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The Relationship Between Monocyte Level on Admission and in Hospital Mortality in ST-elevation Myocardial Infarction Patients

ST-yükselmeli Miyokard İnfaktisü Hastalarında Başvuru Monosit Seviyesinin Hastane İçi Mortalite ile İlişkisi

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ABSTRACT

Background: Inflammation plays a key part in atherosclerotic processes. For inflammation balance, monocytes mission is essential. The importance of regulated inflammations has been known in ST-segment elevation patients for a long time. Therefore, we investigated the relationship between monocyte level on admission and in-hospital mortality in ST-elevation myocardial infarction (STEMI) patients.

Materials and Methods: A total of 2.341 serial patients in STEMI treated by primary percutaneous coronary intervention in a tertiary heart center between December-2008 and October-2014 were enrolled and categorized into two groups as low and high monocyte groups.

Results: There were 1.594 (68.0%) patients in the low monocyte (≤0.7x10^3/μL) group and 747 (31.9%) patients in the high monocyte (>0.7x10^3/μL) group. High monocyte group had larger size infarct area so impaired left ventricular ejection fraction. In multivariate analysis, monocyte count remained as an independent factor for in-hospital deaths (odds ratio: 2.63, 95% confidence interval: 1.07-6.47; p=0.040).

Conclusion: The current study demonstrated that admission monocyte level was independently related to in-hospital death. Therefore, admission monocyte count might be a useful tool in early risk scoring for STEMI patients.

Keywords: Primary PCI, ST-segment elevation myocardial infarction, monocyte level

ÖZ

Amaç: Enflamasyon, aterosklerozun patogenezinde anahtar rol oynar ve monositler enflamasyonun ana düzenleyicilerinden biridir. ST yükselmeli miyokard enfarktüsü (STyME) hastalarında iyi dengelenmiş enflamasyonun önemi uzun yıllardır tanımlanmıştır. Bunun sonucu olarak, STyME ile hastaneye başvuran hastaların başvuru monosit değeri ile hastane içi ölüm arasındaki ilişkiyi araştırdık.

Gereç ve Yöntemler: Aralık 2008-Ekim 2014 tarihleri arasında üçüncü basamak bir kalp merkezine başvuran ve primer perkütan girişim uygulanmış 2,341 STyME hastası kayıt altına alınıp yüksek ve düşük monosit sayısına göre iki gruba ayrıldı.

Bulgular: Düşük monosit (≤0,7x10^3/μL) grubunda 1,594 (%68,1) ve yüksek monosit(>0,7x10^3/μL) grubunda 747 (%31,9) hasta bulunmaktaydı. Yüksek monosit grubunda daha fazla infarkt alanı ve dolayısıyla daha düşük ejeksiyon fraksiyonu tespit edildi. Yapılan çoklu değişkenli analizde monosit değeri ile hastane içi ölüm arasında bağımsız ilişki bulundu (odds oranı: 2,63, %95 güven aralığı: 1,07-6,47; p=0,040).

Sonuç: Bu çalışmada başvuru monosit değeri ile hastane içi ölüm arasında bağımsız ilişki gösterildi. Sonuç olarak başvuru monosit değeri, STyME hastalarının erken risk skorlamasında kullanışlı olabilir.

Anahtar Kelimeler: Primer PKG, ST-yükselmeli miyokard infarktüsü, monosit sayısı

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Introduction

ST-segment elevation myocardial infarction (STEMI) is the most important type of acute coronary syndromes (1). Inflammation and immunological processes play an important role particularly in the development and pathogenesis of acute coronary syndromes: STEMI, non-STEMI, and unstable angina pectoris (2). Immune system cells like lymphocytes, neutrophils and monocytes are significantly associated with atherosclerotic processes, endothelial dysfunction, and ventricular remodeling in patients with STEMI. Monocytes are a part of innate immunity and are involved in reparative processes. Recent studies revealed that plateletcrit (3) ratio of neutrophil-to-lymphocyte (NLR) (4,5), ratio of lymphocyte-to-monocyte (6,7) and ratio of eosinophil-to-monocyte (EMR) (8) were directly related to severity, mortality and clinical outcomes in STEMI and coronary artery diseases. Here, our purpose was to determine the relationship between the monocyte level on admission and in-hospital mortality in STEMI patients.

