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Original Article

Monocyte count to high-density lipoprotein ratio predicts occlusion of the infarct-related artery in STEMI

Monosit sayısı /yüksek yoğunluklu lipoprotein oranı, STEMI'de enfarktla ilişkili arterin oklüzyonunu öngörür

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ABSTRACT

Aim: Patency of infarct-related artery (IRA) in patients with ST-segment elevation myocardial infarction (STEMI) before primary percutaneous coronary intervention (pPCI) is associated with better clinical outcomes. However, there were limited data regarding the predictors of IRA patency before pPCI in the setting of STEMI. We intended to evaluate the association of monocyte count to high-density lipoprotein ratio (MHR) with IRA patency in STEMI.

Material and Methods: A total of 726 patients were recruited. IRA patency was determined by the thrombolysis in myocardial infarction (TIMI) flow grade. According TIMI flow grade in the IRA before PCI, the study population was divided into two groups as TIMI 0,1 or 2 group (occluded IRA, n=624) and TIMI 3 group (patent IRA, n=102). Blood samples were collected on admission to calculate MHR. Of all patients, 92 (20.4%) patients revealed pre-pPCI TIMI 3 flow in IRA.

Results: The MHR was significantly higher in occluded IRA group (22.4 ± 5.4 vs 17.8 ± 6.9, $P < 0.001$). Glucose, troponin I, and platelet to lymphocyte ratio (PLR) levels were also higher in occluded IRA group ($P < 0.05$). Multivariate regression analysis demonstrated the MHR on admission (odds ratio [OR]: 1.191; 95% confidence interval [CI]: 1.116-1.272, $P < 0.001$) and pre-hospital use of prasugrel or ticagrelor (OR: 7.045; CI: 1.687-29.414, $P = 0.007$) as independent predictors of IRA patency.

Conclusion: IRA patency is more frequently found in patients having received fast acting antiplatelet therapy before pPCI and a higher MHR value independently predicts it.

Keywords: monocyte count to high-density lipoprotein ratio, ST-segment elevation myocardial infarction, infarct-related artery patency

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ÖZ

Amaç: ST segment yükselmeli miyokard enfarktüsü (STEMI) olan hastalarda, primer perkütan koroner girişim (pPKI) öncesi enfarktüs ilişkili arter acıklığı daha iyi klinik sonuçlar ile ilişkilidir. Bununla birlikte, STEMI ortamında pPKI öncesinde IRA açıklığının öngördürücüleri ile ilgili sınırlı veri vardır. STEMI'de monosit sayısı /yüksek yoğunluklu lipoprotein oranı (MHR) ile enfarktla ilişkili arterin acıklığı arasındaki ilişkiyi değerlendirmek istedik.

Gereç ve Yöntemler: Toplam 726 hasta çalışmaya alındı. IRA açıklığı, miyokard enfarktüsünde tromboliz (TIMI) akım sınıflaması ile belirlendi. PKI öncesi IRA'da TIMI akım derecesine göre çalışma popülasyonu, TIMI 0,1 veya 2 grup (tıkalı IRA, n=624) ve TIMI 3 grubu (patent IRA, n=102) olmak üzere iki gruba ayrıldı. MHR hesaplamak için basvuruda kan örnekleri toplandı. Tüm hastaların 92'sinde (%20,4) IRA'da pre-pPKI TIMI 3 akımı vardı.

Bulgular: MHR, tıkanan IRA grubunda anlamlı derecede yüksekti (22,4 ± 5,4'e karşılık 17,8 ± 6,9, P < ,001). Tıkalı IRA grubunda, glikoz, troponin İ ve trombosit/lenfosit oranı (PLR) düzeyleri de yüksekti (P < 0.05). Çok değişkenli regresyon analizinde, başvuru sırasındaki MHR değeri (odds oranı [1,391]; %95 güven aralığı [CI]: 1,116-1,272, P < 0,001) ve prasugrel veya tikagrelorun hastane öncesi kullanımı (OR: 7,045; CI:1,687-29,414, P = 0,007) IRA açıklığının bağımsız öngördürücüleri olarak bulundu.

Sonuçlar: IRA açıklığı, pPKI öncesi hızlı etkili antitrombosit tedavi alan hastalarda daha sık görülmektedir ve daha düşük bir MHR değeri IRA açıklığını bağımsız bir şekilde tahmin eder.

