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The relationship between corrected QT interval and neutrophil to lymphocyte ratio in patients with acute coronary syndrome

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Ethics Committee Approval
The study protocol was made with the approval of Diskapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee with the number 11.01.2021 / 102/19.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: In recent years, prolonged corrected QT (QTc) interval is thought to be an independent risk factor in patients with Acute Coronary Syndrome (ACS). Our aim in this study is to determine whether there is a relationship between the Neutrophil/Lymphocyte Ratio (NLR), which is a new inflammatory parameter, and prolonged QTc corrected (QTc) interval in patients with ACS.
Methods: In a retrospective cohort study, 649 patients with ACS were enrolled from January 2017 to July 2019, out of which ninety-two patients died during follow-up. Patients were divided into two groups according to the prolonged QTc interval (QTc ≥450 msec). The relationship between QTc interval prolongation and NLR was evaluated. The primary endpoint was early all-cause death.
Results: Thirty-one of 135 patients (22.9% *P*=0.002) with QTc interval prolongation and 61 of 514 patients without QTc prolongation (11.8% *P*=0.002) died. Prolonged QTc interval was positively correlated with NLR (r=0.20, *P*=0.001). Both NLR (OR: 1,016; 95% CI: 1.004–1.028; *P*=0.01) and QTc interval (OR: 1.016; 95% CI: 1.004–1.028; *P*=0.006) independently predicted early mortality. In the ROC curve analysis, the AUC value of QTc interval to predict in-hospital mortality was 0.680 (95% CI: 0.597-0.763; *P*=0.001), with a sensitivity of 35%, a specificity of 82% and an optimum cut-off value of ≥450 msec. The AUC value of NLR to predict in-hospital mortality was 0.711 (95% CI: 0.653-0.769; *P*<0.001), with a sensitivity of 64%, a specificity of 68% and an optimum cut-off value of ≥3.9.
Conclusion: In this study, we showed that prolonged QTc interval was positively associated with NLR, which is an indicator of systemic inflammation in patients with ACS, for the first time. Also, QTc interval prolongation and increased NLR were independent predictors of early mortality.

Keywords: Systemic inflammation, Early mortality, Electrocardiography

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Introduction

Acute Coronary Syndromes (ACS) are among the most important causes of morbidity and mortality worldwide, especially in developed countries [1]. The heart rate-corrected QT interval predisposes patients with ACS to serious ventricular arrhythmias and is considered an indicator of arrhythmic risk. It also represents the action potential duration of depolarization and repolarization of the ventricle [2, 3]. The reason for prolongation in the QTc interval can be congenital or acquired, and include structural heart diseases, bradyarrhythmias, endocrine diseases, liver diseases, nervous system traumas, some infections such as HIV infection, hunger, hypothermia, drugs, and toxins [3].

In acute coronary events, inflammatory cells play an essential role in the initiation, progression, and rupture of atherosclerotic plaques. Neutrophil/Lymphocyte Ratio (NLR) has been evaluated in many cardiovascular diseases as a new inflammatory biomarker, especially in patients with ACS. The predictive effect of adverse cardiac events was reported in previous studies [4, 5]. It has been stated recently that systemic inflammation may cause prolongation of the QTc interval. To the best of our knowledge, no studies examine the relationship between the QTc interval and NLR, one of the new inflammatory parameters. We aimed to investigate the relationship between prolonged QTc interval and NLR and early hospital mortality in patients with ACS.

