Usefulness of Mean Platelet Volume and Neutrophil-To-Lymphocyte Ratio for Development of Atrial Fibrillation After Acute Myocardial Infarction

Akut Miyokard İnfarktüsü Seyrinde Atriyal Fibrilasyon Gelişmesinde Ortalama Trombosit Hacmi ve Nötrofil / Lenfosit Oranı Kullanımı

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Abstract

Objective: Atrial fibrillation (AF) is the most common supraventricular arrhythmia following ST-elevated myocardial infarction (STEMI). Mean platelet volume (MPV) is an indicator of platelet activation and function. Mean platelet volume has been identified as an independent risk factor for future stroke and myocardial infarction. The neutrophil-to-lymphocyte ratio (NLR), fast and easy method for detecting inflammatory status, have been recently explored as a predictor for cardiovascular risk and AF. The aim of the present study was to evaluate a possible relationship between NLR and MPV levels on development of AF after STEMI.

Material-Method: This prospective study consisted of 743 patients with acute STEMI who were admitted to coronary care unit. Patients were divided into two groups, patients with and without AF. Predictors of AF were determined by multivariate regression analysis.

Results: From a total of 743 patients presenting with STEMI, 82 (11%) developed AF. Mean platelet volume and NLR was significantly higher in patients with AF compared to without AF (p<0.001, respectively). Multivariate regression analysis results showed that age [Odds Ratio (OR)=1.03; 95% Confidence Interval (CI)=1.01-1.05; p=0.001), ejection fraction (OR=0.95; 95% CI=0.93-0.98; p<0,001), MPV (OR=1.738; 95% CI=1.29-2.33; p<0.001), NLR (OR=1.08; 95% CI=1.01-1.15; p=0,025) and previous angiotensinogen converting enzyme blockers (OR=3.04; 95% CI=1.22-7.54; p=0,017) using were associated with development of AF in patients with acute STEMI.

Conclusions: This study showed that MPV and NLR were associated with the development of AF in patients presenting STEMI, other independent predictors of AF included age and ejection fraction.

Keywords: Myocardial Infarction, Atrial Fibrillation, Mean Platelet Volume, Neutrophil-To-Lymphocyte Ratio.

Özet

Amaç: Atriyal fibrilasyon (AF), ST yükselmiş miyokard enfarktüsünü (STEMI) takiben en sık görülen supraventriküler aritmidir. Ortalama trombosit hacmi (MPV) trombosit aktivasyonunun ve fonksiyonunun bir göstergesidir. Ortalama trombosit hacmi, gelecekteki inme ve miyokard enfarktüsü için bağımsız bir risk faktörü olarak belirlenmiştir. Nötrofil / lenfosit oranı (NLR) tespiti, inflamatuar durumu değerlendirmek için hızlı ve basit bir yöntem olup son zamanlarda kardiyovasküler risk ve AF için bir ön gördürücü olarak saptanmıştır. Bu çalışmanın amacı, STEMI sonrası AF gelişiminde NLR ve MPV düzeyleri arasındaki olası bir ilişkiyi değerlendirmektir.

Materyal-Metot: Bu prospektif çalışmaya, koroner bakım ünitesine başvuran, akut STEMI'li 743 hasta dahil edildi. Hastalar AF olan ve olmayan iki gruba ayrıldı. AF gelişimin ön gördürücüleri çok değişkenli regresyon analizi ile belirlendi.

Bulgular: STEMI ile başvuran toplam 743 hastanın 82 sinde (%11) AF gelişti. Ortalama trombosit hacmi ve NLR, AF gelişen hastalarda AF gelişmeyen hastalara göre anlamlı derecede yüksekti (sırasıyla p<0,001). Çok değişkenli regresyon analizi sonuçları, yaş (Odds ratio (OR)=1,03; %95 Güven Aralığı (GA)=1,01-1,05; p=0,001), ejeksiyon fraksiyonu (OR=0,95; %95 GA = 0,93-0,98; p<0,001), MPV (OR=1,738; %95 GA = 1,29-2,33; p<0,001), NLR (OR=1,08; %95, GA=1,01-1,15; p=0,025) ve hastane öncesi anjiyotensinojen dönüştürücü enzim blokerleri kullanımı (OR=3.04; %95 GA=1,22-7,54; p=0,017), STEMI hastalarında AF gelişimi ile ilişkiliydi.

