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The association of serum uric acid levels on coronary flow in patients with STEMI undergoing primary PCI

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ABSTRACT

Objective: Uric acid has been shown as a predictor and an independent risk factor for coronary heart disease, but little is known regarding the association of uric acid levels with coronary blood flow in STEMI. We hypothesized that elevated uric acid levels would be associated with impaired flow and perfusion in the setting of STEMI treated with primary PCI.
Methods: Two hundred and eighty nine patients with STEMI who treated primary PCI were enrolled to study. Patients were divided into two groups based upon the TIMI flow grade. No-reflow was defined as TIMI Grade 0, 1 and 2 flows (group 1). Angiographic success was defined as TIMI 3 flow (group 2). Uric acid, MPV and high sensitive CRP were measured. Major adverse cardiac events (MACE) were defined as in stent thrombosis, non-fatal myocardial infarction and in-hospital mortality.
Results: There were 126 patients (mean age 63 ± 11 and 71% male) in group 1 and 163 patients (mean age 58 ± 12 and 80% male) in group 2. Uric acid, MPV, and hs-CRP levels on admission were higher in group 1 ($p = 0.0001$ for each). A uric acid level ≥5.4 mg/dl measured on admission had a 77% sensitivity and 70% specificity in predicting no-reflow at ROC curve analysis. In-hospital MACE was significantly higher in group 1 (29% vs. 7%, $p = 0.0001$). At multivariate analyses, high plasma uric acid (odds ratio (OR) 2.05, <95% confidence interval(CI) 1.49–2.81; $p < 0.0001$), hs-CRP (OR 1.02, <95% CI 1.01–1.03; $p = 0.0007$) and MPV (OR 3.09, <95% CI 1.95–4.89; $p < 0.0001$) levels were independent predictors of no-reflow post primary PCI and uric acid (OR 2.75, <95% CI 1.93–3.94; $p < 0.0001$), hs-CRP (OR 1.01, <95% CI 1–1.02; $p = 0.006$) levels, but not MPV, were independent predictors of in-hospital MACE.
Conclusion: Plasma uric acid level on admission is a strong and independent predictor of poor coronary blood flow following primary PCI and in hospital MACE among patients with STEMI. Except for predictive value, uric acid levels may be a useful biomarker for stratification of risk in patients with STEMI and may also lead to carry further therapeutic implications.

1. Introduction

Rapid restoration of infarct related arterial (IRA) flow is associated with improved ventricular performance and lower mortality among patients with myocardial infarction [1,2]. However, poor arterial flow and no-reflow phenomena may limit the benefits of recanalization of the IRA [3].

Several biomarkers are associated with poorer outcomes in ST-elevation myocardial infarction (STEMI). Mean platelet volume (MPV) is an easily measured platelet indices, which increase during platelet activation [4]. Furthermore, increased MPV levels have been associated with poor clinical outcome in survivors of myocardial infarction [5] and higher MPV correlates with thrombolysis failure in patients presenting with STEMI treated with thrombolytic therapy [6]. C-reactive protein (CRP) is an acute phase protein and several studies have shown that CRP may have prognostic value in patients with acute coronary syndromes and undergoing percutaneous coronary intervention (PCI) [7–10].

Uric acid, the end product of purine metabolism in circulation, is an independent risk factor for cardiovascular disease but the underlying pathophysiology is not clear. The relationship between circulatory uric acid levels and endothelial dysfunction has been demonstrated previously [11–13]. It has been shown that coronary flow reserve, a marker of coronary microvascular function,

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is significantly greater in participants with lower serum uric acid concentrations [14]. It has been also demonstrated that high serum uric acid level is associated with slow coronary flow in patients underwent elective angiography [15].

Uric acid has been shown as a predictor and an independent risk factor for cardiovascular events and is also an independent risk factor for coronary heart disease [16,17], but little is known regarding the association of uric acid levels with coronary blood flow in the setting of STEMI. Given that elevated uric acid is associated with poorer flow during elective angiography, we hypothesized that elevated uric acid levels would be associated with impaired flow and perfusion in the setting of STEMI treated with primary PCI.

2. Materials and methods

2.1. Study population

Two hundred and eighty nine consecutive patients (male 76% and mean age 60 ± 12) who were admitted with STEMI within 6 h from symptom onset were enrolled the study. All of the patients were treated with primary PCI at our institution from 2006 to 2010. STEMI was defined as: typical chest pain >30 min duration with ST elevation >1 mm in at least two consecutive leads on the electrocardiogram or new onset left bundle brunch block. Patients were divided into two groups based upon the Thrombolysis In Myocardial Infarction (TIMI) flow grade score [18]. No-reflow was defined as TIMI grade 0, 1 and 2 flows (group 1) [5,8,19–21] post PCI. Angiographic success was defined as TIMI 3 flow (group 2). Exclusion criteria included treatment of STEMI in the previous 24 h with thrombolytic drugs, a history of gout, active infections, systemic inflammatory disease, known malignancy, end stage liver and renal failure. Informed consent was obtained from all patients and the protocol was approved by the Ethics Committee and the institutional review board of Erciyes University Medical School.