Materials and methods

We retrospectively collected demographic and clinical data of patients with ACS who were admitted to the Coronary Intensive Care Unit (CICU) between January 2017 and July 2019. A total of 700 ACS patients were included in the study, and fifty-one were excluded due to lack of data [Electrocardiography (ECG) or laboratory data]. Finally, 649 patients were evaluated, including 365 (56.2%) patients with ST-elevation myocardial infarction (MI), 220 (33.8%) patients with non-ST-elevation MI, and 64 (9.8%) patients with unstable angina. The AMI diagnostic criteria are based on the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force [6]. Diagnostic criteria for MI are as follows: (a) Electrocardiographic changes (ST-segment depression or 1 mm ST-segment elevation in 2 standard leads or two adjacent precordial leads, development of new left bundle branch block), (b) angina pectoris or angina equivalent symptoms, (c) specific cardiac biomarker elevations in troponin-I (>99th percentile of normal value), and (d) new marks of viable myocardial loss or regional wall motion defect on imaging methods [7]. Patients with STEMI were characterized by typical chest pain lasting >30 minutes at rest and met the above criteria on ECG with positive cardiac markers. Patients identified as NSTEMI had positive cardiac enzymes with typical chest pain symptoms but no ST-segment elevation in ECG. Unstable angina was defined as the occurrence of one or more angina episodes at rest in the last 48 hours or a progressive worsening of chest pain with normal cardiac biomarker values and no ST-segment elevation criteria in ECG. Coronary angiograpy was performed to all study patients and primary angioplasty of the culprit lesion was performed according to standard techniques. The treatment of all patients was arranged by the current guideline recommendations, and antiaggregant, angiotensin-converting enzyme inhibitors, beta-blockers and statin treatment were initiated within the first 24 hours after hospitalization in patients without contraindications.

Hypertension (HT) was defined as repeated blood pressure measurements with systolic blood pressure higher than 140 mmHg and diastolic blood pressure higher than 90 mmHg or previously using antihypertensive drugs. Diabetes mellitus (DM) was defined as fasting blood glucose levels above 126 mg/dL or above 200 mg/dL at any given time, using blood glucose-lowering medication or hemoglobin (Hb) A1c levels greater than 6.5%.

Patients with various ECG features such as atrial fibrillation, left or right bundle branch block or paced rhythm, complete atrioventricular block, incomplete or unreadable ECG printout, unreadable QT intervals, left ventricular (LV) hypertrophy, those with advanced heart valvular disease, history of cardiomyopathy, history of congenital heart disease, or implantable heart defibrillators, antidepressant, antipsychotic, and antiarrhythmic use, and patients with severe electrolyte disturbances were excluded from the study. Follow up was performed for all patients during their hospital stay and for one month after discharge. All-cause death was the primary endpoint, observed within 30 days of release from the hospital.

Traditional cardiovascular risk factors such as age, gender, HT, DM, hyperlipidemia, smoking and biochemical parameters such as glucose, creatinine, low-density lipoprotein (LDL) cholesterol, triglycerides, troponin I, and highly sensitive-C Reactive Protein (hs-CRP) were recorded. Transthoracic echocardiography was performed in all patients following standard images and techniques.

White blood cell (WBC) and differential counts (Beckman Coulter Inc., Hialeah, Florida, USA) were measured from blood samples (filled into tubes with standardized EDTA: Ethylenediamine tetraacetic acid) obtained at the time of admission to the Emergency Department (ED). Total neutrophil and lymphocyte counts were found, and NLR was automatically calculated with the statistical program used.

Our study adhered to the Helsinki Declaration principles. The study protocol was approved by Diskapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee with the number 11.01.2021/ 102/19.

Assessment of ECG

In all patients, 12-lead ECG recordings were taken in the supine position using a new generation ECG system (Cardiofax V model 9320, Nihon Kohden, Tokyo, Japan) with a paper speed of 25 mm/sec and a voltage of 10 mm/mV. After the patients were admitted to the CICU, the first ECG (or the first ECG before admission to the ED) was examined. ECG data was collected by two researchers who did not know of the patients' clinical statuses. The QT interval in ECG was measured as the time elapsed from the beginning of the QRS wave to where the T wave returned to its starting point on ECG [8]. The QTc interval was measured using the Bazett formula on the entire standard 12-lead ECG. We accepted the cut-off point defining the QTc interval extension as 450 msec [9]. Therefore, we divided our patients into two groups according to the QTc interval: Patients

without a prolonged QTc interval: <450 msec, and those with a long QTc interval: ≥450 msec