Anahtar Kelimeler: monosit sayısı /yüksek yoğunluklu lipoprotein oranı, ST segment yükselmesi miyokard enfarktüsü, infarktla ilişkili arter açıklığı

Introduction

Immediate reperfusion of ischemic myocardium is crucial for restoring normal cardiac function in ST-segment elevation myocardial infarction (STEMI). Infarct-related artery (IRA) patency prior to mechanical reperfusion is associated with better clinical outcomes in patients with STEMI [1]. Early reperfusion of the culprit artery before the procedure also improves post procedural success and maintenance of ventricular function [2]. Thus, factors related to pre-procedural IRA patency may yield additional prognostic information.

Monocytes are involved in evolvement of vulnerable plaques in STEMI [3]. On the other hand, low high-density lipoprotein (HDL) levels were associated with increased in-hospital mortality after myocardial infarction [4]. Monocyte counts to HDL ratio (MHR) is a novel parameter independently and significantly predicting short-term and long-term mortality in STEMI [5]. Moreover, MHR serves as a simple assessment tool for inflammatory status and represents atherosclerotic burden [6].

However, there were no data about its predictive value for spontaneous recanalization of blood flow in the IRA. In this study, we aimed to investigate the relationship between on admission MHR and IRA patency in patients with STEMI.

Material and methods

We retrospectively enrolled 726 consecutive patients who underwent coronary angiography with a diagnosis of STEMI between February 2015 and May 2016 in our tertiary center. The study was conducted in accordance with the principles of the Declaration of Helsinki. The STEMI was defined as symptoms of acute myocardial infarction lasting ≥ 30 minutes with the presence of new or presumed new >1 mm ST-segment elevation in ≥ 2 contiguous leads or left bundle branch block [7]. Diagnosis was later confirmed by subsequent increase in Troponin I level. Patients with clinical evidence of severe valvular heart disease, active cancer, hematological proliferative disorders, active hepatobiliary diseases, chronic antihyperlipidemic treatment, active infection, chronic inflammatory disease, receiving steroid therapy for autoimmune disease, and patients without a recorded measurement of admission laboratory parameters including cholesterol levels before coronary angiography were excluded from this study. Previous history of MI either STEMI or non-STEMI was also accepted as an exclusion criteria. The study was confirmed by the local ethics committee.

The baseline demographic, cilinical and angiographic features, admission laboratory test results were obtained from hospital

files and computer records. Lipid parameters were measured on emergency admission. Troponin I levels were measured with a Beckman Image 800 analyzer. Monocyte count was calculated using the data elicited from the complete blood count differential analysis. The reference value for monocyte in our laboratory is 2% to 10%. Monocyte to HDL ratio was calculated by dividing monocyte count (103/μL) to HDL level (mg/dL) and reported as 106/mg.

Hypertension was defined as use of blood pressure lowering drugs at admission, systolic pressure >140 mm Hg, or diastolic pressure >90 mm Hg in measurements. Patients being treated with glucose-lowering drugs or had a fasting plasma glucose concentration >7 mmol/l or a nonfasting plasma glucose concentration >11.1 mmol/L were considered to have diabetes. Echocardiography was performed in all patients and the left ventricular ejection fraction (EF) was calculated by using the modified biplane Simpson's method.

Coronary angiography was performed using either femoral or radial approach. Each coronary artery were displayed in at least 2 different plane images. The infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification [8].

Angiograms and the TIMI scale were assessed by at least 2 experienced interventional cardiologists who did not have knowledge of the clinical data. Before coronary intervention, TIMI flow grade was documented for each patient. Patients were divided into 2 groups according to the TIMI scale. Non-patent flow was defined as TIMI grade 0, 1, and 2 flows and patent flow was defined as TIMI 3 flow.

Statistical analysis

The analyses were carried out using the SPSS version 22.0 statistical package program (IBM SPSS Statistics for Windows, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess normality of distribution. All data were presented as a mean ± SD for parametric variables and as percentages for categorical variables. The comparisons between the two groups were performed with Student's t-test for continuous variables and with the chi-squared test for the categorical variables. The correlation between IRA patency and clinical variables and laboratory parameters was assessed by the Pearson correlation test. Multivariate logistic regression analysis was performed to detect the independent predictors of IRA patency. The parameters that were significant in univariate analysis were included. For all analyses, a p value <0.05 was considered significant.

