

Novel predictors of infarct-related artery patency for ST-segment elevation myocardial infarction: Platelet-to-lymphocyte ratio, uric acid, and neutrophil-to-lymphocyte ratio

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ABSTRACT

Objective: The neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), and uric acid (UA) are inflammatory markers in cardiovascular disease. However, there are not enough data on infarct-related artery (IRA) patency in ST-segment elevation myocardial infarction (STEMI). We aimed to investigate the association of NLR, PLR, and UA with IRA patency before percutaneous coronary intervention (PCI) in STEMI.

Methods: The study was designed as a retrospective study. Three hundred and twenty-four consecutive patients with STEMI were divided into two groups according to pre-PCI Thrombolysis in Myocardial Infarction flow grade (TIMI). Patients with a TIMI flow grade of into the spontaneous reperfusion (SR) group, while patients with TIMI flow grade of 0, 1 and 2 were placed into the non-SR group. The χ^2 and independent-samples t-test, Mann-Whitney U test, multivariate logistic regression analysis, and receiver-operator characteristic (ROC) curve analysis were used for the statistical analysis.

Results: PLR, NLR, and UA values in the SR group were lower than in the non-SR group ($p<0.004$, $p<0.001$, $p<0.001$, respectively). In the multivariate analysis, serum UA level and PLR were found to be independent predictors of pre-PCI IRA patency. In the ROC curve analysis, PLR >190 , UA >5.75 mg/dL, and NLR >4.2 predicted non-SR. The sensitivity and specificity of the association between low IRA TIMI flow grade and PLR were 88% and 84%, 72% and 66% for UA, and 74% and 44% for NLR, respectively.

Conclusion: We determined that PLR and UA are novel predictors of IRA patency before PCI. We suggest that PLR and UA may be used in risk-stratifying STEMI. (*Anatol J Cardiol* 2015; 15: 648-56)

Keywords: platelet-to-lymphocyte ratio, uric acid, neutrophil-to-lymphocyte ratio, coronary angiography, acute myocardial infarction, infarct-related artery patency

Introduction

Atherosclerosis is the major cause of cardiovascular disease that still accounts for most of the mortality worldwide (1). Inflammation plays a significant role in initiating atherosclerosis and facilitating its progression (2). Inflammation characterizes all phases of atherothrombosis, and the presence of inflammation at the site of the atherosclerotic lesion has a critical pathophysiological role in plaque formation and acute rupture (3, 4).

The neutrophil-to-lymphocyte ratio (NLR) is calculated from the WBC-c (white blood cell count) and is a novel prognostic and inflammatory marker in patients with cardiovascular disease (5-7). Recently, increased NLR was reported to be linked

with the degree of pre-PCI IRA patency, the no reflow phenomenon after primary PCI, and cardiac mortality in STEMI patients (8-10).

Platelet activation is one of the main contributors to the development of acute coronary syndromes (ACSs) (11). In addition, lymphopenia is an indicator of physiologic stress and poor general health (12). Recently, the platelet-to-lymphocyte ratio (PLR) has been proposed to be a novel pro-thrombotic and inflammatory marker, especially in cancer patients (13, 14).

Serum uric acid (UA) mediates leukocyte activation and so triggers an inflammatory response, which has a deleterious effect on the endothelium. In fact, a consistent association has been identified between elevated UA levels and higher levels

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of inflammatory markers (15). The correlation between UA levels and post-intervention coronary blood flow is well established and affects the worse prognosis of STEMI patients undergoing primary PCI (16-18). Even though previous studies reported that increased UA and NLR contribute to worse post-PCI outcomes in STEMI patients (8, 18, 19), little is understood about other risk factors that contribute to decreased IRA patency and hence poorer PCI outcomes. In this study, we aimed to investigate the association of the concomitant NLR, PLR, and UA level with IRA patency in patients with STEMI who underwent primary PCI. To our knowledge, the relationship between concomitant PLR, NLR, and serum UA levels in STEMI patients with a patent IRA has not been investigated. In this study, we evaluated the relationship between PLR, NLR, and serum UA in STEMI patients with patent IRAs as confirmed by angiography before receiving primary PCI.

Methods

Study population

A total of 715 patients that retrospectively and consecutively presented with STEMI and underwent primary PCIs within 12 hours of symptom onset between January 2012 and November 2013 were included in the study. The study was conducted in Diyarbakır Dicle University Faculty of Medicine in collaboration with the department of cardiology. STEMI was defined based on criteria created by the American College of Cardiology and the European Society of Cardiology (20): an increase in troponin I >1 ng/mL and a new ST elevation as measured from the J-point in 2 or more contiguous leads with leads V1, V2, and V3 measuring at least 0.2 mV or at least 0.1 mV in the remaining leads during the first 12 hours after symptom onset.