Statistical analysis

SPPS 25 (IBM Corp. Published 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used to evaluate the data. Variables were calculated as mean (standard deviation) and percentage and frequency values. Shapiro Wilk and Levene tests were used for assessing the variables for normality and variance homogeneity preconditions. Independent 2-group t-test (Student's t-test) was used to compare the two groups' analysis, and Mann Whitney-U test was used if the prerequisites were not met. Chi-Square and Fisher's exact tests were used for categorical data. The relationship between two continuous variables was evaluated with Pearson's Correlation Coefficient and Spearman's Correlation Coefficient. Binary logistic regression analysis was used to evaluate the significance of the data on mortality and adjusted odd ratios (OR) at 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve analysis was performed for the cut-off values in the variables' responses. The area under the curve (AUC) was calculated such that sensitivity and selectivity were maximum. Values of $P<0.05$ and $P<0.01$ were considered significant.

Results

The study population consisted of 649 patients with ACS, and 68% of which were males (n=469). The ages of the patients ranged between 28-98 years, with a mean of 60.67 (13.03) years. Table 1 shows the overall characteristics of all patients included in this study. Also, baseline characteristics of patients divided according to QTc interval prolongation are presented in Table 1. In the group with prolonged QTc interval, age, the number of diabetic patients and the number of patients with pre-existing coronary artery disease (CAD), and NLR ($P=0.02$) were higher, while Hb and LV ejection fraction (LVEF) were significantly lower.

Table 1: Baseline characteristics of patients

Variables	All patients (n=649)	No QTc prolonged (n=514)	QTc prolonged (n=135)	*P*-value
Age, (years)	60.67 (13.03)	59.93 (12.79)	63.46 (13.60)	0.005
BMI, (kg/m^2)	27.52 (4.50)	27.42 (4.54)	27.96 (4.35)	0.490
Gender, men, n (%)	469 (68)	372 (72.3)	97 (71.8)	0.914
HT, n (%)	314 (45)	239 (46.4)	75 (55.5)	0.065
DM, n (%)	189 (27)	140 (27.2)	49 (36.2)	0.043
Smoker, n (%)	326 (47)	271 (52.7)	55 (40.7)	0.008
Previous CAD, n (%)	201 (29)	148 (28.7)	54 (40.0)	0.008
HR, (beats/min)	76.19 (15.09)	75.98 (15.41)	76.99 (13.84)	0.492
SBP, (mmHg)	134.4 (26.52)	134.0 (26.43)	135.92 (26.91)	0.457
DBP, (mmHg)	78.53 (16.54)	78.52 (17.07)	78.60 (14.39)	0.961
Glucose,(mg/dL)	141.5 (64.1)	140.47 (64.47)	145.59 (63.15)	0.411
Creatinine,(mg/dL)	1.22 (0.91)	1.19 (0.80)	1.34 (1.25)	0.098
Sodium, (mEq/L)	136.8 (2.8)	136.76 (2.82)	137.03 (2.93)	0.336
Potassium, (mEq/L)	4.1 (0.48)	4.10 (0.46)	4.07 (0.54)	0.515
ALT, (mg/dL)	67.9 (101.2)	66.09 (103.28)	75.22 (93.05)	0.353
LDL-C, (mg/dL)	128.4 (34.9)	128.81 (35.02)	127.05 (34.96)	0.609
Triglycerides, (mg/dL)	154.43 (96.52)	158.97 (99.82)	137.24 (80.91)	0.023
Hb, (g/dL)	14.2 (2.0)	14.37 (2.03)	13.70 (2.07)	0.001
Platelet, (10^9/µL)	250.7 (73.7)	249.05 (72.47)	257.01 (78.40)	0.265
WBC, (10^9/µL)	11.02 (3.7)	11.0 (3.75)	11.08 (3.78)	0.825
Neutrophile, (10^9/µL)	7.49 (3.39)	7.35 (3.54)	8.00 (3.55)	0.053
Lymphocyte, (10^9/µL)	2.57 (1.49)	2.73 (1.88)	2.36 (1.39)	0.015
Hs-CRP, (mg/L)	30.66 (50.14)	30.37 (51.99)	31.83 (42.17)	0.800
Troponin T, (ng/mL)	7.35 (20.8)	7.29 (20.97)	7.57 (20.21)	0.887
EF (%)	48.18 (9.43)	48.60 (9.40)	46.57 (9.41)	0.030
QT interval, (msec)	386.30 (40.56)	376.46 (35.83)	424.07 (35.24)	0.001
QTc interval,(msec)	421.97 (34.02)	409.40 (24.44)	469.62 (20.31)	0.001
NLR	4.11 (3.77)	3.93 (3.75)	4.76 (3.78)	0.026

