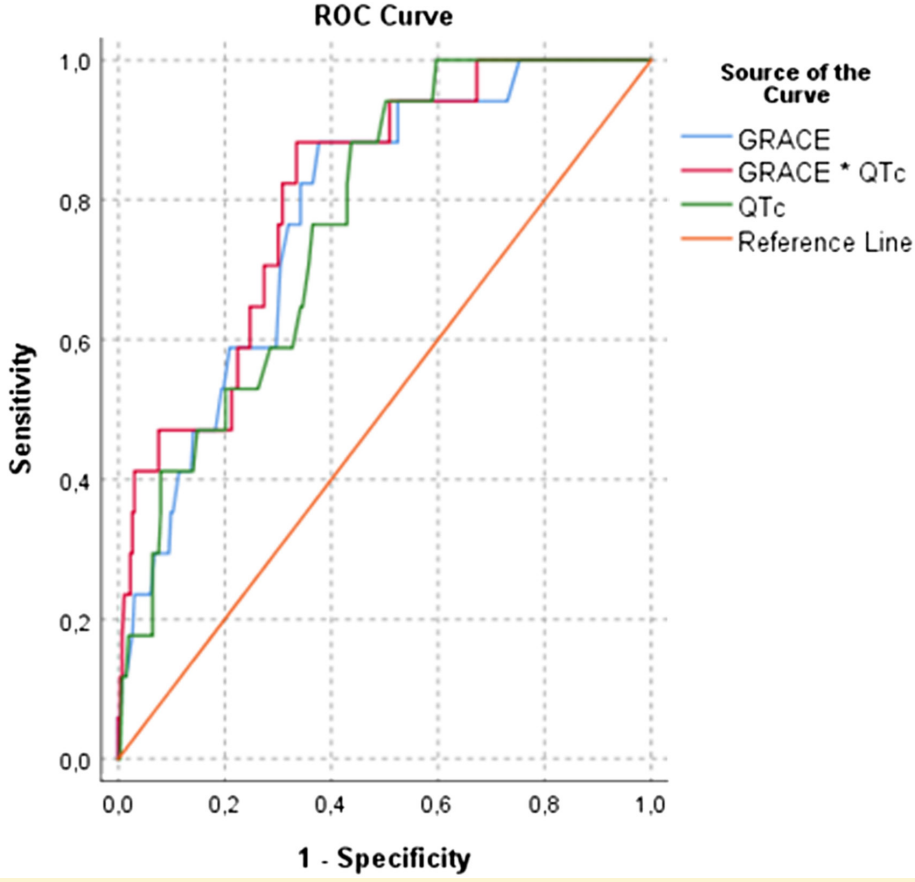
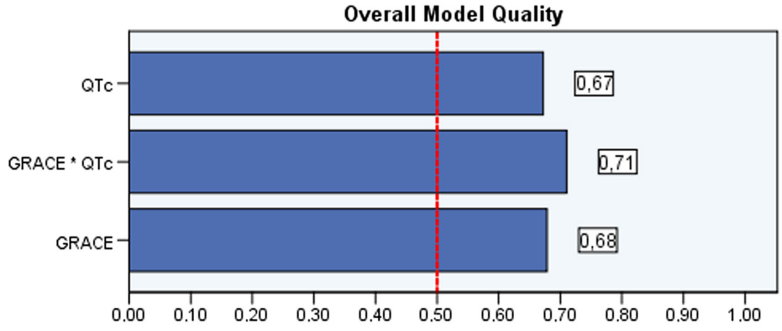


Figure 2. Receiver operating characteristic (ROC) curves analysis. The area under value was 0.769 (95% CI:0.674–0.863, *P*<0.001) for the QTc interval and 0.780 (95% CI:0.681–0.878; *P*<0.001) for the GRACE risk score alone. However, when the QTc interval and the GRACE risk score were combined, it was found to be 0.808 (95% CI:0.713–0.904, *P*<0.001).



Paired-Sample Area Difference Under the ROC Curves

Test Result Pair(s)	Asymptotic z	Asymptotic Sig. (2-tail)[a]	AUC Difference	Std. Error Difference[b]	Asymptotic 95% Confidence Interval Lower Bound	Asymptotic 95% Confidence Interval Upper Bound
GRACE - QTc	.217	.828	.011	.313	-.088	.110
GRACE - QTc_1_1	-2.384	.017	-.029	.311	-.052	-.005
QTc - QTc_1_1	-.962	.336	-.040	.310	-.120	.041

a. Null hypothesis: true area difference = 0

b. Under the nonparametric assumption

Figure 3. The results of the comparison of the ROC curves. ROC, receiver-operating characteristic.

The QTc interval showed a significantly positive correlation with age ($r = 0.214$, $P < .001$), GRACE risk score ($r = 0.266$, $P < .0001$), and QRS duration ($r = 0.256$, $P < .001$). When the QTc interval was evaluated according to the GRACE risk strata, the high-risk group had a QTc interval of 432.30 ± 34.24 ms, the medium-risk group had a QTc interval of 424.08 ± 31.59 ms, and the low-risk group had a QTc interval of 414.07 ± 30.82 ms ($P < .001$) (Figure 1).