Materials and Methods

Study Population

We enrolled a total of 2.341 consecutive patients with STEMI, who were treated with primary percutaneous coronary intervention (PPCI) and whose chest pain duration was lower than 24 hours, from December, 2008 to October, 2014 in a tertiary heart center. STEMI was described to be typical angina pectoris longer than 20 minutes, with new onset of left bundle branch block or ST elevation >1 mm at minimum two contiguous leads on the electrocardiogram and >2 fold up in serum cardiac markers, specifically troponin (9). Patients having cardiogenic shock and active infections and being treated with thrombolytic therapy were excluded. We divided all patients into two groups. The first group was named as the low monocyte group, which meant monocyte count was equal or lower than 0.7x10^3/uL, and the other group was named as the high monocyte group, which meant monocyte count was higher than 0.7x10^3/uL. Ethics committee approval and patient consent were obtained for the study.

Coronary Angiography

All patients received antiaggregant therapy with clopidogrel (600 mg) and aspirin (300 mg) prior to PPCI. Also, during the procedure, patients were treated with intravenous bolus of unfractionated heparin at a dose of 70-100 U/kg of body weight. The statin, beta-blocker agents which had no contraindications were ordered for the patients. Stenting was the main interventional treatment in our center. Radial or femoral approach, using of balloon for predilatation or postdilatation, stent type, and all equipment were left to the operator's decision.

Data Collection

All patients' age, gender, current smoking status, comorbidities such as hypertension, diabetes, hyperlipidemia, and chronic renal failure were recorded. Also, past medical histories including myocardial infarction, PCI, or coronary artery bypass graft stories of patients were recorded. Blood samples were taken prior to aspirin and clopidogrel administration for the measurement of laboratory parameters. Blood samples were taken into standard Ethylenediaminetetraacetic acid containing tubes and evaluated by an automated blood cell counter (LH 780; Beckman co.). All biochemical parameters were noted. Echocardiographic assessment was performed before PPCI with GE ViVidE7 ultrasound machine by using the Simpson's method. Left ventricular ejection fraction was measured in apical four chamber view. We also recorded the patients' angiographic characteristics.

Statistical Analysis

All continuous variables were expressed as mean±standard deviation. The Kolmogorov-Smirnov test was used for testing normality. The independent sample t-test was used for continuous variables displaying normal distributions. The Mann-Whitney U test was performed for continuous variables with skewed distributions. Categorical variables were expressed as number and percentages and the Pearson's chi-square test was employed for the evaluation of differences. For multivariable analysis, hierarchical logistic regression model was used. The odds ratio (OR) demonstrated the relative risk of death in the groups. Confounders of multivariate analysis were the predictors of in-hospital mortality. The p-value of <0.05 was considered statistically significant, and 95% confidence intervals (CI) were presented for all hazard and ORs. Statistical Package for Social Sciences software, version 15.0 (SPSS; IBM, Armonk, New York, USA) was used for analyses.

Results

A total of 2.341 patients were included in our study and treated with PPCI, and stent implantation was technically successful. The patients were classified into two groups: low monocyte and high monocyte groups, as shown in Table 1. The mean age of patients was 57 years, and 1.989