2.2. Coronary angiography and PCI procedure

All of primary PCI procedures were performed with standard femoral approach with a 7-French guiding catheter. After administration of 5000 IU of heparin and 300 mg clopidogrel loading dose conventional wire crossing, direct stenting was implanted whenever possible; in the remaining cases, balloon pre-dilatation was carried out. The type of stents (bare metal or drug-eluting stent) were left to the operator's discretion. In each patient who treated with tirofiban, tirofiban was administrated after primary PCI procedure in coronary care unit. Use of systemic bolus of tirofiban, followed by a 12-h continuous infusion, was left to the operator discretion. To achieve maximal dilatation each coronary angiogram was preceded by intracoronary injection of 100 μg nitroglycerine. The Thrombolysis in Myocardial Infarction (TIMI) grade was assessed by three independent interventional cardiologists. Intra and inter-observer variabilities were obtained from random samples of 100 patients. The intra- and inter-observer variabilities for TIMI 0–1 were 6 and 8%, respectively; for TIMI 2 the corresponding values were 1 and 3%, respectively; and for TIMI 3 both intra- and inter-observer variability were 0%.

2.3. Laboratory analysis and echocardiography

In all patients, antecubital venous blood samples for the laboratory analysis were drawn on admission in the emergency room. Uric acid, glucose and lipid profile were determined by standard methods. High sensitive CRP was measured by using a BN2 model nephlometer (Dade-Behring). Citrate based anticoagulated blood samples stored at +4 °C and MPV levels were measured by *Sysmex* K-1000 auto analyzer within 30 min of sampling. Transthoracic echocardiography was performed for each patient immediately after primary PCI in intensive cardiac care unit. All measurements were performed using a commercially available machine (Vivid 7® GE Medical System, Horten, Norway) with a 3.5-MHz transducer.

2.4. Follow-up and major adverse cardiac events

Major adverse cardiac events (MACE) were defined as in stent thrombosis, non-fatal myocardial infarction and in-hospital mortality during in-hospital follow up period. In-stent thrombosis was defined as angiographically documented total occlusion. Non-fatal myocardial infarction was defined as recurrent chest pain and/or development of new ECG changes accompanied by a new rise ≥20% of cardiac biomarkers measured after the recurrent event. In-hospital mortality had to be verified death due to myocardial infarction, cardiac arrest or other cardiac causes.

2.5. Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using Student *t*-test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson correlation coefficients examined the degree of association between examined variables. p value <0.05 was considered as significant. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of Uric acid, MPV, hs-CRP and their respective, optimal cut-off value for predicting poor coronary flow after primary PCI in patients with STEMI. The effects of different variables on No-reflow and in hospital MACE were calculated in univariate analysis for each. The variables for which the unadjusted p value was <0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. p value <0.05 was considered as significant and confidence interval (CI) was 95%. All statistical analyses were performed with the SPSS version 15 (SPSS, Inc., Chicago, Illinois).

3. Results

There were 126 patients (mean age 63 ± 11 and 71% male) in group 1 and 163 patients (mean age 58 ± 12 and 80% male) in group 2. Baseline characteristics are shown in Table 1. Mean age was significantly higher in group1 ($p = 0.0001$). With respect to coronary risk factors; there was significant difference in the presence of diabetes mellitus (DM) ($p = 0.0001$) and prior coronary artery disease ($p = 0.0001$) but there was no significant difference in hypertension and active smoking ($p = 0.169$ and $p = 0.254$, respectively).

With respect to baseline laboratory status, the serum glucose level on admission was significantly higher in group 1 ($p = 0.0001$), while there was no significant difference in serum lipid profile, glomerular filtration rate (GFR), hemoglobin (Hg), platelet and white blood cell count (WBC) between groups. Also, left ventricular ejection fraction (LVEF) and pain to balloon time were not significantly different between groups ($p = 0.112$ and $p = 0.429$, respectively).

A greater proportion of patients with multi-vessel disease (more than 50% occlusion for each coronary artery) were in group 1 ($p = 0.0001$). Left anterior descending artery is the more common infarct related artery (IRA) in both groups, but there is no significant difference in involvement of circumflex, right coronary artery, left anterior descending artery and saphenous graft or left internal mammarian artery as IRA between groups ($p = 0.381$,

Table 1
Baseline characteristics.