Results

A total of 726 patients with STEMI who had been treated with primary PCI were included. On the admission angiography, infarct-related artery was LAD in 290 (39%) patients, Cx in 96 (13%) patients, RCA in 334 (46%) patients and graft in 2 (0.2%) patients. According to TIMI flow grade, patients divided into two groups as infarct related artery occluded group and infarct related artery patent group. 624 (85%) patients had TIMI 0,1 or 2 flow grade (occluded IRA group) and 102 (15%) patients had TIMI 3 flow grade (patent IRA group) in the IRA. Baseline and angiographic characteristics, and prehospital medications of the study groups are demonstrated in Table 1.

There were no significant differences in terms of age, male gender, rate of hypertension, diabetes mellitus, smoking, hyperlipidemia, systolic blood pressure, heart rate and having history of myocardial infarction, previous PCI or coronary bypass operation.. Admission EF was significantly higher in the patent IRA group (47±12 versus 44±13, p=0.02). Significant difference wasn't detected between pre-hospital medications, except superior use of prasugrel or tikagrelor in the occluded IRA group as compared to the patent IRA group (12 % versus 2%, P < 0.01). The laboratory parameters are also shown in Table 2.

Platelet count, monocyte count, serum glucose, troponin I, platelet to lymphocyte ratio and monocyte to HDL ratio (MHR) were significantly higher in the occluded IRA group as compared to the patent IRA group (251.2 ± 75.4 versus 231.3 ± 59.4, P = 0.01; 792 ± 230 versus 586 ± 196, P < 0.001; 163 ± 90 versus 134 ± 36, P = 0.002; 2.3 ± 2.1 versus 1.7 ± 1.8, P = 0.008; 189.9 ± 144.7 versus 138.8 ± 123.7, P < 0.001; 22.4 ± 5.4 versus 17.8 ± 6.9, P < 0.001). Lymphocyte count was significantly higher in the patent IRA group (2.3 ± 1.4 versus 1.7 ± 0.9 P < 0.001).

When univariate logistic regression analysis was performed to define possible independent predictors of IRA patency; platelet, lymphocyte and monocyte counts, serum glucose, troponin I, platelet to lymphocyte ratio and monocyte to HDL ratio remained significant and were included in the multivariate analysis. In the multivariate logistic regression analysis; serum glucose, monocyte to HDL ratio and pre-hospital use of prasugrel or tikagrelor remained as independent predictors of IRA patency (Table 3).

Multivariate regression analysis demonstrated the MHR on admission (odds ratio [OR]: 1.191; 95% confidence interval [CI]: 1.116-1.272, P < 0.001) and pre-hospital use of prasugrel or ticagrelor (OR: 7.045; CI: 1.687-29.414, P = 0.007) as independent predictors of IRA patency.

Table 1. Baseline and angiographic characteristics of patients

Parameters	Infarct related artery occluded group (n=624)	Infarct related artery patent group (n=102)	P value
Clinical variables			
Age , years	63±11	62±12	0.50
Male, n (%)	449(72)	67(65)	0.17
Hypertension , n (%)	197(31)	35(34)	0.60
Diabetes mellitus, n (%)	186(30)	23(22)	0.12
Smoking, n (%)	178(28)	23 (22)	0.20
Hyperlipidemia, n (%)	142(22)	17(16)	0.16
Systolic blood pressure (mmHg)	133(49)	130(17)	0.64
Heart rate (bpm)	88±30	82±12	0.07
Previous myocardial infarction, n (%)	82(13)	9(8)	0.21
Previous percutaneous coronary intervention, n (%)	105(160	14(13)	0.42
Previous coronary artery bypass grafting, n (%)	20(3)	2(2)	0.49
Admission LVEF, mean ± SD (%)	44±13	47±12	0.02
Pre-hospital medications , n (%)			
Aspirin	307(49)	58(56)	0.16
Clopidogrel	255(41)	36(35)	0.27
Prasugrel or Ticagrelor	13(12)	13(2)	<0.01
Beta-blockers	7(1)	3(2)	0.14
Statins	4(0.6)	2(2)	0.17
ACE-inhibitors or ARB	116(18)	21(20)	0.64
Infarct-related artery, n (%)			
LAD	250(40)	40(39)	0.88
CX	82(13)	14(14)	
RCA	287(45)	47(46)	
GRAFT	2(0.3)	1(0.9)	
TIMI flow in IRA, n (%)			
0	501(81)	-	
1	69(11)	-	
2	51(8)	-	
3	-	102(100)	

ACE= angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CX=circumflex artery; IRA=infarct-related artery; LVEF = left ventricular ejection fraction; LAD= left anterior descending artery; RCA=right coronary artery.

