

Relationship between Neutrophil-To-Lymphocyte Ratio and Electrocardiographic Ischemia Grade in STEMI

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Abstract

Background: Neutrophil-to-lymphocyte ratio (NLR) has been found to be a good predictor of future adverse cardiovascular outcomes in patients with ST-segment elevation myocardial infarction (STEMI). Changes in the QRS terminal portion have also been associated with adverse outcomes following STEMI.

Objectives: To investigate the relationship between ECG ischemia grade and NLR in patients presenting with STEMI, in order to determine additional conventional risk factors for early risk stratification.

Methods: Patients with STEMI were investigated. The grade of ischemia was analyzed from the ECG performed on admission. White blood cells and subtypes were measured as part of the automated complete blood count (CBC) analysis. Patients were classified into two groups according to the ischemia grade presented on the admission ECG, as grade 2 ischemia (G2I) and grade 3 ischemia (G3I).

Results: Patients with G3I had significantly lower mean left ventricular ejection fraction than those in G2I (44.58 ± 7.23 vs. 48.44 ± 7.61 , $p = 0.001$). As expected, in-hospital mortality rate increased proportionally with the increase in ischemia grade ($p = 0.036$). There were significant differences in percentage of lymphocytes ($p = 0.010$) and percentage of neutrophils ($p = 0.004$), and therefore, NLR was significantly different between G2I and G3I patients ($p < 0.001$). Multivariate logistic regression analysis revealed that only NLR was the independent variable with a significant effect on ECG ischemia grade (odds ratio = 1.254, 95% confidence interval 1.120–1.403, $p < 0.001$).

Conclusions: We found an association between G3I and elevated NLR in patients with STEMI. We believe that such an association might provide an additional prognostic value for risk stratification in patients with STEMI when combined with standardized risk scores. (Arq Bras Cardiol. 2015; 104(2):112-119)

Keywords: ST elevation myocardial infarction; neutrophil-to-lymphocyte ratio; electrocardiographically grade 3 ischemia.

Introduction

Early risk stratification is recommended in daily clinical practice to predict the infarct size, success of epicardial recanalization and risk of adverse outcomes in patients presenting with ST-segment elevation myocardial infarction (STEMI). In addition to the current risk scores, interest has recently been directed to the development of a set of bedside tools obtained from admission data to promptly predict the prognosis of arterial recanalization. Electrocardiographic and biochemical parameters are the mostly studied admission parameters to define the prognosis of patients with STEMI.

Complete blood count (CBC) analysis is routinely performed on admission and carries important prognostic information.

The neutrophil-to-lymphocyte ratio (NLR), a combination of two independent markers of inflammation, is regarded as a simple, non-specific marker of inflammation¹. In this context, the NLR has been evaluated in various studies of coronary artery disease (CAD), especially STEMI, and emerged as a new, inexpensive risk assessment tool for patients with STEMI prior to revascularization²⁻⁵. Additionally, a number of parameters on the presenting electrocardiogram (ECG) have previously been associated with adverse outcomes following STEMI⁶. One of these parameters is the grade of ischemia, which can be readily determined by the presence of distortion of the terminal portion of the QRS complex on admission ECG without requiring any measurement⁷. Increased ischemia grade has been found in association with failure of myocardial reperfusion independent of other key predictors of outcomes in STEMI patients⁸. Although both NLR and ischemia grade have been shown to be useful in predicting adverse outcomes in patients with STEMI, their mechanisms are unclear and therefore, NLR and ischemia grade are not integrated in any risk scoring system.

We hypothesized that the prognostic value of leukocyte subtypes may at least be partially linked to a possible association with ECG ischemia grades in STEMI. In our study, we sought to identify available clinical and ECG characteristics

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on admission that might predict myocardial reperfusion and investigate whether NLR is related to ischemia grade on the admission ECG in patients with STEMI.