	Group 1 (TIMI 0–2) $n=126$	Group 2 (TIMI 3) $n=163$	p value
Age (year)	63 ± 11	58 ± 12	0.0001
Male	90 (71%)	131 (80%)	0.076
Hypertension	62 (49%)	67 (41%)	0.169
DM	54 (42%)	28 (17%)	0.0001
Smokers	81 (64%)	94 (57%)	0.254
Previous CAD	48 (38%)	24 (14%)	0.0001
BMI (kg/m^2)	26.4 ± 2.5	25.9 ± 2.7	0.118
MPV (fl)	10.9 ± 0.8	10 ± 0.7	0.0001
CRP (mg/l)	35.6 ± 25	9.5 ± 4.6	0.0001
Uric acid (mg/dl)	6.4 ± 1.7	5.3 ± 0.9	0.0001
GFR ml/min/1.73 m^2	78 ± 23	83 ± 24	0.103
LVEF on admission	47.2 ± 11.1	49.3 ± 10.2	0.112
Trigliserid (mg/dl)	111.6 ± 50	117.8 ± 68	0.397
LDL (mg/dl)	119 ± 34.8	117 ± 31.3	0.482
HDL (mg/dl)	39.9 ± 14.8	38.3 ± 12.1	0.55
Total cholesterol (mg/dl)	181.2 ± 52.7	178.2 ± 33.7	0.477
Serum glucose (mg/dl)	203 ± 123.8	156 ± 63	0.0001
Hemoglobine (g/l)	14.3 ± 1.7	14.5 ± 1.8	0.49
Platelet (/mm^3)	242 ± 63	245 ± 68	0.741
WBC (10^3/μl)	12.6 ± 5.3	12.1 ± 4.2	0.352
Glycoprotein IIb/IIIa antagonist	26 (21%)	19 (12%)	0.037
Pain to balloon time (h)	4.8 ± 1.4	4.9 ± 1.3	0.429
Hospitalization (day)	7.1 ± 1.8	6.3 ± 2.1	0.0001
Previous medications			
ACEi	59 (47%)	78 (48%)	0.862
B-bloker	50 (40%)	46 (28%)	0.04
Statin	54 (43%)	43 (26%)	0.003
Aspirine	58 (46%)	46 (28%)	0.002
Diuretics	18 (14%)	25 (15%)	0.803
Infarct related artery			
Cx	24 (19%)	38 (23%)	0.381
RCA	37 (29%)	51 (31%)	0.725
LAD	62 (49%)	69 (42%)	0.244
Saphenous graft or LIMA	3 (2%)	5 (3%)	0.724
Coronary artery involvement			
Single-vessel disease	34 (27%)	105 (64%)	0.0001
Multi-vessel disease	92 (72%)	58 (36%)	0.0001
Primary PCI			
Stent implantation	112 (89%)	148 (91%)	0.840
BMS	98 (78%)	131 (80%)	
DES	14 (11%)	17 (10%)	
Stent length (mm)	3.24 ± 0.37	3.23 ± 0.33	0.755
Stent diameter (mm)	18.2 ± 3.31	17.6 ± 3.74	0.169
In-hospital MACE	37 (29%)	11 (7%)	0.0001
In stent thrombosis	13 (10%)	3 (2%)	0.002
Non-fatal MI	20 (16%)	6 (4%)	0.0001
In-hospital mortality	20 (16%)	2 (1%)	0.0001

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. DM: diabetes mellitus, CAD: coronary arterial disease, MPV: mean platelet volume, CRP: C-reactive protein, GFR: glomerular filtration rate, LVEF: left ventricular ejection fraction, LDL: low density lypoprotein, HDL: high density lypoprotein, WBC: white blood cell, BMI: Body mass index, ACEi: angiotensin converting enzyme inhibitors, LAD: left anterior descending, CX: circumflex artery, RCA: right coronary artery, LIMA: left internal mammarian artery, PCI: percutaneous coronary intervention, BMS: bare metal stent, DES: drug eluting stent, MACE: major advanced cardiovasculary events, MI: myocardial infarction.

$p=0.725$, $p=0.244$ and $p=0.724$, respectively). In the PCI procedure, stent implantation percentage and used stent types were similar between groups ($p=0.840$). Also, there was no significantly difference in the stent length (3.24 ± 0.37 vs. 3.23 ± 0.33, $p=0.755$) and stent diameter (18.2 ± 3.31 vs. 17.6 ± 3.74, $p=0.169$) between groups.

In previous medication history of patients, b-blocker, statin group drugs and aspirine usage significantly higher in group 1 ($p=0.04$, $p=0.003$ and $p=0.002$ respectively). But there was no significant difference in angiotensin converting enzyme inhibitors (ACEi) and diuretic drugs usage between groups ($p=0.863$ and $p=0.803$, respectively).

In-stent thrombosis, non-fatal MI, and in-hospital mortality were significantly higher in group 1 ($p=0.002$, $p=0.0001$, and $p=0.0001$, respectively). Over all, in-hospital MACE was also significantly higher in group 1 (29% vs. 7%, $p=0.0001$).