Exclusion criteria from the study were patients with severe liver disease, autoimmune diseases, cancer, hematological disorders, severe valvular disease, hypothyroidism, gout, other inflammatory or infectious diseases, and a history of bleeding diathesis. Patients on the following medications were excluded from the study: corticosteroids, cytotoxic drugs, thrombolytic therapy, glycoprotein IIb/IIIa inhibitors, diuretics, and UA-lowering agents. If the patient did not undergo coronary angiography, did not follow up for blood work, and had poor echocardiographic windows, then he was also eliminated from the investigation. After accounting for all of these exclusion criteria, a total of 324 patients remained in the study sample.

All patients received a complete physical examination, assessment of coronary risk factors, and medical histories and presenting clinical symptoms were also recorded. Patients were evaluated for heart failure prognosis according to Killip clinical examination guidelines (21). Monitoring for major adverse cardiac events (MACEs) was performed during the in-hospital follow-up period. Examples of MACEs were cardiogenic shock, new advanced heart failure, pulmonary edema, complete atrioventricular block (AVB) requiring a temporary

pacemaker, severe ventricular arrhythmia, major bleeding requiring blood transfusion, and in-hospital mortality during the post-PCI follow-up period. An in-hospital mortality was only considered a MACE if the death was due to myocardial infarction, cardiac arrest, or some other cardiac-related cause. Cardiogenic shock was defined as marked and persistent hypotension lasting more than 30 minutes with a systolic arterial pressure less than 80 mm Hg, with signs of hypoperfusion due to left ventricular dysfunction, right ventricular infarction, or cardiac mechanical complications. New-onset advanced heart failure was diagnosed if the patient qualified for a New York Heart Association functional classification of III or greater. In order for a severe ventricular arrhythmia to be considered a MACE, it needed to occur within 48 hours of admission, and the rhythm must have been ventricular fibrillation, ventricular tachycardia, or asystole.

Blood work and echocardiography

Venous blood samples were collected when the patient initially presented to the emergency department or intensive coronary care unit (ICCU) before primary PCI. Hematologic indices were measured by an automated hematology analyzer system (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). Absolute cell counts were utilized to perform subsequent analyses. Baseline PLR was measured by dividing the platelet count by the lymphocyte count. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glucose, UA, and creatinine levels were measured with the Abbott Architect C16000 autoanalyzer (Abbott Laboratory). Creatinine kinase-MB (CK-MB) levels were measured with a Beckman Access analyzer (USA). Troponin I levels were measured with a Beckman Image 800 analyzer (USA). Normal UA levels were defined as ranging between 2.6-7.2 mg/dL. Transthoracic two-dimensional echocardiography was performed upon admission to the ICCU to determine left ventricular ejection fraction (LVEF), left ventricular systolic diameter (LVSD), left ventricular diastolic diameter (LVDD), and left atrial diameter (Vivid S6, GE Medical Systems, Horten, Norway).

Coronary angiography (TIMI flow grade)

All patients underwent selective coronary angiography using the Judkins technique. Primary PCIs were performed with the standard femoral approach using a 7 French guiding catheter. Pre-PCI TIMI flow grades were documented for every patient. Patients were divided into two groups based on the TIMI flow grade (22). Patients were stratified into the normal flow or spontaneous coronary reperfusion group (SR group) if they demonstrated TIMI flow grades of 3 (8, 18). If patients demonstrated impaired coronary reperfusion with TIMI flow grades 0, 1, or 2, then they were placed in the non-SR group. For all study participants, only one artery was identified as the IRA. Coronary vessel disease was defined as greater than 50% stenosis in one of the major coronary arteries. The Gensini scoring system was used

Table 1. Comparison between STEMI patient demographic and medical characteristics