Methods

Patients

We investigated 253 patients who underwent primary percutaneous coronary intervention (pPCI) between February 2011 and June 2013 after diagnosis of STEMI. The diagnosis of myocardial infarction (MI) was determined by the occurrence of classic symptoms of coronary ischemia within 12 hours, elevation in cardiac biomarkers and detection of ST-segment elevation in two contiguous leads, as well defined by the guidelines of the American College of Cardiology and the European Society of Cardiology^{9,10}. Clinical and demographic characteristics were obtained from patients' medical records retrieved from the computerized hospital database. The following variables were retrospectively analyzed: age, cardiovascular risk factors (hypertension, smoking, diabetes mellitus and hypercholesterolemia), cardiovascular history (prior coronary revascularization, congestive heart failure and MI), and relevant family history of CAD, as well as systolic and diastolic blood pressures and heart rate on admission. Exclusion criteria included clinical evidence of active infection, systemic inflammatory disease, hematological disease, end-stage liver and kidney diseases, systemic autoimmune disease, known malignancy, isolated posterior MI, presence of left bundle branch block, paced / ventricular rhythm or grade 1 ischemia (G1I) on the presenting ECG, lack of laboratory data and unavailable ECG records. A total of 50 patients who met the exclusion criteria were not considered for the study. The final cohort analyzed consisted of 203 patients. The local ethics committee of our institute approved the study protocol.

Electrocardiographic analysis

On admission, 12 lead ECGs were immediately obtained at 25 mm/sec paper speed, and 10 mV gain. STEMI was determined by the occurrence of ST segment elevation, of 0.2 mV measured at the J point in leads V1-V3 or 0.1 mV on at least two contiguous leads of the remaining leads. The first ECG obtained after pPCI was analyzed for ST segment resolution (STR). As recommended by guidelines^{9,10}, we evaluated the percentage difference between the sum of the ST-segment elevation on the ECGs performed on admission and after the procedure. We defined as a complete STR the finding of a resolution $\geq 70\%$, as partial STR a resolution between 30% and 69%, and as having no STR a resolution $< 30\%$. The grade of ischemia was analyzed on the admission ECG. A G1I was defined as the presence of symmetrical, tall and peaked T waves, grade 2 ischemia (G2I) as ST elevation without distortion of the terminal portion of the QRS complex (J-point elevation > 1.0 mm but $< 50\%$ of the R-wave amplitude) and grade 3 ischemia (G3I) as ST elevation with distortion of the terminal portion of the QRS complex (ST-J-point amplitude $> 50\%$ of the R wave in leads with qR configuration, or absence of the S wave in leads with Rs configuration), as previously described^{7,11-13}. Two investigators

blinded to the patients' angiographic and clinical data analyzed the ECGs. After excluding patients with G1I, the remaining were classified into G2I and G3I according to their ischemia grade.

Biochemical analysis

Blood samples were drawn from the antecubital vein within 1 hour of admission. White blood cells (WBC) and subtypes were measured as part of the automated CBC analysis before pPCI and prior to starting any medication to prevent interference with the results. The NLR was automatically computed as the neutrophils to lymphocytes ratio, both obtained from the same blood sample. Other biochemical measurements including cardiac biomarkers, renal function, electrolytes and lipid panel were measured using standard laboratory methods.

Angiographic analysis

After an administration of bolus injection of intravenous heparin (70 U/kg), a coronary angiography was performed using the Judkins technique as immediately as possible. The decision on the type of coronary revascularization (pPCI or urgent coronary artery bypass grafting) was established according to current guidelines^{9,10}. The pPCI only targeted the infarct-related artery (IRA). Direct stenting was performed whenever possible, while the remaining cases were managed with balloon predilatation. A pPCI was considered successful when associated with angiographic success and relief of presenting symptoms, without adverse procedural results (coronary dissection, no-reflow, coronary emboli, residual thrombus or $> 50\%$ residual stenosis) or major adverse outcome (stroke, emergent coronary artery bypass graft or death). Stented patients received adjunctive dual antiplatelet therapy with clopidogrel and aspirin. The selection criterion for drug-eluting or bare-metal stent and the use of platelet glycoprotein IIb/IIIa receptor antagonists were left to the operator's discretion.

Statistical analysis

The data were tested for normal distributions using the Kolmogorov-Smirnov test. Continuous variables were presented as mean \pm standard deviation (SD) and categorical variables as percentages. Independent samples t test and chi-square test were used to compare quantitative and categorical data, respectively, between groups. Univariate correlation with NLR was performed with Spearman's and Pearson's correlation coefficients. Following univariate correlations, a multivariate linear regression model with a backward selection process was applied to identify independent predictors of NLR. The effects of various variables on ECG ischemia grade were evaluated with backward stepwise multivariate logistic regression analysis. Differences were considered statistically significant when the p value was < 0.05 . The Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA) version 20 was used for all calculations and statistical analyses.