Uric acid, MPV, and hs-CRP levels on admission were higher in group 1 when compared with group 2 ($p=0.0001$ for each). There was a significant correlation between each of these three parameters with each other (Fig. 1): hs-CRP and MPV levels were correlated (Fig. 1A) ($r=0.61$; $p=0.0001$), and uric acid was correlated with both MPV and hs-CRP levels (Fig. 1B and C) ($r=0.56$; $p=0.0001$ and $r=0.49$; $p=0.0001$, respectively).

The ROC curves of uric acid, hs-CRP, and MPV for predicting no-reflow are shown in Fig. 2. A uric acid level ≥5.4 mg/dl measured on admission had a 77% sensitivity and 70% specificity in predicting no-reflow. Hs-CRP level ≥5.4 mg/l predicted no-reflow with an 89% sensitivity and 80% specificity and MPV level ≥10.4 fl predicted no-reflow with a 75% sensitivity and 73% specificity.

When we divided the study population into two groups according to the 5.4 mg/dl uric acid level cut-off value used in the ROC analysis, multi-vessel disease and no-reflow phenomena were

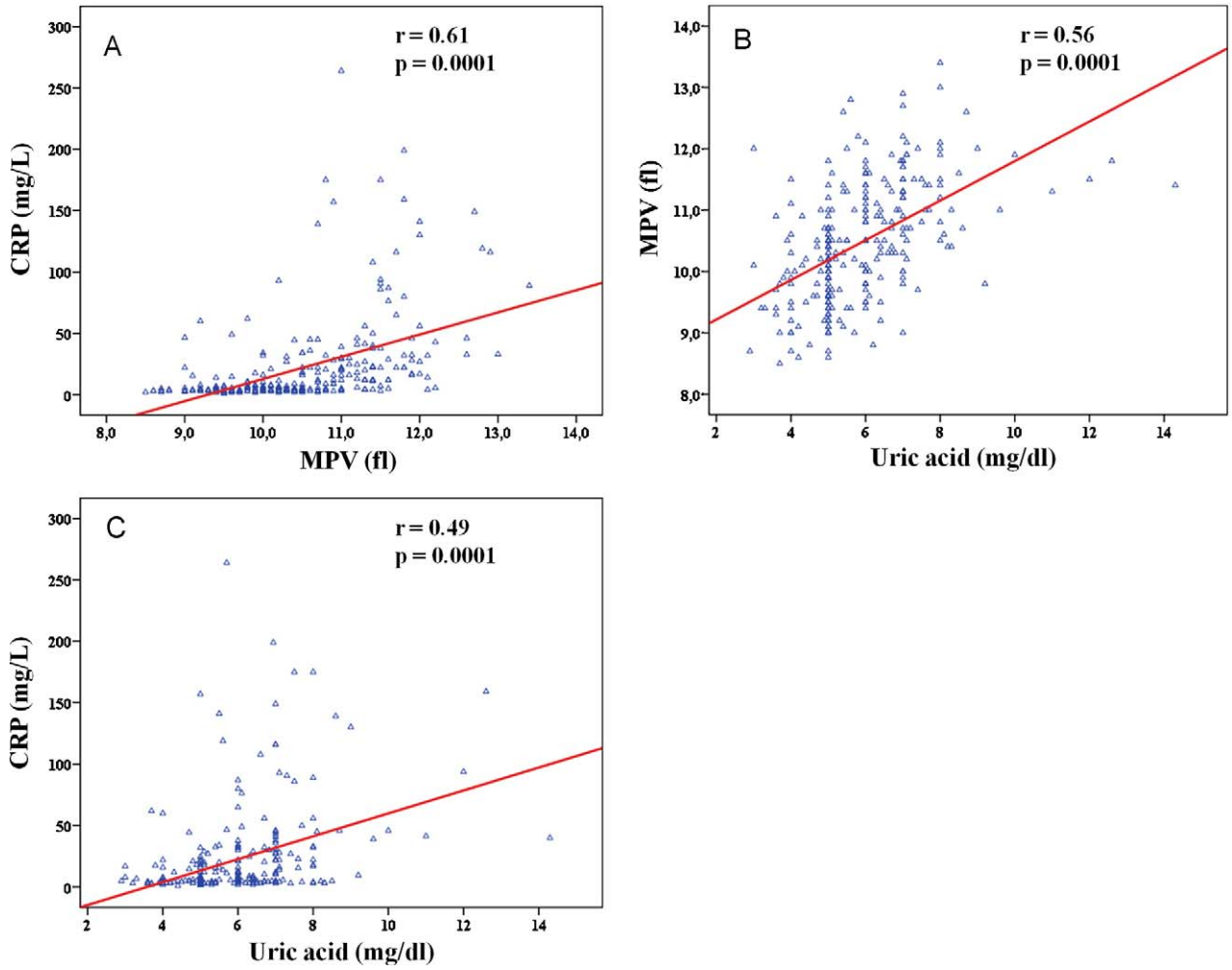

Fig. 1. Correlation between hs-CRP and MPV levels (A), MPV and uric acid levels (B), hs-CRP and uric acid levels (C).