Variables	SR (n=88)	Non-SR (n=236)	P
Age, years	60.2±14.3	62.1±13.9	0.276*
Sex, male, n, %	72 (82)	165 (70)	0.032
Medical history			
Hypertension, n, %	29(33)	87(37)	0.514
Diabetes mellitus, n, %	20 (23)	52 (22)	0.894
Smoking, n, %	51 (29)	126 (71)	0.463
Hyperlipidemia, n, %	5 (6)	10 (4)	0.562**
Family history of CAD, n, %	20 (23)	44 (19)	0.412
MI or CAD, n, %	5 (5)	11 (5)	0.774**
PCI, n, %	2 (2)	11 (5)	0.526**
CABG, n, %	3 (3)	4 (2)	0.395**
Cerebrovascular event, n, %	3 (3)	14 (6)	0.575**
Chronic renal failure, n, %	0 (0)	5 (2)	0.329**
Medications			
Preadmission aspirin use, n, %	73 (83)	165 (70)	0.018
Preadmission clopidogrel use, n, %	51 (58)	111 (47)	0.080
Beta-blocker, n, %	10 (11)	21 (9)	0.502
ACE inhibitors, n, %	12 (14)	22 (9)	0.260
Statin, n, %	10 (11)	14 (6)	0.097
Preadmission enoxaparin use, n, %	72 (82)	222 (93)	0.002
Killip class on presentation, n, %			
I-II	86 (98)	214 (91)	0.031
III-IV	2 (2)	22 (9)	
Admission SBP, mm Hg	130.7±20.5	125.1±24.4	0.056*
Admission heart rate, bpm	83.0±16.5	83.5±17.3	0.823*
Location of STEMI			
Anterior, n, %	41 (47)	105 (45)	0.736
Non-anterior, n, %	47 (53)	131 (56)	
Duration of chest pain, hours	5.7±3.4	5.7±3.2	0.876
Admission LVEF, %	46.2±9.5	42.4±10.2	0.003
LVDD, mm	45.1±4.9	46.9±5.3	0.014
LVSD, mm	32.2±5.6	34.0±6.1	0.023
Left atrial diameter, mm	36.5±5.9	36.6±4.9	0.810
Location of culprit lesion			
LAD, n, %	44 (50)	107 (45)	0.059
RCA, n, %	25 (28)	97(41)	
CX, n, %	19(22)	32 (14)	
Number of narrowed coronary arteries			
1 vessel, n, %	40 (46)	102 (43)	0.718
>1 vessel n, %	48 (54)	134 (57)	

Gensini score	39.9±25.1	67.5±28.5	
	4-124 (32)****	16-162 (60)****	<0.001****

*Student's t-test; **Fisher's exact test; ***Mann-Whitney U test; for other statistics, χ^2 test; ****For Gensini score (min-max), median
ACE - angiotensin-converting enzyme; bpm - beat per minute; CABG - coronary artery bypass graft; CAD - coronary artery disease; CX - circumflex coronary artery; LAD - left anterior descending coronary artery; LVDD - left ventricular diastolic diameter; LVEF - left ventricular ejection fraction; LVSD - left ventricular systolic diameter; MI - myocardial infarction; non-SR - non spontaneous reperfusion; PCI - percutaneous coronary intervention; RCA - right coronary artery; SBP - systolic blood pressure; SR - spontaneous reperfusion

to determine the severity of CAD (23). TIMI flow grade was determined by three independent interventional cardiologists. Intra- and inter-observer reliability was determined from a random sample of 200 patients from the study sample.

Statistical analysis

All analyses were performed with SPSS for Windows, version 18.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as the mean±one standard deviation (SD) and/or min-max; median and categorical variables were expressed as percentages. The two-sample Kolmogorov-Smirnov test assessed whether continuous variables followed a normal distribution. Comparisons between categorical and continuous variables between the SR and non-SR groups were performed using the χ^2 or Fischer's exact test and independent-samples t-test or Mann-Whitney U test, respectively. Statistical significance was defined as a p value less than 0.05.

Multivariate stepwise forward logistic regression analysis was used to assess independent predictors of IRA patency, TIMI flow grades, and MACEs. All variables that were significant predictors in the univariate analysis were then included in the logistic regression model, and the results were expressed as the odds ratio (OR) with the corresponding 95% confidence interval (CI). Inter- and intra-rater reliability between all three cardiologists in assigning TIMI flow grades was determined via the kappa (κ) test. A p value less than 0.05 was statistically significant. The cut-off values for the sensitivity and specificity of UA, PLR, and NLR in predicting IRA patency were estimated by performing receiver operator characteristic curve analysis.

The study protocol was reviewed and approved by the Ethics Committee in accordance with the Declaration of Helsinki.