Results

A total of 203 patients (163 men, mean age = 59.78 ± 13.49 years) with STEMI were included in this study. Patients

were classified into two groups according to the ischemia grade on admission ECG. Group 1 consisted of 126 patients with G2I (103 men, mean age = 59.15 ± 13.36 years) and group 2 consisted of 77 patients with G3I (60 men, mean age = 60.83 ± 13.71 years). Baseline clinical and demographic characteristics were similar in both groups (Table 1). A transthoracic echocardiography, performed on admission on all patients, showed that patients with G3I had significantly lower mean left ventricular ejection fraction than those with G2I (44.58 ± 7.23 vs. 48.44 ± 7.61 , $p = 0.001$). All patients had subtotal or total occlusion of the IRA before pPCI procedure. The LAD was defined as the IRA in 39.7% of patients with G2I and 59.7% of patients with G3I ($p = 0.031$), therefore, the frequency of anterior MI was significantly higher than that of non-anterior MI in patients with G3I compared with G2I patients (46 patients vs. 50 patients, $p = 0.002$). pPCI with stent implantation was performed in 147 (72.1%) patients participating in the study.

There were no statistically significant differences between groups in terms of time from symptoms to admission, door-to-needle time, PCI with stent implantation, type of stent used and medication administered (including glycoprotein IIb/IIIa inhibitors and dual antiplatelet therapy).

For STR, there was a statistically significant difference between the groups. Partial and no STR were more frequent in G3I patients, whereas the rate of complete STR was higher in G2I patients ($p = 0.008$). As expected, in-hospital mortality rate increased proportionally to the increase in grade of ischemia ($p = 0.036$).

There were significant differences in percentages of lymphocytes ($p = 0.010$) and neutrophils ($p = 0.004$), consequently, NLR was significantly different in G2I and G3I patients ($p < 0.001$). In contrast, WBC did not differ between groups. After categorizing the patients according to their STR findings, we found that patients with no STR had higher NLR values compared with those with complete and partial STR. Mean NLR value was 3.55 ± 2.48 for patients with complete STR, 6.26 ± 3.62 for those with partial STR and 8.44 ± 5.67 for those with no STR ($p < 0.001$). NLR was also higher in patients in whom in-hospital mortality occurred than the remaining patients (6.42 ± 6.11 vs. 4.03 ± 2.84 , $p = 0.007$). Other hematological and biochemical parameters were similar in both groups (Table 2).

In univariate correlation analysis, STR, ischemia grade, time from symptoms to admission, in-hospital mortality, hospitalization duration, admission systolic blood pressure, and serum glucose and urea correlated significantly with NLR ($p < 0.05$ for all). Variables that correlated significantly with NLR and other variables (hyperlipidemia, left ventricular ejection fraction, anterior MI and infarct related artery) that exhibited significant differences between the G2I and G3I groups were included in the univariate regression analysis. To determine the independent variables likely to predict NLR, including variables that remained in the univariate regression model ($p < 0.05$), a backward multivariate linear regression analysis was performed. We found that ECG ischemia grade ($\beta = 1.017$, $p = 0.001$), STR ($\beta = 2.527$, $p < 0.001$) and in-hospital mortality ($\beta = -2.445$, $p = 0.025$) were significant independent predictors of NLR (Table 3). Variables included

in the univariate regression model for prediction of NLR and other variables (NLR, age and gender) considered as predictors of ECG ischemia grade were evaluated with univariate logistic regression analysis. Variables that remained in the univariate regression model ($p < 0.05$) were included in the backward stepwise multivariate regression analysis to determine independent predictors of ECG ischemia grade. Multivariate logistic regression analysis showed that only NLR (odds ratio = 1.254, 95% confidence interval 1.120–1.403, $p < 0.001$) emerged as an independent variable after demonstrating a significant effect on the ECG ischemia grade (Table 4).

Discussion

In this study, we showed that NLR was independently associated with ECG ischemia grade in patients with STEMI.