A total of 17 (6%) patients died during the follow-up. Of these, 10 (16.9%, $P < .001$) had a prolonged QTc interval. When the patients were divided into 2 groups based on mortality, the group with early mortality rate had higher age, lower EF, lower Hb value, higher QRS duration, and higher GRACE risk score. Coronary artery disease risk factors such as hypertension (HT) and history of CAD were more common in the mortality group, but smoking was less common in that group (Table 2). The QTc interval was significantly higher in the group showing early mortality (450.47 ± 27.26 vs. 419.97 ± 31.89, $P < .001$). In multivariate logistic regression analysis, QTc interval and GRACE risk score emerged as only independent predictors (Table 3).

A ROC curve analysis was performed to evaluate the power of a combination of the QTc interval with the GRACE risk score to predict early mortality in patients with NSTE-ACS. The area under the ROC curve was 0.769 (95% CI: 0.674-0.863, $P < .001$) for the QTc interval alone and 0.780 (95% CI: 0.681-0.878; $P < .001$) for the GRACE risk score alone. However, when the QTc interval and the GRACE risk score were combined, the area under the ROC curve increased to 0.808 (95% CI: 0.713-0.904, $P < .001$) (Figure 2). The results of the comparison of the ROC curves are presented in Figure 3.

Discussion

Our results demonstrate that both QTc interval and GRACE risk score can independently predict early mortality in patients with NSTE-ACS. Moreover, the combination of the QTc interval and GRACE risk score may increase the predictive value compared to use of only one of these parameters.

Patients presenting with NSTE-ACS are at high risk for death and other serious cardiovascular events. In our patient population, the early death rate was 6%, which is slightly higher than in previous studies.[14] To identify the patients with high mortality risk, baseline risk assessment is one of the most important steps in NSTE-ACS management. Appropriate treatment based on the risk stratification has the potential to improve clinical outcomes in these patients.[15,16] The GRACE risk score across the entire ACS spectrum has provided an excellent ability to assess the early and long-term mortality risk in patients.[17] However, several studies are still being conducted to determine the risk level of these patients more accurately and rapidly. Previous studies have reported that the GRACE risk score increases the predictive value of cardiovascular events when combined with other potential ACS risk factors such as the B-type natriuretic peptide[18] and the neutrophil to lymphocyte ratio.[19] To our knowledge, none of the previous studies have demonstrated the relationship between the GRACE risk score and the QTc interval. Our study is the first to show that the QTc interval has a significant and positive correlation with the GRACE risk score and that the combination of these 2 factors may better predict early mortality in NSTE-ACS patients.

The prolongation of the QTc interval is an important clinical tool for the early diagnosis of ischemia[20,21] and the identification of patients at high risk of developing life-threatening arrhythmias that cause sudden cardiac death. Evidence from the recent

studies has provided important information revealing the prognostic role of the measurement of QTc interval in patients with NSTE-ACS. Gadelata et al[8] have reported that the prolongation of the QTc interval (>458 ms) on the admission ECG was an independent predictor of cardiovascular risk in patients with NSTE-ACS. Jiménez-Candil et al[22] reported that there was an increase in death, recurrent ischemia, or the need for urgent revascularization within 17 months of follow-up in NSTE-ACS patients with a QTc interval of >450 ms on admission. These researchers later demonstrated that a QTc interval of >450 ms on admission had independent prognostic value apart from ST-segment abnormalities and troponin I values.[5] Similarly, it was stated that QTc prolongation predicts ACS and death in patients with chest pain and at least one risk factor presenting to ED.[23] In our study, QTc interval prolongation was more common among NSTE-MI patients than USAP patients. Previous studies have reported a significant prolongation of the QTc interval in patients with USAP and NSTEMI, which is associated with the incidence of short-term adverse events.[7,24-25]

Limitations

This was a single-center, retrospective cohort study with limited sample size and a short follow-up duration. It has increasingly been acknowledged that STE/NSTE dichotomy maybe not as appropriate as previously thought.[26] Subtle acute coronary occlusions may present without obvious ST-segment elevation and this may cause prolonged QTc as well as increased mortality. However, we did not use an acute coronary occlusion endpoint[27] in our study, which may have accounted for the observed outcomes. The QT, QTc, and QRS time intervals were measured by 2 physicians, but interobserver variability was not assessed. Lastly, our sample size was not sufficient to run a ROC comparison for the GRACE risk score alone and in-combination with QTc interval.

Conclusion

The GRACE risk score and prolonged QTc independently predict early mortality in patients with NSTE-ACS. A combination of the QTc interval with the GRACE risk score may increase the accuracy of predicting early mortality. Further studies are needed to evaluate the utility of QTc interval as an addition to the GRACE risk score.

Ethics Committee Approval: Approval for this study was obtained from the Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Approval Date: January 11, 2021; Approval Number: 102/19).

Informed Consent: The need for a written informed consent form from each participant was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.D.I.; Design – S.D.I.; Supervision – S.D.I., M.A.T.; Funding – H.S., N.B.Ö.; Materials – A.T., M.A.; Data Collection and/or Processing – S.D.I., H.S.; Analysis and/or Interpretation – S.D.I., M.A.T.; Literature Review – S.T.Ş., C.A.; Writing – S.D.I.; Critical Review – M.A.T., H.G.

Declaration of Interests: The authors in this study did not declare any conflict of interest to disclose.

Funding: This study did not receive financial support.

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