Results

A total of 324 patients were included in the data analysis. Out of all study participants, 27% was in the SR group, and the remaining 73% was stratified into the non-SR group. Baseline ECG, echocardiography, and coronary angiography results, organized according to SR grouping, are shown in Table 1. No significant differences regarding known atherogenic risk factors, systolic blood pressure (SBP), and heart rate on admission were identified between each group, and preadmission aspirin

Table 2. A comparison of initial laboratory values

Variables	SR (n=88)	Non-SR (n=236)	P
WBC, 10 ³ /mm ³	12.5±4.0	14.2±6.0	0.012
RBC, 10 ³ /mm ³	4.9±0.6	4.8±0.5	0.077
Hemoglobin, g/dL	13.9±1.7	13.9±1.6	0.953
RDW, %	15.9±1.5	16.1±1.6	0.410
PDW	17.8±1.2	17.9±1.2	0.406
Platelet count, 10 ⁹ /mm ³	248.8±68.3	252.7±63.4	0.637
Lymphocyte count, 10 ³ /mm ³	2.1±1.0 0.3-7.1 (1.9)**	1.91±1.3 0.2-10.0 (1.6)**	0.005*
Monocyte count, 10 ³ /mm ³	0.7±0.3	0.65±0.3	0.090
Basophil count, 10 ³ /mm ³	0.08±0.0	0.07±0.0	0.115
Neutrophil count, 10 ³ /mm ³	9.4±3.7 3.5-19.4 (8.9)**	11.6±5.5 0.2-10.0 (1.6)**	<0.001*
PLR	140.5±75.4 33.2-533.3 (126.7)**	176.1±103.7 25.7-758.6 (145.8)**	0.004*
NLR	5.61±4.62 0.8-38.7 (4.6)**	8.15±6.13 3.6-44.4 (10.7)**	<0.001*
MPV	8.2±1.3	8.3±1.5	0.611
Glucose, mg/dL	167.2±88.7	171.2±81.0	0.703
Creatinine, mg/dL	0.9±0.3	0.9±0.4	0.809
Sodium, mmol/L	136.6±3.0	136.2±3.6	0.391
Potassium, mmol/L	4.0±0.4	3.9±0.5	0.242
Total cholesterol, mg/dL	181.8±39.7	174.9±36.9	0.143
LDL, mg/dL	115.9±31.8	112.3±29.8	0.336
HDL, mg/dL	35.2±9.0	34.8±9.9	0.711
Triglycerides, mg/dL	158.6±69.7	150.9±101.5	0.515
Uric acid, mg/dL	5.2±1.1 2.8-8.1 (5.4)**	7.8±2.7 3.4-14.2 (7.6)**	<0.001*
Peak troponin I, ng/mL	38.1±36.9 0.02-103.0 (23.5)**	64.7±34.7 0.01-102 (80.4)**	<0.001*
Peak CK-MB, ng/mL	140.9±115.9 1.9-312 (119.4)**	207.8±106.4 0.9-312.0 (272.7)**	<0.001*

Values are mean±SD or %. *Mann-Whitney U test; for other statistics, student's t-test.
** min-max (median)
CK - creatinine kinase; HDL - high-density lipoprotein; LDL - low-density lipoprotein;
MPV - mean platelet volume; NLR - neutrophil-to-lymphocyte ratio; non-SR - non spontaneous reperfusion; PDW - platelet distribution width; PLR - platelet-to-lymphocyte ratio; RBC - red blood cell count; RDW - red cell distribution width; SR - spontaneous reperfusion; WBC - white blood cell count

(p=0.018) and enoxaparin (p=0.002) use was greater in the SR group. SR group was 32% and non-SR group was 23% in clopidogrel using patients. (p=0.08). Killip class III-IV designations were more common in non-SR patients (p=0.031). Patients in the non-SR group had lower LVEF measurements than patients in the SR group (42.4±10.2% versus 46.2±9.5%, respectively; p=0.003).

Table 3. A comparison of in-hospital major adverse cardiovascular events

Variables	SR (n=88)	Non-SR (n=236)	P
In-hospital MACEs, n, %	9 (10)	64 (27)	0.001
Advanced heart failure, n, %	5 (6)	17 (7)	0.628
Advanced pulmonary edema, n, %	2 (2)	12 (5)	0.366*
Cardiogenic shock, n, %	1 (1)	24 (10)	0.007
Complete AVB requiring transient pacemaker, n, %	1 (1)	16 (7)	0.049
Serious ventricular arrhythmia, n, %	1 (1)	19 (8)	0.021
Major bleeding requiring blood transfusion, n, %	0 (0)	1 (0.4)	1.000*
In-hospital mortality, n, %	2 (2)	33 (14)	0.003
Cardiac arrest on admission, n, %	1 (4)	24 (96)	0.007

*Fisher's exact test; for other statistics, χ^2 test. AVB - atrioventricular block; MACE - major adverse cardiovascular event; non-SR - non spontaneous reperfusion; SR - spontaneous reperfusion

Table 4. Binary forward stepwise logistic regression analysis of variables related to infarct-related artery patency