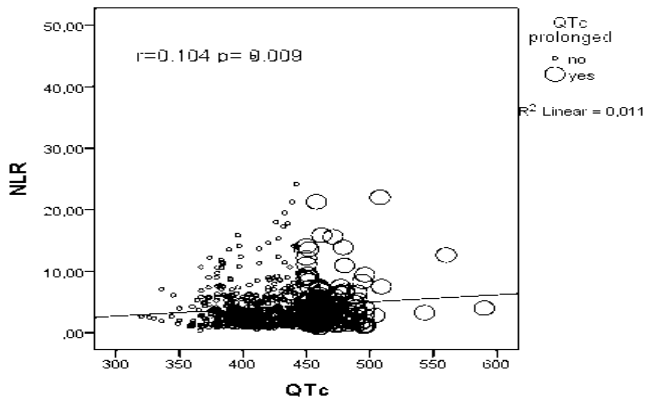
BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: Alanine aminotransferase, LDL-C: low density lipoprotein cholesterol, Hb: Hemoglobin, EF: ejection fraction, WBC: White blood cell, Hs-CRP: highly sensitive C-reactive protein, QTc: corrected QT, NLR: Neutrophile / lymphocyte ratio

Pearson's and Spearman's Correlation analysis was performed for the factors associated with the QTc interval prolongation. In correlation analysis, QTc interval prolongation significantly positively correlated with age and NLR and negatively correlated with Hb and LVEF (Table 2). The correlation between QTc interval prolongation and NLR is shown in Figure 1.

Table 2: Factors correlated with the QTc interval

Variables	QTc interval	
	r	*P*-value
Age, years	0.176	<0.001
EF, (%)	0.097	0.016
Hb, (g/dL)	-0.153	<0.001
Lymphocyte, (10^9/µL)	-0.061	0.120
NLR	0.104	0.009

Figure 1: Correlation of QTc interval with NLR



A total of 92 (14.1%) patients died during follow-up. When patients were grouped in terms of mortality, risk factors such as age, DM, HT, and CAD history were higher in the mortality group (Table 3). Also, there was a significant difference in heart rate, LVEF, creatinine, and Hb in the mortality group. The QTc interval and NLR values were significantly higher ($P<0.001$) in the mortality group (Table 3). Independent variables affecting mortality were age, LVEF, Hb, creatinine, QTc interval, and NLR in binary logistic regression analysis (Table 4). In the ROC curve analysis, the AUC value of QTc interval to predict early hospital mortality was 0.680 (95% CI: 0.597-0.763; $P=0.001$), with a sensitivity of 35%, a specificity of 82% and an optimum cut-off value of ≥450 msec. The AUC value of NLR to predict early hospital mortality was 0.711 (95% CI: 0.653-0.769; $P<0.001$), with a sensitivity of 64%; a specificity of 68% and an optimum cut-off value of ≥3.9 (Figure 2).