With the growing understanding of the pathophysiological role of WBC counts in the STEMI process, many studies that have focused on this topic have shown that the increase in WBC count is associated with worse clinical outcomes and all-cause mortality in patients with STEMI^{14,15}. Nonetheless, WBC subtypes have been found to be superior to WBC in modulating the inflammatory response in the setting of STEMI. Neutrophils are the first leukocytes to be found in the damaged myocardial area¹⁶. Activated neutrophils exacerbate the inflammatory response through secretion of a variety of inflammatory mediators including myeloperoxidase, elastase, oxygen free radicals and arachidonic acid derivatives¹⁷⁻¹⁹. These neutrophil-mediated inflammatory processes that occur during STEMI cause additional tissue damage, plaque disruption, activation of coagulation pathways and thrombosis, microvascular plugging, myocyte necrosis and enlargement of the infarct size^{20,21}. In contrast to neutrophils, lymphocytes infiltrating the ischemic myocardium represent the regulatory arm of the inflammatory and cytotoxic response²² and play a significant role in the healing process of the heart during the course of STEMI²³. However, in patients presenting with MI, low lymphocyte count – particularly CD4+ count – is a common finding²⁴. Consequently, the inflammatory process occurring during the course of STEMI is mediated by the complex interaction between innate neutrophil mediated reactive immune responses and subsequent lymphocyte mediated adaptive immune responses. Also, many previous studies have demonstrated that NLR has superior predictive value compared with counts of leukocytes and their subtypes in predicting worse clinical outcomes in patients with STEMI^{2-4,25}. As a result of these studies, the addition of NLR to conventional risk factors for early risk stratification of STEMI patients has been suggested.

Various parameters on the admission ECG, such as sum of ST elevation, number of Q waves and bundle branch block, have been correlated with short- and long-term adverse outcomes in patients with STEMI^{26,27}. In addition, recent studies have focused on one such presenting ECG parameter, the determination of distortion of the terminal portion of the QRS complex in leads in which ST segment elevations are seen. The local Purkinje fibers

Table 1 – Basal demographic and clinical characteristics

	Grade 2 Ischemia (n = 126)	Grade 3 Ischemia (n = 77)	p
Age, (years)	59.15 ± 13.36	60.83 ± 13.71	0.391
Male, n (%)	103 (81.7)	60 (77.9)	0.312
Hypertension, n (%)	56 (44.4)	38 (49.4)	0.296
Hyperlipidemia, n (%)	39 (31.2)	15 (19.5)	0.047
Diabetes mellitus, n (%)	30 (24)	21 (27.3)	0.360
Smoking, n (%)	37 (29.4)	22 (28.6)	0.517
Previous coronary artery disease, n (%)	32 (25.4)	15 (19.5)	0.213
Admission systolic blood pressure, (mmHg)	129.79 ± 23.63	133.89 ± 22.83	0.231
Admission diastolic blood pressure, (mmHg)	76.24 ± 13.80	78.86 ± 16.47	0.229
Admission heart rate, (bpm)	76.69 ± 11.79	78.92 ± 11.51	0.188
Time from symptoms to admission (hour)	4.36 ± 3.18	5.15 ± 3.88	0.129
Hospitalization (days)	5.26 ± 1.23	5.44 ± 1.38	0.359
Left ventricular ejection fraction (%)	48.44 ± 7.61	44.58 ± 7.23	0.001
Anterior myocardial infarction, n (%)	50 (39.7)	46 (61.0)	0.002
Infarct-related artery			
Left anterior descending artery	50 (39.7)	46 (59.7)	0.031
Circumflex artery	26 (20.6)	14 (18.2)	
Right coronary artery	46 (36.5)	15 (19.5)	
LMCA/SVG/intermediate/diagonal/ obtuse	4 (3.2)	2 (2.6)	
PCI with stent implantation, n (%)	87 (69.0)	60 (77.9)	0.112
ST-segment resolution, n (%)			
Complete	109 (86.5)	54 (70.1)	0.008
Partial	14 (11.1)	15 (19.5)	
No	3 (2.4)	8 (10.4)	
In-hospital mortality, n (%)	5 (4.0)	9 (11.7)	0.036

LMCA: left main coronary artery, SVG: saphenous vein graft, PCI: percutaneous coronary intervention.