significantly higher in increased uric acid group ($p = 0.0001$). In-hospital MACE was significantly higher in increased uric acid group ($p = 0.001$) (Table 2). Age and sex were not significantly different between groups ($p = 0.09$ and $p = 0.46$ for male sex, respectively). With respect to coronary risk factors, only previous coronary artery disease history was significantly higher in increased uric acid group ($p = 0.009$).

In the groups; some of variables that can be effective on impaired flow after primary PCI and in hospital MACE were significantly different between groups. So, the effects of multiple variables on the TIMI grade score analyzed with univariate and multivariate logistic regression analyses (Table 3). The variables for which the unadjusted p value was <0.10 in univariate analysis were identified as potential risk markers for no-reflow and included in the full model.

Table 2
Baseline risk factors and in-hospital MACE stratified by uric acid levels.

	Uric acid <5.4 $n = 141$	Uric acid ≥5.4 $n = 148$	p value
Age (year)	59 ± 12	61 ± 12	0.09
Male	107 (76%)	114 (77%)	0.46
Coronary risk factors			
DM	37 (26%)	45 (30%)	0.26
Hypertension	63 (45%)	66 (45%)	0.54
Smokers	85 (60%)	90 (61%)	0.51
Previous CAD	26 (18%)	46 (31%)	0.009
Severity of coronary artery disease			
Single-vessel disease	84 (60%)	55 (37%)	0.0001
Multi-vessel disease	57 (40%)	93 (63%)	0.0001
In hospital MACE	9 (6%)	39 (26%)	0.0001
In stent thrombosis	4 (3%)	12 (8%)	0.05
Non-fatal MI	5 (3%)	21 (14%)	0.002
In-hospital mortality	3 (2%)	19 (13%)	0.001
No-reflow	28 (20%)	98 (66%)	0.0001

Data are expressed as percentage (%) for categorical variables and mean ± standard deviation. DM: diabetes mellitus, CAD: coronary artery disease, MACE: major advanced cardiovascular events, MI: myocardial infarction.