Table 2. Laboratory parameters of patients			
Parameters	Infarct related artery occluded group (n=624)	Infarct related artery patent group (n=102)	P value
Hemoglobin, g/dL	13±1.9	13.2±2.1	0.21
Platelet, 103/mm3	251.2±75.4	231.3±59.4	0.01
Mean platelet volume, fL	8.8±3	8.2±1.2	0.07
White blood cell,103/mm3	11.2±5.1	10.4±3.2	0.11
Neutrophil,103/mm3	9.2±3.5	8.6±2.2	0.10
Lymphocyte,103/mm3	1.7±0.9	2.3±1.4	<0.001
Monocyte, 109/L	792±230	586±196	<0.001
Serum glucose, mg/dL	163±90	134±36	0.002
Serum creatinine, mg/dL	0.96±0.4	0.92±0.3	0.22
Total cholesterol, mg/dL	172.1±43.5	164±36.2	0.14
HDL-cholesterol, mg/dL	36.7±9.2	37.2±8.8	0.68
LDL-cholesterol, mg/dL	105.7±38.4	101.7±31.6	0.42
Triglyceride, mg/dL	145.1±92.8	136.7±59.8	0.36
Troponin I, ng/mL	2.3±2.1	1.7±1.8	0.008
Platelet to lymphocyte ratio	189.9±144.7	138.8±123.7	<0.001
Monocyte to HDL ratio	22.4±5.4	17.8±6.9	<0.001
Data are given as mean±SD. HDL=high-density lipoprotein; LDL=low-density lipoprotein.			

Table 3. Multivariate Logistic Regression Analysis Showing the Predictors for the Patency in Infarct-Related Artery.			
Variables	OR	95% CI	P
Mean platelet volume	1.236	0.992-1.541	0.05
Platelet to lymphocyte ratio	1.004	1.000-1.007	0.03
Serum glucose	1.008	1.001-1.014	0.01
Troponin I	1.129	0.967-1.318	0.12
LVEF	0.993	0.976-1.010	0.41
Monocyte to HDL ratio	1.191	1.116-1.272	<0.001
Pre-hospital use of prasugrel or ticagrelor	7.045	1.687-29.414	0.007
CI=confidence interval; HDL=high-density lipoprotein; LVEF = left ventricular ejection fraction; OR, odds ratio.			

Discussion

In the present study, we investigated the relationship between MHR and IRA patency in patients with STEMI, and our data demonstrated that (i) MHR was significantly increased in patients with STEMI who had an occluded IRA before primary PCI; (ii) also MHR was found as an independent predictor of IRA patency in patients with STEMI. We also showed that patients with pre-PCI patent IRA had decreased value of admission troponin I levels and increased EF compared with patients with pre-PCI impaired IRA flow.

Primary PCI is the most effective reperfusion strategy for STEMI. Rapid attainment of a patent infarct artery is crucial for survival and improved short and long term outcomes. Even if the excellent prognosis is generally obtained after successful primary PCI, it may be further enhanced if TIMI-3 flow is restored before angioplasty. Some IRAs are completely occluded in patients with STEMI and some are not. Although these patients come with similar clinical presentations, Stone et al proved that early reperfusion with initial TIMI-3 flow before PCI was a powerful and independent predictor of in-hospital and late survival in patients undergoing a mechanical reperfusion strategy [1]. Patency status of IRA after coronary occlusion is associated with spontaneous and pre-PCI medication-mediated lysis of intracoronary thrombin. Patients who spontaneously achieve TIMI 3 flow may have different fibrinolytic properties related to their balance between coagulation, inflammation, thrombosis, and atherosclerosis.