are less sensitive to ischemia and conduct impulses more slowly than the contracting myocytes²⁸. Increases in the R-wave amplitude and decreases in the S-wave amplitude and, therefore, changes in the terminal portion of the QRS develop due to prolonged delay in the electrical conduction of the Purkinje system induced by ischemia^{29,30}. With respect to these changes, the grade of ischemia can be readily determined by changes in the terminal portion of the QRS on the surface ECG of STEMI patients and does not require any calculations. Three different ischemic ECG patterns can be seen in the leads corresponding to the ischemic zone⁷ (G11, G21 and G31). Among these ischemia grades, G31 has been correlated with more severe ischemia, more tissue damage, higher peak CKMB levels³⁰, less collateral circulation³¹ and pre-infarction angina which might precondition the heart and prevent G31 changes by either metabolic protective mechanisms or residual blood supply¹². This study also found that the frequency of G31 was higher in patients presenting with anterior STEMI than in those with non-anterior STEMI. We propose that

microcirculatory and increased tissue damages occur in patients with anterior STEMI because of the usually larger myocardial territory involved in the infarction of the left anterior descending coronary artery. In patients with STEMI, the grade of ischemia has emerged as an independent, strong predictor of adverse procedural outcome and mortality to a much greater extent than other initial ECG parameters^{32,33}. Many studies have demonstrated that patients with G31 on admission ECG have larger infarcts, poor tissue myocardial perfusion grades irrespective of the reperfusion modality, failure of STR, higher rates of reinfarction, lower left ventricular ejection fraction and therefore, increased mortality and longer hospital stay as compared with G21 patients^{30,34}.

STR is considered a simple and perhaps more accurate marker of microvascular reflow and adequate myocardial reperfusion after pPCI in STEMI³⁵. Recently, numerous studies have pointed to STR as a stronger prognostic marker in identifying tissue reperfusion than epicardial TIMI flow grade in the IRA^{35,36}. We therefore used STR

Table 2 – Hematological and biochemical parameters

	Grade 2 Ischemia (n = 126)	Grade 3 Ischemia (n = 77)	p
Serum glucose (mg/dL)	141.36 ± 56.51	155.85 ± 60.00	0.085
Urea, (mg/dL)	37.78 ± 15.92	41.88 ± 19.18	0.102
Creatinine, (mg/dL)	1.08 ± 0.33	1.19 ± 0.81	0.194
Serum uric acid, (mg/dL)	6.08 ± 1.64	5.98 ± 2.09	0.759
High-density lipoprotein cholesterol, (mg/dL)	41.08 ± 8.41	39.68 ± 8.07	0.260
Low-density lipoprotein cholesterol, (mg/dL)	118.44 ± 35.55	112.49 ± 40.70	0.296
Triglycerides, (mg/dL)	140.48 ± 77.64	151.47 ± 141.43	0.494
Total serum cholesterol, (mg/dL)	186.99 ± 39.37	177.10 ± 45.20	0.117
White blood cells, (10 ³ µL)	11.40 ± 33.34	12.30 ± 40.52	0.088
Neutrophils, (10 ³ µL)	7.45 ± 3.15	8.95 ± 4.03	0.004
Lymphocytes, (10 ³ µL)	2.86 ± 1.55	2.28 ± 1.47	0.010
Neutrophil / lymphocyte ratio	3.40 ± 2.38	5.51 ± 3.90	< 0.001
Hemoglobin, (g/dL)	14.12 ± 1.93	14.05 ± 2.16	0.800
Hematocrit, (%)	41.51 ± 5.19	41.19 ± 5.61	0.682
Platelet count, (10 ³ µL)	252.11 ± 72.25	254.54 ± 73.70	0.818
Mean platelet volume, (fL)	8.24 ± 1.01	8.27 ± 0.95	0.833
Red cell distribution width (%)	12.78 ± 1.27	13.09 ± 1.82	0.170

Table 3 – Univariate and multivariate regression models based on independent variables likely to predict the neutrophil-to-lymphocyte (NLR) ratio

Independent variables	Univariate Analysis		Multivariate Analysis*	
	Beta	p	Beta	p
STR	0.432	< 0.001	2.527	< 0.001
Electrocardiographic ischemia grade	0.321	< 0.001	1.497	0.001
Time from symptoms to admission (min)	0.162	0.028	0.052	0.383
In-hospital mortality	0.189	0.007	-2.445	0.025
Hospitalization duration (days)	0.165	0.019	0.114	0.558
Admission SBP	-0.151	0.033	-0.016	0.081
Serum glucose	0.159	0.023	0.003	0.555
Serum urea	0.187	0.008	0.023	0.080
Hyperlipidemia	-0.081	0.251	-0.009	0.985
LVEF	-0.123	0.087	-0.029	0.319
Anterior MI	0.012	0.870	0.566	0.230
Infarct-related artery	-0.018	0.803	-0.377	0.428

* = p value at the last step with the independent variables that remained in model.