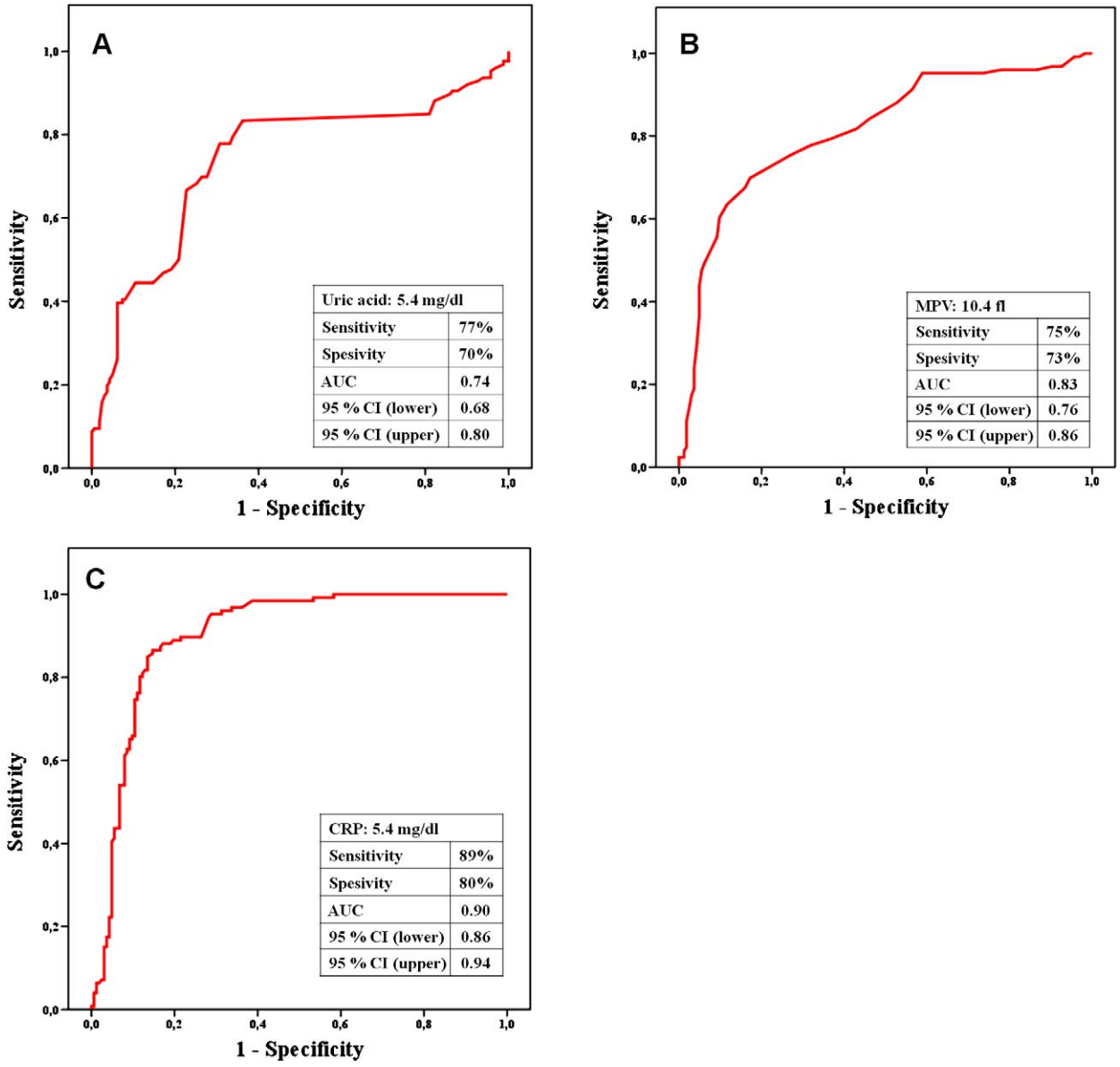

Fig. 2. The receiver-operating characteristic (ROC) curve of uric acid (A), MPV (B) and hs-CRP (C) for predicting angiographic no-reflow.

Table 3
Effects of multiple variables on the no-reflow in univariate and multivariate logistic regression analyses.

Variables	Unadjusted OR	95% CI	*p* value	Adjusted OR[a]	95% CI	*p* value
Age	1.04	1.02–1.06	0.0006	1.03	0.99–1.06	0.1615
MPV	4.69	3.17–6.95	<0.0001	3.09	1.95–4.89	<0.0001
CRP	1.04	1.03–1.06	<0.0001	1.02	1.01–1.03	0.0007
Uric acid	1.94	1.55–2.43	<0.0001	2.05	1.49–2.81	<0.0001
Aspirine	2.23	1.36–3.65	0.0015	0.19	0.05–0.67	0.0102
B-blocker	2.72	1.66–4.46	0.0001	0.61	0.18–2.10	0.4295
Male	0.62	0.36–1.08	0.0886	0.62	0.28–1.37	0.233
Hypertension	1.43	0.89–2.30	0.1376			
Diabetes mellitus	3.69	2.14–6.35	<0.0001	6.70	2.31–19.50	0.0005
Smoking	1.36	0.84–2.22	0.2125			
Previous CAD	3.73	2.11–6.58	<0.0001	11.11	2.25–54.99	0.0032
Glucose on admission	1.01	1–1.01	0.0002	1.00	0.99–1.01	0.4354
CK-mb	1.01	1–1.01	0.0057	1.01	0.99–1.01	0.0722
GFR ml/min/1.73 m^2	0.96	0.84–1.10	0.5691			
Multivessel disease	4.98	2.97–8.34	<0.0001	2.99	1.43–6.26	0.0037

[a] Adjusted for age, MPV, CRP, uric acid, b blocker, aspirine, DM, previous CAD, glucose on admission, multivessel disease, sexual status and Ck-mb. OR: odds ratio, CI: confidence interval, MPV: mean platelet volume, CRP: C-reactive protein, CAD: coronary artery disease, LVEF: left ventricular ejection fraction, GFR: glomerular filtration rate

Table 4
Effects of various variables on in-hospital MACE in univariate and multivariate logistic regression analyses.

Variables	Unadjusted OR	95% CI	*p* value	Adjusted OR[a]	95% CI	*p* value
Age	1.04	1.01–1.07	0.004	1.00	0.96–1.04	0.987
MPV	2.09	1.44–3.03	0.0001	1.43	0.89–2.29	0.138
CRP	1.01	1.01–1.02	0.0004	1.01	1–1.02	0.006
Uric acid	2.89	2.07–4.03	<0.0001	2.75	1.93–3.94	<0.0001
Aspirine	1.38	0.70–2.71	0.356			
B-blocker	1.24	0.63–2.44	0.534			
Male	2.87	1.43–5.77	0.003	0.34	0.13–0.87	0.025
Hypertension	1.44	0.74–2.82	0.283			
Diabetes mellitus	1.63	0.81–3.28	0.171			
Smoking	2.09	1.06–4.09	0.033	0.56	0.23–1.35	0.195
Previous CAD	1.55	0.75–3.20	0.235			
Glucose on admission	1.01	1–1.01	<0.0001	1.01	1–1.01	0.007
CK-mb	1.00	0.99–1.01	0.182			
GFR ml/min/1.73 m^2	1.01	0.91–1.13	0.800			
Multivessel disease	0.53	0.27–1.07	0.077	1.09	0.43–2.79	0.858
Glycoprotein IIb/IIIa antagonist	2.39	1.10–5.25	0.028	1.96	0.69–5.52	0.204