Inflammation is accused for both initiation and progression of atherosclerosis, and contributes to acute rupture of atherosclerotic plaques with superimposed thrombus formation. Platelets, leukocytes, and endothelial cells are the active players of this process. Monocyte activation and macrophages (their mature form) have pivotal role both in the development and exacerbation of atherosclerotic process, a lipid driven inflammatory disease [9]. Blood monocytes are recruited into the intima and sub-intimal layers of the vessel wall, differentiate into the foam cells by taking up oxidized LDL and other lipids via the scavenger receptors. These migratory properties of monocytes are shown to be accelerated in patients with hypercholesterolemia [10]. Foam cells secrete pro-inflammatory cytokines, matrix metalloproteinases and tissue factor into the local vessel wall. While metalloproteinases digest the internal elastic lamina and cause plaque rupture, released tissue factor comes in contact with circulating blood and yields thrombus formation [11].

HDL cholesterol exhibits anti-inflammatory and anti-thrombotic effect on human monocytes by counteracting the activation and migration of them. Activted monocytes can also be reversed by HDL and its major protein component apolipoprotein A-1. Moreover, it inhibits LDL oxidation and removes cholesterol from those cells [12]. As the blood HDL cholesterol levels decrease, monocyte chemoattractant protein -1 (potent chemotactic factor for monocytes) levels increase [13]. Reddy et al. demonstrated that lower levels of HDL cholesterol, theoretically related to inadequate limitation of inflammatory response, were associated with increased in-hospital mortality following acute myocardial infarction [4].

MHR has been accepted as a vascular inflammatory marker and is a good predictor for atherosclerosis development, progression and cardiovascular outcomes. Its value in acute STMI been investigated some previous clinical studies. Karatas et al showed that admissionMHR values are found to be independently correlated with inhospital major adverse cardiovascular events and mortality after primary PCI [14]. Likewise, Cicek et al have recently found that rates of in-hospital mortality, major adverse cardiovascular events, late mortality, target vessel revascularization, stroke, and reinfarct were higher in the higher MHR group compared with the other MHR groups. They conclude that admission MHR is associated independently and significantly with short-term and long-term mortality in STEMI [5]. Cetin et al documented that MHR was a novel marker of inflammation seemed to be an independent predictor of stent thrombosis in STEMI patients [15]. Finally, Balta et al have recently investigated the relation between MHR and no-reflow phenomenon in patients with STEMI [16]. No-reflow was defined as post intervention TIMI flow grades 0-2 and reflow was defined as TIMI 3 flow grade. They found no-reflow more comon in higher MHR group and suggested MHR as an independent predictor of non-TIMI 3 flow after intervention in STEMI. Likewise, we found higher MHR levels in IRA occluded group and suggested MHR as an independent predictor of non-TIMI 3 flow before intervention in STEMI. It was also proven that pre-PCI IRA flow rate is closely related topost-PCI coronary flow rate and TIMI flow rate after primary PCI is closely related to worse outcomes in patients with STEMI [17].

Similiarly to literature, we found platelet to lymphocyte ratio (PLR) (another inflammatory indicator) was significantly higher in patients with a pre-PCI occluded IRA [18]. It is accepted as a indirect measure of inflammatory and thrombotic

pathways since both platelets and lymphocytes contribute STEMI pathophysiology. MHR is more like a inflammatory and oxidative stress marker.

In our study, pre-hospital administration of anti-platelet agents of rapid onset of action (prasugrel and ticagrelor) were associated with higher rates of pre PCI TIMI 3 flow. Our findings parallel to the guidelines support the idea to give potent anti-platelet agents as early as possible after first medical contact in patients with STEMI who referred for PCI [19].

Study limitations: Our study has some limitations. First, it was a retrospectively designed single center study and cardiovascular end points were not evaluated. Therefore we cannot make any conclusions on the role of MHR in cardiovascular morbidity and mortality. Second, study population is relatively small. Using only admission laboratory values rather than values at a time interval is the another limitation. We did not evaluate other cytokines or inflammatory markers such as C-reactive protein and fibrinogen, NLR. Lastly, we did not measure others markers of myocardial damage such as CK-MB.

As a conclusion our study findings demonstrated that MHR was an independent negative predictor of IRA patency in patients with STEMI undergoing PCI. Higher MHR was associated with lower TIMI flow grade on admission coronary angiogram. MHR may play a role in the pathogenesis of pre-PCI IRA patency as well as no-reflow phenomenon pathogenesis. MHR can be easily derived from complete blood count and might be used as an indicator of IRA patency in daily practice.

Declaration of conflicting interests

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