	B	P	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Uric acid	0.706	<0.001	2.026	1.569	2.616
Peak troponin I	0.19	<0.001	1.019	1.009	1.029
PLR	0.009	<0.001	1.009	1.004	1.013
Gensini score	0.033	<0.001	1.033	1.018	1.049

Nagelkerke R²: 0.542 Step 4 comparing SCR to non-SCR; CI - confidence interval; PLR - platelet-to-lymphocyte ratio

Table 5. Binary forward stepwise logistic regression analysis of variables related to MACE

	B	P	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Age	0.056	<0.001	1.057	1.028	1.087
Admission SBP	-0.022	0.013	0.978	0.961	0.995
Uric acid >7.11	0.844	0.016	2.326	1.169	4.625
Neutrophil	0.082	0.017	1.086	1.015	1.162
Killip class >2	-4.595	<0.001	0.010	0.001	0.092
HDL	-0.051	0.015	0.950	0.912	0.990
Creatinine	1.093	0.017	2.983	1.218	7.305

Nagelkerke R²: 0.465 Step 7 comparing MACE. CI - confidence interval

Furthermore, patients with normal TIMI flow grades were less likely to demonstrate LVDD (p=0.014) and LVSD (p=0.023). The Gensini score was higher in the non-SR group as compared to the SR group (67.4±28.5 versus 39.9±25.1; p<0.001).

Initial laboratory findings and in-hospital MACE findings were compared according to SR grouping in Tables 2 and 3; non-SR group UA (p<0.001), PLR (p<0.004), and NLR (p<0.001) values

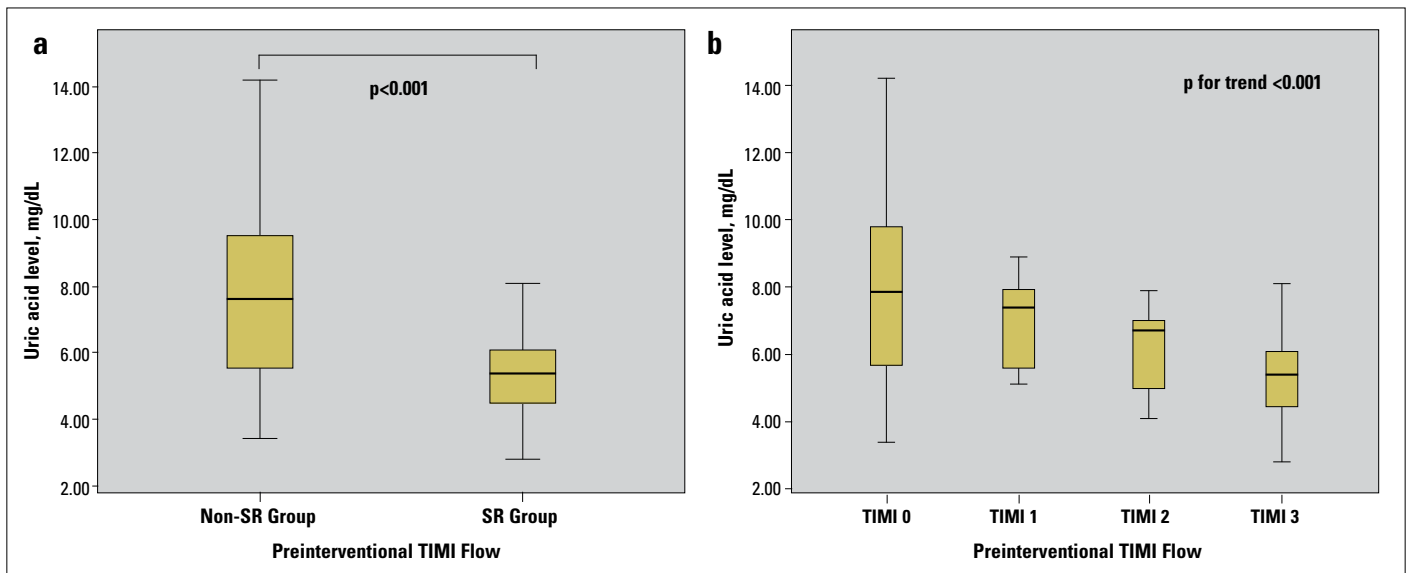


Figure 1. a, b. (a) Box plot comparison between serum UA levels between SR and non-SR patient groups before primary PCI. (b) Box plot comparison between patient serum UA levels according to pre-PCI TIMI flow grades