Sonuç: Bu çalışma, MPV ve NLR'nin STEMI hastalarda AF gelişimi ile ilişkili olduğunu ve AF'nin diğer bağımsız ön gördürücülerinin ise yaş ve ejeksiyon fraksiyonunu olduğunu göstermiştir.

Anahtar kelimeler: Miyokard Enfarktüsü, Atriyal Fibrilasyon, Ortalama Trombosit Hacmi, Nötrofil Lenfosit Oranı.

Introduction

Atrial fibrillation (AF) is a common arrhythmia in the course of acute ST-elevated myocardial infarction (STEMI) and affects 1–2% of the general population (1). Advanced age, heart-failure signs on arrival, elevated admission heart rate, and left-ventricular dysfunction have been identified as predictors for AF in patients with acute myocardial infarction (AMI) (2, 3). Mean platelet volume (MPV) is an indicator of platelet activation and function (4).

DOI: 10.22312/sdusbed.543444
Müracaat tarihi / Received date: 22.03.2019
Kabul tarihi / Accepted date: 26.07.2019

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Larger platelets have more granules, aggregate more rapidly with collagen, more active metabolically and enzymatically, and have greater pro-thrombotic potential compared to smaller platelets (5). Elevated levels of MPV have been showed to be an independent risk factor for future stroke and myocardial infarction (6, 7). Mean platelet volume has been elevated in patients with AF compared to in patients with sinus rhythm (8). Furthermore, higher MPV has been observed in subjects with cardiovascular risk factors (9). Similarly, the neutrophil-to-lymphocyte ratio (NLR) detection, an easy method for assessing inflammatory status, has been recently researched as a predictor for cardiovascular risk and AF (10, 11).

However, the associations of MPV and NLR with development of AF after AMI have not yet been studied. The aim present study was to evaluate whether a possible relationship between MPV levels and NLR on the development of atrial fibrillation after acute myocardial infarction.

Material and Methods

Patient Population and Study Protocol

This study consisted of 743 patients with STEMI who admitted to coronary intensive care unit in our university hospital between 2011 November and 2014 January. Patient's clinical data, previous medication history and medications started after hospitalization were recorded. Patients were divided into two groups with and without atrial fibrillation. We evaluated the standard 12-lead electrocardiogram (ECG) recorded at a paper speed of 25 mm/s obtained for each patient after admission. All patients were monitored by Petas KMA 800 (Turkey) monitors in coronary care unit. Twenty-six patients were excluded. The study was approved by the institutional ethics committee and all patients gave their informed consent.

Exclusion criteria were unstable angina pectoris, non-ST elevated myocardial infarction, moderate-to-severe valvular heart disease, hyperthyroidism, chronic obstructive pulmonary disease associated, end stage renal disease, taking anti-arrhythmic drugs previously, known severe psychiatric disease, permanent AF, history of malignancy, venous thrombosis, systemic or pulmonary embolism, congenital hemorrhagic disease, thrombocytopenia, thrombocytosis, transfusion, acute or chronic inflammatory disease, autoimmune disease or current use of oral contraceptives.

Each patient was questioned about major cardiovascular risk factors, including family history of coronary artery disease, current smoking status, hyperlipidemia, hypertension, diabetes mellitus and obesity. A family history of coronary artery disease was defined as manifestation of the disease in first-degree male relatives younger than 55 years of age or in first-degree female relatives younger than 65 years. Hyperlipidemia was defined as fasting total cholesterol level >200 mg/dl or pharmacotherapy with lipid-lowering agents. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, measured before hospitalization or pharmacotherapy with antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose ≥126mg/dl or pharmacotherapy with insulin or oral antidiabetic agents. Obesity was defined as body mass index >30kg/m2. Patients who were smoking prior to hospitalization were deemed to be smokers.