[a] Adjusted for age, MPV, CRP, uric acid, sexual status, smoking, glucose on admission, multivessel disease. OR: odds ratio. CI: confidence interval. MPV: mean platelet volume. CRP: C-reactive protein. CAD: coronary artery disease. LVEF: left ventricular ejection fraction. GFR: glomerular filtration rate

Age, MPV, hs-CRP, uric acid, b-blocker, aspirine, DM, previous CAD, glucose on admission, multivessel disease, sexual status (male) and ck-mb were analyzed with multivariate logistic regression model. At multivariate analyses, high plasma uric acid (odds ratio (OR) 2.05, <95% confidence interval (CI) 1.49–2.81; $p < 0.0001$), hs-CRP (OR 1.02, <95% CI 1.01–1.03; $p = 0.0007$) and MPV (OR 3.09, <95% CI 1.95–4.89; $p < 0.0001$) levels were still independent predictors of no-reflow post primary PCI (Table 3). In the multivariate analyses for in-hospital MACE, age, MPV, hs-CRP, uric acid, sexual status (male), smoking, glucose on admission, multivessel disease and the use of glycoprotein IIb/IIIa antagonist were analyzed with multivariate logistic regression model. High plasma uric acid (OR 2.75, <95% CI 1.93–3.94; $p < 0.0001$), hs-CRP (OR 1.01, <95% CI 1–1.02; $p = 0.006$) levels were still independent predictors of in-hospital MACE (Table 4). But, the statistically significance of MPV level (OR 1.43, <95% CI 0.89–2.29; $p = 0.138$) for prediction to in-hospital MACE disappeared in the multivariate analyses (Table 4).

4. Discussion

This study includes three major findings in patients with STEMI. There is a significant relationship between serum uric acid levels and post primary PCI myocardial perfusion grade. Baseline serum uric acid, MPV and hs-CRP are specific and sensitive predictors of poor coronary blood flow after primary PCI in STEMI. Additionally, these parameters are correlated with each other.

Although the pathophysiology of no-reflow has not been fully elucidated, its etiology appears to be multi-factorial. These factors include ischemic endothelial damage, microvascular leukocytes and platelet plugging, reactive oxygen species and complex interactions between leukocytes and platelets induced by the inflammatory process [22]. It is known that angiographic no-reflow is strongly correlated with short and long-term morbidity and mortality in acute myocardial infarction [5]. There is also a relationship between the recovery of left ventricular function after an acute myocardial infarction and the no-reflow phenomenon, as well [23].

With the growing understanding of the role of inflammation in the atherosclerotic process, studies have focused on hs-CRP as a marker of risk [24]. Hs-CRP is an acute phase reactant and marker of inflammation with a half-life of 19 h and it is released 6 h after a coronary event, on average [25]. Elevation of hs-CRP has been demonstrated in acute coronary syndromes and it has been shown to be associated with cardiac events [7]. Several studies demonstrated a significant correlation between the vascular occlusion score and baseline hs-CRP levels [8–10]. Inflammation has also been implicated in the development of the no-reflow phenomenon. But, there are some controversial reports about relationship between hs-CRP and post PCI coronary flow in patients with STEMI. Celik et al. [9] reported that admission high hs-CRP level in patients with only acute anterior MI undergoing primary PCI is likely to be in the causal pathway leading to the development of poor myocardial perfusion. Tomoda et al. [8] reported that CRP levels within 6 h after the onset of acute myocardial infarction reflect the vulnerability of culprit coronary lesions and predict adverse coronary events after primary PCI. However, Niccoli et al. [21] inversely reported that there is not a significant role of systemic inflammatory status (groups were divided due to CRP levels >5.4 or below) as a main determinant of no-reflow in acute myocardial infarction (AMI) patients treated by primary or rescue PCI within 6 h of symptom onset. These studies have relatively small population. However, in our study we demonstrate that hs-CRP level $\geq$5.4 mg/l predicts the no-reflow with an 89% sensitivity and 80% specificity and hs-CRP level is a significant, independent predictor of no-reflow and in hospital MACE.