Table 1. Baseline and laboratory characteristics of patients

Variables	Low monocyte (≤0.7x10^3/μL) (n=1.594)	High monocyte (>0.7x10^3/μL) (n=747)	p
Age, y	57.82±11.6	55.44±11.87	<0.001
Male, n	1323 (56.5%)	666 (28.4%)	<0.001
Diabetes, n	410 (17.5%)	183 (7.8%)	0.542
Hypertension, n	477 (20.3%)	201 (8.5%)	0.146
Current smoking, n	607 (25.9%)	343 (14.65%)	<0.001
Hyperlipidemia, n	434 (18.53%)	196 (8.3%)	0.638
Stroke, n	24 (1.0%)	8 (0.3%)	0.413
Previous CABG, n	40 (1.7%)	28 (1.1%)	0.095
Previous PCI, n	207 (8.8%)	94 (4.0%)	0.874
In-hospital mortality, n	30 (1.2%)	24 (1.0%)	0.046
Hemoglobin, g/L	13.5±1.7	13.9±1.9	<0.001
White blood cell count, 10^9/L	11.1±4.0	14.5±4.6	<0.001
Platelet count, 10^9/L	233±67	249±70	<0.001
Monocyte count, 10^9/L	0.48±0.1	1.02±0.6	<0.001
Serum creatinine, mg/dL	0.91±0.3	0.94±0.3	0.014
Total cholesterol, mmol/L	184±51	178±45	0.018
Triglyceride, mmol/L	156±102	163±103	0.141
HDL, mmol/L	38.2±10.2	36.8±10.2	0.004
LDL, mmol/L	114.6±39.1	109.0±36.6	0.003
Glucose, mg/dL	159.2±80.1	157.9±82.0	0.712
CKMB, U/L	156±144	177±171	0.004
Troponin, ng/mL	49.0±4.5	49.1±5.7	0.915

CABG: Coronary artery bypass graft, CKMB: Creatine kinase-myocardial band, HDL: High density lipoprotein, LDL: Low density lipoprotein, PCI: Percutaneous coronary intervention

Table 2. Angiographic characteristics of patients

Variables	Low monocyte (≤0.7x10^3/μL) (n=1594)	High monocyte (>0.7x10^3/μL) (n=747)	p
Infarct-related coronary artery LAD LCx RCA	 681 (29.0%) 230 (9.8%) 649 (27.7%)	 339 (14.4%) 127 (5.4%) 261 (11.1%)	0.031
Number of used stents	1345 (57.4%)	607 (25.4%)	0.074
Contrast agent use, mL	244±85	250±87	0.132
Multivessel disease	301 (12.8%)	157 (6.7%)	0.214
Tirofiban use	759 (32.4%)	387 (16.5%)	0.051

LAD: Left anterior descending artery, LCx: Left circumflex artery, RCA: Right coronary artery

patients were male, 352 patients were female. We listed the demographic, laboratory and clinical characteristics in Table 1. We also analyzed angiographic characteristics and demonstrated them in Table 2. We searched the variables' effects on in-hospital mortality and reached the result that high monocyte count, high LDL level, old age (>65 age), male gender, diabetes, high serum creatine level (>2 gr/dL), low left ventricular EF (<%50) and high CK-MB directly were associated with in-hospital death (Table 3). Multivariate analysis determined that the independent parameters of in-hospital mortality, high monocyte count (OR: 2.63; 95% CI: 1.07-6.47; p= 0.03), older age, diabetes, high LDL level, low left ventricular EF and high CK-MB level were independently related to in-hospital mortality (Table 4).

Table 3. Univariate analysis

Variables	Odds ratio	95% confidence interval	p
Male	0.45	0.24-0.83	0.013
Age	1.07	1.05-1.10	<0.001
Creatinine	9.20	5.52-15.34	<0.001
Diabetes	3.82	2.21-6.59	<0.001
Hypertension	1.70	0.98-2.96	0.051
Current smoking	0.66	0.37-1.19	0.174
Hyperlipidemia	0.21	0.07-0.59	0.003
Chronic renal failure	9.33	3.95-22.04	<0.001
Peak CKMB	1.00	1.00-1.00	<0.001
Previous PCI	0.84	0.35-1.98	0.696
LVEF	0.91	0.89-0.93	<0.001
White blood cell count	1.11	1.06-1.16	<0.001
Hemoglobin count	0.83	0.72-0.96	0.012
Platelet count	1.00	0.99-1.00	0.926
HDL	0.95	0.91-1.00	0.053
LDL	0.96	0.95-0.98	<0.001
Peak troponin	0.98	0.94-1.03	0.513
High monocyte	1.73	1.00-2.98	0.041

CKMB: Creatine kinase-myocardial band, HDL: High density lipoprotein, LDL: Low density lipoprotein, LVEF: Left ventricular ejection fraction, PCI: Percutaneous coronary interventio