Atrial fibrillation was diagnosed according to the European Society of Cardiology criteria (1). Atrial fibrillation was defined as having typical disorganized atrial activation the 12-lead ECG.

Transthoracic Echocardiography

Patients underwent transthoracic echocardiographic (GE VingMedSystemFive, Norway) examination. M-mode measurements were obtained from parasternal long-axis view for left atrium diameter, end-diastolic and end-systolic diameters of the left ventricle, septum and posterior wall thickness according to the recommendations of the American Society of Echocardiography. Left ventricular ejection fraction was calculated by Simpson's method.

Blood Sampling

Blood samples were drawn from the antecubital vein by careful vein puncture in a 21 G sterile syringe and collected into EDTA (ethylene dinitro tetraacetic acid) tubes in the morning, after a fasting period of 12 hours. Glucose, creatinine and lipid profiles were determined by Standard methods. Mean platelet volume was measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter (Beckman-Coulter Co, Miami, Florida, USA) was used for whole blood counts including MPV.

Mean platelet volume was measured within an hour after sampling. NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count. NLR was calculated in terms of 109/L.

Statistical Analysis

Data were analyzed with the SPSS software version 10.0 for Windows. Continuous variables from the study groups were reported as mean SD, categorical variables as percentages. To compare continuous variables, the Student's t-test or Mann–Whitney U test were used where appropriate. Categorical variables were compared with the x2 test. Variables with $p<0.05$ in the univariate analysis were selected and evaluated by multivariate regression models. Statistical significance was defined as $P<0.05$.

Results

A total of 743 patients (mean age: 62.76±12 years; range, 23-91 years) were included in this study. During the follow-up period, 82 patients (11%) developed AF. Demographic and clinical characteristics of the patients with and without AF are listed in Table 1. The patients with AF were older and female gender was dominant when compared to the patients without AF ($p<0.001$ and $p=0.005$, respectively). Hypertension was more common ($p=0.001$), but smoking was less common in patients with AF as compared to those without AF ($p=0.003$). Diabetes mellitus,

Table 1. Demographic and clinical characteristics of the patients with and without AF

	Without AF (n=661)	With AF (n=82)	P-value
Age, year	61.8±13.1	70.3±11.0	<0.001
Female gender n, (%)	122 (18.5)	26 (31.7)	0.005
Smoking n, (%)	381 (57.6)	33 (40.2)	0.003
Diabetes mellitus n, (%)	164 (24.8)	24 (29.3)	0.227
Hypertension n, (%)	292 (39.3)	51 (62.2)	0.001
Hyperlipidemia n, (%)	147 (22.2)	16 (19.5)	0.343
Cerebrovascular accident n, (%)	7 (1.1)	4 (4.9)	0.02
Obesity n, (%)	317 (49.1)	47 (58.0)	0.082
Ejection fraction (%)	45.3±9.6	40.4±10.0	<0.001
Left atrial diameter (mm)	37.95±4.1	39.2±5.0	0.01
Total cholesterol (mg/dL)	173,3±41.3	170.3±39.3	0.53
HDL cholesterol (mg/dL)	40.34±8.99	41.64±8.39	0.21
LDL cholesterol (mg/dL)	107.47±32.4	106.98±28.9	0.89
Triglycerides (mg/dL)	128.01±87.0	106.8±47.5	0.031
Creatinine (mg/dL)	1.08±0.25	1.09±0.27	0.55
WBC, 109/L	10750±6812	9700±2964	0.013
Platelet, 109/L	231.85±83.6	229.45±75.4	0.804
Neutrophil, 109/L	7.50±2.55	7.77±2.51	0.37
Lymphocyte, 109/L	1.61±0.93	1.14±0.58	<0.001
NLR	5.98±3.5	7.81±3.61	<0.001
MPV	8.58±1.05	9.14±0.70	<0.001
Troponin T at baseline (ng/ml)	0.45±1.2	0.69±1.1	0.46
Troponin T at peak (ng/ml)	4.95±5.1	5.25±3.67	0.56
CK MB at peak (mg/dl)	77.5±138	137. 20±182. 78	<0.001
Duration of hospitalization during coronary intensive care unit (day)	2.06±0.51	2.27±1.21	<0.001
Pre-hospital treatment			
Statin	82 (12.4)	8 (9.8)	0.313
Beta blocker	114(17.2)	16 (19.5)	0.353
RAS blockers	116 (17.5)	6 (7.3)	0.009
Acetyl salicylic acid	154(23.3)	20 (24.4)	0.460
Clopidogrel	28 (4.2)	5 (6.1)	0.295
Hospital treatment			
Statin	638 (96.5)	81 (98.8)	0.235
Beta blocker	625 (94.6)	72 (87.8)	0.022
RAS blockers	582 (88.0)	60 (73.2)	0.001
Acetyl salicylic acid	654 (98.9)	82 (100)	0.439