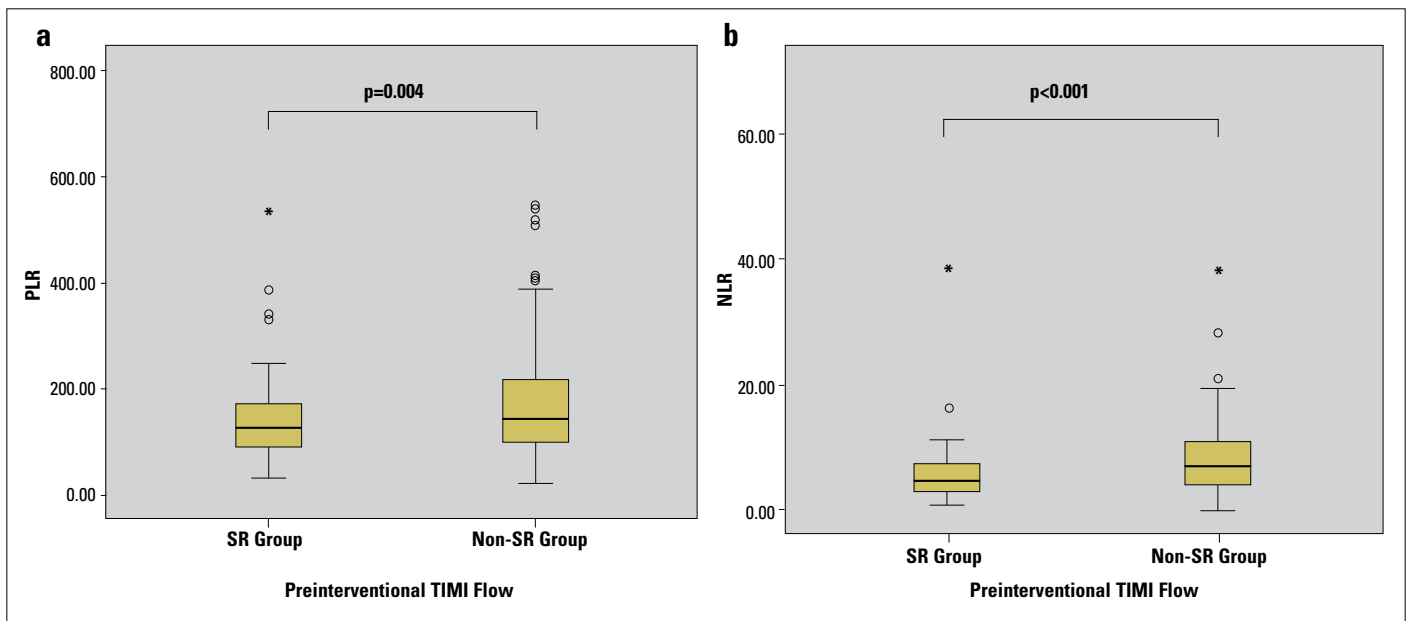


Figure 2. a, b. (a) Box plot comparison of the platelet-to-lymphocyte ratio among SR and non-SR patient groups. (b) Box plot comparison of the neutrophil-to-lymphocyte ratio among SR and non-SR patient groups

were significantly greater than those of the SR group (Fig. 1 and 2). CK-MB ($p < 0.001$) and troponin I ($p < 0.001$) peak values in the non-SR group were significantly higher than in the SR group. In-hospital mortality ($p = 0.003$) and MACEs ($p = 0.001$) were also significantly higher in non-SR patients. Similarly, in-hospital cardiogenic shock, complete AVB requiring a transient pacemaker, severe ventricular arrhythmia, cardiac arrest on admission, and cardiopulmonary resuscitations were more common in non-SR group patients. Duration of hospital stay was also significantly longer in the non-SR patient group (5.5 versus 4.3 days; $p = 0.006$).

Pearson's correlation analysis revealed significant associations between higher UA values and non-SR flow ($r = 0.430$, $p < 0.001$), Gensini score ($r = 0.226$, $p < 0.001$), age ($r = 0.140$, $p = 0.012$), and peak troponin I ($r = 0.119$, $p = 0.033$).

Multivariate binary forward stepwise logistic regression analysis was compared according to SR grouping in Table 4 non-SR group. Multivariate binary forward stepwise logistic regression analysis revealed that a high level of UA (cut-off level 7.11 mg/dL) was an independent predictor of MACEs (Table 5).