Platelets play a pivotal role in acute coronary syndromes [26,27]. It has been showed that a higher MPV is correlated with greater platelet activation [28]. Larger platelets are more aggregable and are components of both platelet–leukocyte and platelet–platelet plugging in the IRA which may lead to no-reflow following PCI [5]. Previous studies have suggested that MPV could be a marker of the success of coronary reperfusion in STEMI patients [5,6,28]. Huczek et al. [5] found that, MPV levels are an independent predictor of the no-reflow phenomenon after primary PCI. Estévez-Loureiro et al. [28] demonstrated that MPV is associated with IRA patency and 30-day clinical outcomes in patients with STEMI. The present study confirms these findings and extends them to demonstrate that MPV is associated with no-reflow after primary PCI in patients with STEMI and with MPV levels $\geq$10.4 fl predicting no-reflow with 75% sensitivity and 73% specificity. However, Pereg et al. [6] reported that, 30% of patients in low MPV group had failed reperfusion after thrombolytic therapy. Therefore, MPV levels cannot be a single predictor for outcomes of reperfusion in patients with STEMI. But it may be stronger for prediction when used in combination more than one parameter together. So, we evaluated these three parameters together and found significant relationship with TIMI flow grade. Also, these parameters were correlated with each other.

Uric acid is an end product of xanthine oxidase enzyme activity [29]. Thus, the serum uric acid level is a marker of xanthine oxidase enzyme activity. During production of uric acid and the activity of xanthine oxidase enzyme, oxygen free radicals are generated [30]. The generation of oxygen free radicals are another underlying mechanism in the no-reflow phenomena [31]. Synthesis

and secretion of vasodilators and vasoconstrictors regulate blood flow [32]. In particular, endothelial derived nitric oxide with its potent vasodilator effect plays an important role in the regulation of coronary blood flow [33]. Hyperuricemia has been associated with decreased production of nitric oxide in the vascular endothelial cells [34,35]. So, in the elevated levels of uric acid may be implicated in both endothelial dysfunction and oxygen free radical generation. Previous studies have demonstrated a relationship between serum uric acid level and coronary arterial disease [36–38]. Bickel et al. [36] demonstrated that serum uric acid is an independent predictor of mortality in patients with coronary artery disease. Bos et al. [37] have also reported that elevated serum uric acid levels are associated with an increased risk for ischemic heart disease or myocardial infarction. Lazzeri et al. [38] reported that serum uric acid has a prognostic value about in-hospital mortality in the acute phase of STEMI patients, however, there is no difference in TIMI flow grade pre/post PCI in the patients with low and high uric acid level. Inversely, the present study demonstrated that uric acid level $\geq$5.4 mg/dl predicts no-reflow with 77% sensitivity and 70% specificity. Additionally, elevated uric acid levels were also a strong and independent predictor of no-reflow and in-hospital MACE in patients with STEMI undergoing primary PCI.

In this study, patients groups did not differ in respect to LVEF and in pain to balloon time. Some studies that assessing the recovery of LVEF after primary PCI indicate that the improvement of ejection fraction does not recover immediately after reperfusion. In a previous study [39], the improvement of LVEF in the reperfused myocardium is modest after 3 days and significant recovery occurs over the first month. In this study, TTE was performed immediately after primary PCI in coronary care unit. It is possible that stunned myocardial regions caused to reduce the ejection fraction in both groups. However, if we would to evaluate the systolic functions at the end of the hospitalization or several months later, LVEF could be significantly higher in reflow group. In addition, we detected no difference in pain to balloon time between groups. Several recent studies in patients with AMI treated with primary angioplasty demonstrated that especially in the first 6 h, the influence of time-to-treatment interval on the reperfusion success, myocardial salvage and clinical outcomes in patients with AMI depends on the type of reperfusion therapy [40–42]. In the first 6 h from the symptom onset, patients who treated with thrombolytic therapy, these outcomes increase with the prolongation of time to treatment interval. However, patients treated with primary PCI, these outcomes remained stable and independent from the time-to-treatment interval. However in our study, only patients who admitted within 6 h from symptom onset were enrolled and there is no difference in pain to balloon time between groups. We commented that this is an advantage for homogenization of groups.

4.1. Limitations

Possible limitations of the present study are a single center experience and may be represented by the small number of patients. However, our population contain homogeneous unselected STEMI patients submitted to primary PCI within 6 h from symptoms' onset, therefore mirroring the real world scenario.

5. Conclusion

Hs-CRP, MPV and uric acid levels on admission are strong and independent predictors of poor coronary blood flow following primary PCI. Hs-CRP and uric acid levels are also independent predictors of in-hospital MACE among patients with STEMI. Uric acid levels may be a simple, routinely assessed biomarker for risk stratification among STEMI patients. Apart from predictive value, uric acid levels may be a useful biomarker for stratification of risk in patients with STEMI and may also lead to carry further therapeutic implications. Although the clinical significance in the way the patients are treated after developing a STEMI, the association of uric acid levels and primary PCI outcome are still relevant and possibly further studies are needed in order to know if treatment of hyperuricemia prevents no-reflow in patient with STEMI and increased uric acid levels.

Conflict of interest

The authors have no conflicts of interest to disclose.

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