Data presented as mean+SD or number (%) of the patients. WBC indicates white blood cell; MPV indicates mean platelet volume; NLR indicates neutrophil-to-lymphocyte ratio; HDL: High density lipoprotein; LDL: Low density lipoprotein; CK-MB: creatinine kinase myocardial bundle; RAS: Renin angiotensin system.

hyperlipidemia and obesity rates were similar between patients with and without AF (for both parameters P> 0.05).

Total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels were similar between patients with and without AF (for all parameters P>0.05). Ejection fraction was lower (p<0.001) and left atrial diameter was higher in patients with AF than the patients without AF (p=0.01).

Mean platelet volume and NLR values were significantly higher compared to those without AF (p<0.001 and <0.001). Serum glucose, creatinine levels and platelet counts were similar between patients with and without AF (for all parameters P>0.05). We calculated the cut-off point of 8.1 for MPV and 5.9 for NLR to estimate the presence of AF with a sensitivity of 97.5% and 78% and a specify of 33.5% and 49% (AUC=0.65 and 0.66, Confidence interval (CI)=(0.61-0.68 and 0.60-0.71), p<0,001 for both parameters) (Figure 1).

Factors that were ascertained to be significantly different with univariate regression analysis (age, female gender, left atrial diameter, ejection fraction, peak CK-MB levels, white blood cell count, hypertension, pre- and in-hospital angiotensinogen converting enzyme blockers using, MPV and NLR) were entered in a multivariate model. The Multivariate regression analysis results showed that age, ejection fraction, hypertension, pre-hospital angiotensinogen converting enzyme blockers using, MPV and NLR were associated with the development of AF (Table 2).

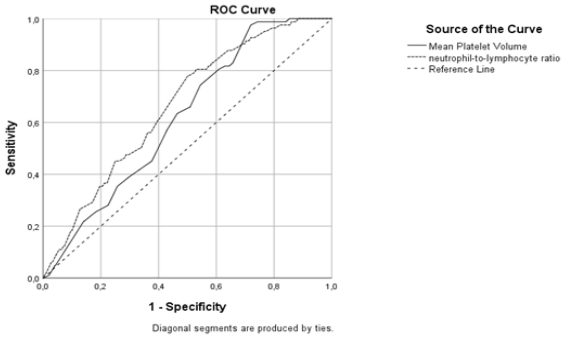

Figure 1. ROC curve with calculated area under the curve and optimal cut-off point for the mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR) to identify the presence of AF. We calculated the cut-off point of 8.1 for MPV and 5.9 for NLR to estimate the presence of AF with a sensitivity of 97.5 % and 78 % and a specify of 33.5 % and 49 % (AUC=0.65 and 0.66, Confidence interval (CI) = (0.61-0.68 and 0.60- 0.71), p<0.001 for both parameters).