NLR: neutrophil-to-lymphocyte ratio; STR: ST-segment resolution; SBP: systolic blood pressure; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

to evaluate tissue reperfusion due to its ease of use and known superiority. Similar to previous studies, our present study revealed that patients with G3I on admission ECG had partial or no STR after pPCI. Additionally, we found that patients with no STR had higher NLR values compared with patients with complete and partial STR.

Although quick restoration of epicardial coronary artery is achieved with pPCI in patients with STEMI, the prognosis is mainly dependent upon restoration of an adequate perfusion of areas with microvascular integrity. Separately, both elevated NLR and G3I on admission are predictors of poor tissue-level reperfusion and poor prognostic markers in patients

Table 4 – Effects of different variables on ECG ischemia grade in multivariate logistic regression analyses

Covariates	Adjusted OR	95% CI	p
NLR	1.254	1.120-1.403	< 0.001
Anterior MI	2.016	0.979-4.151	0.050
Admission SBP	1.015	1.000-1.030	0.075
Hyperlipidemia	2.107	0.927-4.789	0.051
LVEF	0.952	0.906-1.000	0.185

OR: odds ratio; 95% CI: 95% confidence interval; NLR: neutrophil-to-lymphocyte ratio; MI: myocardial infarction; SBP: systolic blood pressure; LVEF: left ventricular ejection fraction.

with STEMI, probably due to severe ischemic damage to the microvasculature. This hypothesis has been explained in part by the poorer collateral supply and the larger clot burden seen in these patients. Activation of inflammation in the infarcted region may contribute to plugging in the microvasculature and developing no-reflow phenomenon via platelet-neutrophil interaction in patients with STEMI³⁷.

Lucchesi et al³⁸ showed that activated leukocytes might modulate the electrical activity of the myocardium by releasing oxygen free radicals. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study, lymphopenia was associated with a widened QRS³⁹. Also, a longer occlusion period causes additional microvascular damage and, therefore, worse final flow rates. However, to our knowledge, no prior study has reported the association between NLR and ECG grades of ischemia, and our present study is the first in this regard. We demonstrated that there is a significant positive correlation between NLR and ECG ischemia grades, and we therefore speculate that the worse effect of G3I on clinical outcome might be at least partially explained by the prognostic value of NLR.

Limitations

The present study has a number of limitations. The major limitations are the study's retrospective design, its location on a single tertiary center and the relatively small number of patients, which may affect study generalizability. However, our study may serve as an inspiration for additional prospective studies with larger sample sizes. Next, we did not assess TIMI flow grade routinely. Since many studies have shown that STR is a more powerful prognostic predictor than epicardial TIMI flow grade, and with a better correlation with late mortality, we chose to use STR and believe our findings are clinically important. Finally, the choice of the ideal blood collection time is challenging since neutrophils have a short life in the circulation (around 7 hours), and because the exact time to peak inflammatory response after STEMI and cut-off points of NLR remains unknown. Although many studies recommend serial sampling for better prognostication, we believe this

unpredictability may be accurate for counts of WBCs and their subtypes, but not for the NLR, which is the reason we evaluated NLR only once on admission.

Conclusion

We found that there is an association between G3I and elevated NLR, both easily ascertainable through low-cost methods. We speculate that this association is likely caused by the same mechanism (adequate perfusion of areas with microvascular integrity). The finding of this association may help elucidate the adverse cardiovascular outcomes seen in patients with STEMI. We believe that the incorporation of NLR and ECG ischemia grade as covariables in well-validated standardized risk scores will provide additional prognostic value for risk stratification of patients with STEMI. However, these findings must be confirmed in additional studies with larger numbers of patients.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Yalcinkaya E, Yuksel UC, Celik M, Kabul HK, Barcin C, Gokoglan Y, Yildirim E, Iyisoy A; Acquisition of data: Yalcinkaya E, Celik M, Gokoglan Y, Yildirim E; Statistical analysis: Yalcinkaya E, Yuksel UC, Celik M, Barcin C; Writing of the manuscript: Yalcinkaya E, Barcin C.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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