A cut-off level of 190 for PLR predicted impaired IRA flow before primary PCI with a sensitivity of 87.5% and a specificity

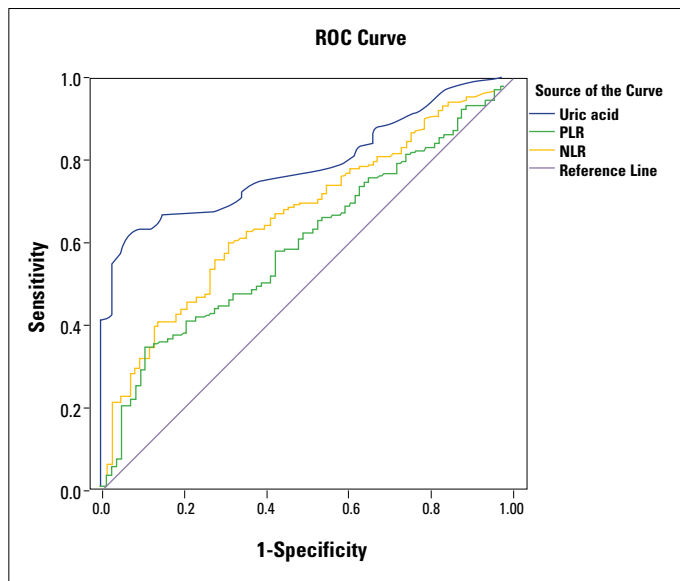


Figure 3. Receiver operator characteristic curve analysis of serum uric acid level, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio in predicting pre-PCI IRA patency

of 83.5% [ROC area under the curve (AUC) 0.603, 95% CI 0.538-0.669, $p=0.004$] (Fig. 3). A cut-off level of 5.75 mg/dL for UA predicted impaired IRA flow on initial coronary angiography with a sensitivity of 72.0% and a specificity of 65.9% (ROC AUC 0.789, 95% CI 0.741-0.837, $p=0.001$) (Fig. 3). A cut-off level of 4.2 for NLR predicted impaired IRA flow before primary PCI with a sensitivity of 74.0% and a specificity of 44.3% (ROC AUC 0.665, 95% CI 0.603-0.728, $p<0.001$) (Fig. 3). The kappa (κ) value for intra-observer reliability was 0.934 ($p<0.001$). The inter-observer reliability was a κ of 0.916 ($p<0.001$) for TIMI flow grade assignments 0 through 3. Inter-rater reliability and the intraclass correlation coefficient had an r value of 0.98 with a p value less than 0.001.

Discussion

This study demonstrates that IRA patency before primary PCI was associated with multiple variables—namely, PLR, NLR, UA level, LVDD, LVSD, and LVEF. Coronary blood flow through the IRA is critical in determining the prognosis for STEMI patients. Patients with pre-PCI IRA flows that are within normal limits have increased post-PCI TIMI flow grades (22), decreased rates of heart failure and cardiogenic shock, improved early and late LVEFs, and reduced short- and long-term mortality (24, 25). Our data demonstrated that normal pre-PCI IRA flows were associated with decreased CK-MB and troponin I peaks, LVDD, and LVSD and increased LVEF as compared to patients with impaired pre-PCI IRA blood flow. In our study, PLR and UA, which are markers of platelet reactivity and inflammation, respectively, are strong independent predictors of IRA patency in acute STEMI patients treated with primary PCI. Moreover, we found that PLR values greater than 190, UA levels greater than 5.75 mg/dL, and

NLR values greater than 4.2 predict initial IRA TIMI flow grades of less than 3. Specifically, the sensitivity and specificity of the association between low IRA TIMI flow grades and PLR are 88% and 84%, 72% and 66% for UA, and 74% and 44% for NLR. SR occurs in up to 30% of STEMI patients (26). In 27% of all patients, we found that a TIMI flow grade of 3 during initial angiography represented SR. In the literature, there are reports asserting that improved IRA patency rates are observed in patients taking antithrombotic medications (25, 27). Specifically, improved IRA patency rates of 21% were reported in patients taking thienopyridine if the medication was administered early in the emergency department (25). In our study, although SR was 32% in clopidogrel using patients, it did not reach statistical significance ($p=0.08$), which may be due to the limited use of clopidogrel in emergency room settings. However, we did discover that patients with normal IRA flows had a higher incidence of preadmission aspirin ($p=0.018$) and enoxaparin use ($p=0.002$). Furthermore, we found that preadmission enoxaparin use was associated with improved coronary blood flow before primary PCI in STEMI patients. Therefore, these data support the beneficial effects of early or preadmission aspirin and enoxaparin use in enhancing coronary microcirculation.