Table 2. Multivariate independent predictors of AF

	Odds Ratio	95% Confidence Interval	P value
Age	1.03	1.01-1.05	0.001
Ejection fraction	0.95	0.93- 0.98	<0.001
Hypertension	1.89	1.11- 3.25	0.019
MPV	1.738	1.294-2.335	<0.001
NLR	1.080	1.014-1.151	0.025
RAS blocker using (prehospital)	3.04	1.22- 7.54	0.017

MPV indicates mean platelet volume; NLR indicates neutrophil-to-lymphocyte ratio; RAS: Renin angiotensin system

Discussion

The main finding of the present study was that increased MPV and NLR were associated with the development of AF in patients presenting with STEMI.

Atrial fibrillation is the most common supraventricular arrhythmia that might develop following STEMI, with a reported incidence as high as 6-21% and patients with AF was associated with worse clinical signs and prognosis compared with patients with sinus rhythm (12-14). In GUSTO I (Global Utilization of Streptokinase and TPA for Occluded Arteries-I) trial, the development of new-onset AF was predicted by older age, low blood pressure, female gender, high heart rate, high Killip class, history of prior MI, hypertension, diabetes, multivessel coronary involvement, low ejection fraction, left main coronary artery disease and TIMI flow<3 (15). Similarly, in GUSTO III (Global Utilization of Streptokinase and TPA for Occluded Arteries-III) and GISSI-3 (Effects of Lisinopril and Transdermal Glycerol Trinitrate Singly and Together on 6-week Mortality and Ventricular Function after AMI), similar results were found with the current study (14, 16).

Elevated levels of MPV have been related to AMI, increased mortality following myocardial infarction, and restenosis (6, 7). Moreover, MPV was an independent risk factor for recurrent MI (17). Dogan et al. showed that higher MPV levels were associated for adverse clinical outcomes among survivors of acute coronary syndromes with non-ST elevation (18). Unal et al. stated that higher preoperative MPV was associated with postoperative myocardial infarction and adverse cardiac events (19). Klovaite et al. in Denmark, examined 1300 patients who developed AMI and they showed that increased MPV was related to increased risk of MI irrespective of known cardiovascular risk factors (20). On the other hand, Erdogan et al. investigated whether an association with increased MPV and idiopathic dilated cardiomyopathy; whether a correlation with increased MPV and degree of coronary micro vascular dysfunction (exists). They showed that MPV was an independent predictor of lower coronary flow reserve (21). The above-mentioned studies have shown that MPV may be associated with both development and adverse outcomes of cardiac diseases.

Neutrophil to lymphocyte ratio represents the balance between neutrophils and lymphocytes and their counts may change according to inflammation or oxidative stress. NLR increase is a predictor of atherosclerotic lesion progression (11). Choudhury et al. reported that patients with AF had increased MPV levels, moreover, platelet activation and MPV may vary according to the subtype of AF (22). Furthermore, Colkesen et al. found that MPV was increased in patients with paroxysmal AF (8). Moreover, Erdem et al. showed that increased MPV levels were associated with the development of AF following coronary artery bypass grafting (23). Karatas et al. showed that admission serum levels of MPV, NLR, monocyte to high-density lipoprotein ratio and uric acid levels was correlated independently with new-onset AF after a primary percutaneous coronary intervention (24). Similarly, the present study found that the MPV and NLR were significantly higher in patients with (STEMI and) AF compared to STEMI patients without AF.

Arslan et al. reported that previous angiotensinogen converting enzyme blockers (ACEB) decreased the incidence of new-onset AF after STEMI and showed that increased LA diameter and low left ventricle EF were associated with new-onset AF after STEMI (25). Similarly, in our study, we demonstrated that increased LA diameter, low left ventricle EF and previous ACEB using were associated with AF development during STEMI.

However, the present study has some limitations. Firstly, this is a single-center study that contained a relatively small numbers of patients. The other platelet activation and

inflammation markers were not studied along with MPV and NLR.

Conclusion

Our present study found that the MPV and NLR were significantly higher in patients with AF compared to without AF in patients with STEMI. Our analysis showed that MPV which is a parameter of thrombosis, and NLR which is a parameter of inflammation may be useful predictors in foreseeing new onset AF following STEMI.

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