Table 3: Comparison of the clinical features of the patients according to early mortality

Variables	Mortality (+) (n=92)	Mortality (-) (n=557)	*P*-value
Age, years	72.47 (11.84)	58.71 (12.78)	<0.001
Men, n (%)	61 (66)	408 (73)	0.169
BMI, kg/m^2	28.10 (5.52)	27.42 (4.32)	0.439
HT, n (%)	63 (68)	251 (45)	<0.001
DM, n (%)	45 (49)	144 (26)	<0.001
Smoker, n (%)	24 (26)	303 (54)	<0.001
Previous CAD, n (%)	41 (45)	160 (29)	0.008
HR(beats/min)	81.87 (15.94)	75.25 (14.25)	<0.001
SBP (mmHg)	134.49 (23.90)	134.39 (26.93)	0.973
EF, (%)	44.83 (10.38)	48.69 (9.19)	0.001
Hb, (g/dL)	12.61 (2.07)	14.49 (1.93)	<0.001
Glucose, (mg/dL)	151.72 (66.7)	139.89 (63.67)	0.105
Creatinine, (mg/dL)	1.54 (1.05)	1.17 (0.88)	0.001
Hs-Troponin, (ng/mL)	8.24 (16.98)	7.20 (21.37)	0.661
WBC, (10^9/µL)	11.36 (4.59)	10.96 (3.62)	0.352
QTc interval, (msec)	434.48 (43.23)	419.86 (31.81)	<0.001
NLR	6.74 (6.14)	3.66 (2.99)	<0.001

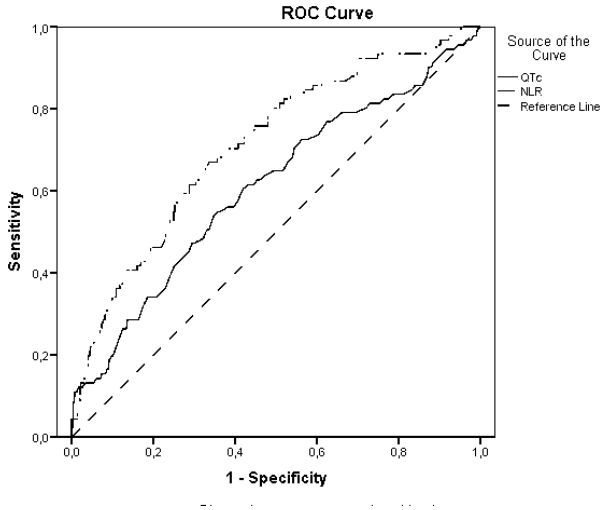
BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HR: heart rate, SBP: systolic blood pressure, EF: ejection fraction, Hb: hemoglobin, WBC: White blood cell, QTc: corrected QT, NLR: Neutrophile / lymphocyte ratio

Table 4: Different variables affecting early mortality in binary logistic regression analysis

Variables	OR	95% CI	*P*-value
NLR	1.080	1.007-1.157	0.031
QTc interval, (msec)	1.011	1.003-1.020	0.009
EF, (%)	0.959	0.930-0.989	0.007
Hb, (g/dL)	0.764	0.651-0.896	0.001
Age, years	1.078	1.049-1.108	<0.001
Creatinine, (mg/dL)	0.942	0.735-1.207	0.637

OR: Odds ratio, CI: Confidence interval, QTc: corrected QT, NLR: Neutrophile / lymphocyte ratio, EF: ejection fraction, Hb: hemoglobin

Figure 2: Receiver operating characteristic curve analysis; NLR (AUC: 0.711, CI: 0.653-0.769; *P*=0.001), QTc (AUC: 0.608, CI 0.542-0.675; *P*<0.001)



Discussion

This study examines the relationship between NLR and QTc interval calculated during admission to CICU in patients with ACS. Our main finding was that NLR was significantly higher in the group with prolonged QTc interval; a significant positive correlation was found between these two parameters. Other inflammatory parameters such as WBC, neutrophil count, and hs-CRP were not significantly different between the groups. Lymphocyte count was lower in the QTc prolonged group, but no correlation was found between lymphocyte count and QTc prolongation.