PLR and NLR: Inflammation and spontaneous coronary reperfusion

Platelets play a central role in the development of ACS (28), which is caused by complex interactions between leukocytes and platelets, causing the production of reactive oxygen species and contributing to ischemic endothelial damage (29). Proliferating megakaryocytes and relative thrombocytosis are consequences of an ongoing inflammatory response that contributes to a pro-thrombotic state in ACS. Platelet activation and plugging are of significant importance in developing impaired pre-PCI flow, because platelet-mediated release of vasoactive mediators increases the tendency of platelet-rich thrombi to form. Prior studies have demonstrated that a low lymphocyte count in patients with acute myocardial infarctions and chronic CAD gives information about a worse prognosis (30). However, the advantage of PLR is that it reflects both coagulation and inflammatory pathways and so may be superior to individual platelet or lymphocyte counts in predicting impaired IRA flow. Moreover, the prognostic significance of PLR has been demonstrated in patients with various cancers (13, 14). Cardiovascular studies have investigated the PLR, such as the work by Azab et al. (31), which reported that higher PLR values were associated with increased long-term mortality in non-STEMI patients. Moreover, Sünbül et al. (32) determined that the PLR was a significant predictor of being a “non-dipper” or a hypertensive patient that sustains high blood pressures throughout the night. Patients with normal pre-PCI IRA flows had significantly lower PLR values than patients with impaired pre-PCI IRA flow in our study. Specifically, PLR was determined to be an independent predictor of pre-PCI IRA patency.

Several recent studies have demonstrated that NLR is a marker of cardiovascular disease prognosis (7, 12, 33-35). Recently, increased NLR was reported to be associated with decreased pre-PCI IRA patency, the increased no-reflow phenomenon after primary PCI, and increased cardiac mortality in STEMI patients (8-10). Şen et al. (33) reported that NLR was independently associated with the coronary no-reflow phenomenon and increased long-term mortality in STEMI patients undergoing primary PCI.

To our knowledge, only one study, by Şahin et al. (10), has investigated the relationship between NLR and pre-PCI IRA patency. Specifically, they investigated the relationship between NLR and UA levels with IRA patency before primary PCI in STEMI patients. They determined that NLR and UA levels were negative predictors of pre-PCI IRA patency. In our study, we also found that high NLR and UA levels were significantly associated with decreased pre-PCI IRA patency. This suggests that PLR, NLR, and serum UA measures may be better indicators of the presence of pre-PCI normal IRA flows in STEMI patients.

Uric acid, inflammation and spontaneous coronary reperfusion

UA levels are closely associated with inflammatory markers, such as C-reactive protein (CRP). The correlation between serum CRP and UA levels was found in a German population-based survey (36). Previous studies have shown that there is a significant relationship between UA levels and CAD (16, 17, 37-39), endothelial dysfunction (40), coronary reserve, (41) and coronary blood flow in patients undergoing elective angiography (42) and in STEMI patients undergoing primary PCI (18). Bickel et al. (37) demonstrated that UA is an independent predictor of mortality in patients with CAD. Bos et al. (38) also reported that elevated UA levels are associated with an increased risk for acute myocardial infarction. In addition, it was published recently that increased UA levels are correlated with impaired coronary flow and increased in-hospital MACEs in a sample of 289 patients (18). Lazzeri et al. (39) reported that UA is a prognostic indicator of in-hospital mortality in acute STEMI patients; however, no differences were found in pre- and post-PCI TIMI flow grades in patients with either low or high UA levels. Conversely, we found that UA levels of 5.75 mg/dL or higher predicted impaired IRA flow with 72% sensitivity and 66% specificity. In our study, we found that elevated UA levels were strong and independent predictors of in-hospital MACEs and mortality in STEMI patients undergoing primary PCI.

Study limitations

This was a single-center study that enrolled a relatively small number of patients. Another limitation is that the majority of patients was male. Further large-scale randomized trials must

be conducted to confirm the associations that we observed between admission PLR, NLR, and UA values with pre-PCI IRA patency. Also, studies focusing on females might reveal that these biomarkers may have differing clinical implications as compared to male STEMI patients. Despite these limitations, this is the first study to evaluate the predictive value of PLR, NLR, and UA biomarkers in determining pre-PCI IRA flow in STEMI patients.

Conclusion

We found a significant relationship between UA levels and the degree of myocardial perfusion before primary PCI. Admission UA and PLR values were independent predictors of impaired coronary blood flow. Reflecting on our study's outcomes, we suggest that the PLR, NLR, and UA biomarkers, which are easily and cheaply measured, may be used in risk-stratifying STEMI patients. STEMI patients with high PLR, NLR, and UA levels must be monitored more closely for adverse outcomes. High UA, PLR, and NLR values may also help clinicians decide what therapeutic modalities to use during hospitalization and follow-up, but further studies are required to determine how these biomarkers may influence treatment.

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