Table 4. Multivariate analysis

Variables	Odds ratio	95% confidence interval	P
Age	1.07	1.03-1.11	<0.001
Diabetes	2.54	1.04-6.18	0.042
LVEF	0.95	0.91-1.04	0.051
LDL	0.97	0.95-0.98	<0.001
Peak CKMB	1.00	1.00-1.00	<0.001
High monocyte	2.63	1.07-6.47	0.031

CKMB: Creatine kinase-myocardial band, LDL: Low density lipoprotein, LVEF: Left venricular ejection fraction

Discussion

Monocytes have an important role in atherogenesis and take part in inflammation (10). Monocytes consist of heterogeneous cell population and contain several surface expressions like CD14 and CD16 (11). CD16+ monocytes entitled proinflammatory cells and answer on inflammation (12). Also, monocytes have been effective in lots of systemic inflammatory diseases like rheumatoid arthritis and systemic lupus erythematosus. In atherosclerotic way, monocytes are related to stable and unstable plaque (13). In more than 900 stable CAD patients, it was shown that high monocyte count was strongly related to adverse cardiovascular events. (14).

Monocytes are modifiable cells enhancing their interaction with endothelial cells and myocardial cells. Increased expression of MAC-1 receptor leads to robust monocyte adhesion to the endothelial tissue (15). Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and L-selectin levels also increase in beginning part of acute coronary syndromes (16). Acute coronary syndromes are related to upregulation of some receptors like fibronectin receptor VLA-5, the mission of which is migration to tissue and very important part of cardiac extracellular matrix proteins (17). In acute coronary syndrome pathogenesis, monocyte chemoattractant protein (MCP-1) and macrophage colony stimulating factor (M-CSF) play a role in monocyte collection into the infarct zone, differentiation of monocytes to macrophages in the infarct area (18). MCP-1 (gene name *CCL2*, receptor gene name *CCR2*) is the most important chemokine that orchestrates to the macrophages' roles. Blood flow reduction stimulates MCP-positive macrophage infiltration of injured myocardium. (19). Circulating monocytes produce high plasma levels of MCP-1 in acute coronary syndromes, and this situation leads to neovascularization, so much macrophage collection and accumulation of myofibroblasts that affects left ventricular remodeling (20).

Our study showed an important relationship between high blood level of monocytes and in-hospital mortality in STEMI patients who were treated with PPCI. In previous studies, researchers have collected lots of information to show an association between inflammatory cells and development processes of atherogenesis. For remembering, monocytes play a key role in atherosclerosis firstly (21). Endothelial dysfunction leads to the accumulation of inflammatory cells in the endothelium of arterial wall (22). Monocytes which migrate to the tissue get the name of macrophage (23). Macrophages release some factors like interleukin-6 (IL-6), tumor necrosis factor alpha for more inflammation (24). Lots of clinical studies have shown that advanced monocyte level is associated with high inflammation, large infarct areas, and left ventricular dysfunction (25). Inhibiting monocytes collecting to infarcted myocardium tissue might prevent loss of left ventricular ejection fraction (26). Some studies focused on eosinophil to monocyte ratio (27) and neutrophil to lymphocyte ratio (28), and they showed again inflammation strongly related to pathogenesis of atherosclerosis.

In present study, we clearly showed that high monocyte level in patients with STEMI was related to larger infarct size, lower left ventricular ejection fraction and higher in-

hospital mortality. Therefore, monocyte level on admission may be useful for the prediction of early risk score for in-hospital mortality.

Study Limitations

Our study has several limitations. First, it was a single center and retrospective study. Second, we excluded STEMI patients having cardiogenic shock on admission, active infection and being treated with thrombolytic therapy. We need larger patient population and prospective and randomized clinical studies for suggestion of our findings.

Conclusion

We showed that higher monocyte level on admission was related to higher risk for in-hospital mortality. Monocyte count could be a simple and useful biomarker for risk stratification in STEMI patients.

Ethics

Ethics Committee Approval: Ethics committee approval and patient consent were obtained for the study (protocol number: 2800l928-501.07.0l-29.07.15).

Informed Consent: Patient consent were obtained for the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.H., Concept: R.H., Design: M.K., Data Collection or Processing: R.H., Analysis or Interpretation: M.K., Literature Search: Ş.Ü.D., Writing: R.H.

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

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