Inflammation plays a vital role in all stages from the initial phase of atherosclerotic plaque to the development of clinical complications such as ACS [10]. Studies have reported that WBC and its subtypes indicate systemic inflammation and have a vital role in regulating the atherosclerotic process's inflammatory response [11, 12]. In acute coronary events, because of the decrease or interruption of the coronary vessel flow, leukocytes accumulate in the infarction area and regulate the response of the inflammation. Neutrophils are thought to be the first to accumulate [13]. They have several functions such as regulating and enhancing the inflammatory process by increasing their numbers in this region and causing the release of various mediators such as prothrombotic, proteolytic enzymes and oxidant substances, while lymphocytes decrease in number because of glucocorticoids secreted due to increased stress response [13, 14]. NLR represents a combination of neutrophils and lymphocytes, which are components of two independent inflammatory reactions. NLR is one of the new, easy and straight-forward inflammatory markers which has been used frequently in recent years. In one study, NLR was predictive of adverse outcomes in 34,000 ACS patients undergoing coronary revascularization and various other cardiovascular diseases [15, 16]. Also, it has been stated in previous studies that inflammation is associated with various types of cardiac arrhythmias [17, 18].

Significant prolongation of the QTc interval poses a significant risk for life-threatening ventricular arrhythmias such as Torsade de pointes [19]. In addition to congenital QT prolongation, many acquired diseases or conditions, such as ischemic heart disease, left ventricular hypertrophy, heart failure, Takotsubo cardiomyopathy, complete atrioventricular block or any bradyarrhythmia, inflammatory rheumatic heart disease (myocarditis, Chagas disease, rheumatic heart disease) or systemic inflammatory diseases (rheumatoid arthritis, connective tissue diseases), end-stage liver disease, endocrine disorders, cerebrovascular diseases, hypokalaemia, hypocalcemia, hypomagnesemia, drugs or toxins may cause QT prolongation [3-20]. Recent studies show that inflammation and immunity may be important determinants of prolonged QTc [3, 21, 22]. Systemic inflammation is thought to play a role in the pathogenesis of QTc prolongation in some non-inflammatory heart diseases. In patients with HT [23], Chang et al. reported that CRP level was associated with QTc and independently predicted prolonged QTc. Similarly, in another study, a significant relationship was reported between QTc duration and CRP level in patients with CAD [24]. There was no significant difference in WBC, neutrophil count, and hs-CRP between the groups in our study, but prolonged QTc group had a lower lymphocyte count. Still, there was no correlation between lymphocyte count and QTc prolongation. A significant positive correlation was found between QTc prolongation and NLR. Both parameters were predictors of early mortality. However, to the best of our knowledge, there are no studies examining the relationship between the QTc interval and NLR.

Limitations

Our study has numerous limitations. This is a single-center retrospective study, and the number of patients is not large due to the exclusion criteria. Unfortunately, the follow-up time was short (up to 30 days after discharge from the hospital), and long-term follow-up data are not available. Likewise, other inflammatory parameters, such as IL-1β, IL-6, and TNF-α, were not evaluated in our study.

Conclusions

It has been reported that prolonged QTc interval in patients with acute coronary syndrome is an early sign of acute ischemia. In these patients, prolonged QTc interval is considered a marker for adverse events, particularly arrhythmia [18, 25]. Systemic inflammation has a major place in the pathophysiology of many heart diseases and may prolong the QTc interval [23-24]. In this study, we found that NLR, a new inflammatory marker, was significantly higher in the group with prolonged QTc interval in patients with ACS, a significant positive correlation existed between these two parameters. Additionally, these two parameters were independent predictors of early mortality. Inflammation alone cannot explain QTc prolongation in patients with ACS, but it may be a synergistically contributing factor. More comprehensive prospective studies are needed to better evaluate this.

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