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Association of mean platelet volume with presence of non viable myocardium in ischemic cardiomyopathy

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Abstract

Background and aims: Parameters derived from complete blood count such as mean platelet volume (MPV), neutrophil to lymphocyte (NLR), platelet to lymphocyte (PLR) are recently proposed as measures of inflammation in addition to C-reactive protein (CRP), a classical inflammatory marker. Significant association of these parameters with atherosclerosis and complications have increasingly been reported. Our aim is to evaluate relationship between these parameters and presence of myocardial viability assessed with positron emission tomography (PET) in patients with ischemic cardiomyopathy.

Methods: A total of 122 ischemic cardiomyopathy patients who had undergone PET were enrolled in this study. The patients were dichotomized depending on the presence of transmural scar. Group 1 consisted of 21 patients who had transmural scar tissue, only, which were accepted as the group having non-viable myocardium. Group 2 consisted of 101 patients who had hibernation and/or non-transmural scar which were accepted as the group having viable myocardium. Hematological parameters within 30 days of PET imaging were retrospectively analyzed.
**Results:** There were no significant differences between two groups regarding values of WBC, neutrophil, lymphocyte, platelet, hemoglobin, RDW, CRP, PLR and NLR. Patients with non viable myocardium have significantly higher levels of MPV (p=0.002). In multiple logistic regression analysis, MPV [odds ratio (OR)=0.373, 95% confidence interval (CI) 0.20-0.69, p=0.002], was identified as independent predictor of non viable myocardium. In ROC analysis, a cut-point of 8.19 identified patients with non viable myocardium (area under curve=0.72, 95% CI 0.60-0.84). MPV value of greater than 8.19 demonstrated a sensitivity of 76%, a specificity of 55%.

**Conclusions:** The present study showed that MPV is an inexpensive, clinical and routinely measurable parameter that is associated with the presence of viable myocardium in ischemic cardiomyopathy.

**Key words:** platelet, positron emission tomography, cardiomyopathy

**INTRODUCTION**

Acute coronary syndromes are the worldwide leading cause of mortality and morbidity. Increased primary percutaneous intervention facilities decreased mortality, however, ischemic cardiomyopathy remained a cause of major morbidity even after successful revascularization. The presence of viable myocardium is correlated with the outcomes after revascularization in ischemic cardiomyopathy. Different imaging modalities, including echocardiography, single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) are studied to determine viable myocardium. Moreover, high diagnostic value of PET in assessment of myocardial viability is well documented (1).

White blood cell (WBC) subsets and its derived parameters such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are accepted as the new inflammatory markers that may be associated with the atherosclerotic process (2). Mean platelet volume (MPV) is an indicator of platelet activity where larger platelets are more active in terms of aggregation and thrombogenicity. NLR and MPV are not only associated with cardiovascular events, but also associated with the severity of atherosclerosis (3).

These two parameters determine the outcome of cardiovascular events. Some studies observed the relationship between NLR, MPV, and myocardial perfusion defects (4,5). However to our best knowledge, the relation of these parameters with the presence of myocardial viability -which is the major determinant of outcome in ischemic cardiomyopathy- is not studied. Our aim is to evaluate this relationship between myocardial viability assessed
with PET and hematologic blood count parameters, such as WBC, neutrophil, lymphocyte, platelet, hemoglobin, red cell distribution width (RDW), MPV, NLR, PLR, and inflammatory marker C-reactive protein (CRP) in patients with ischemic cardiomyopathy.

**METHODS**

*Study population*

Consecutive patients undergoing myocardial PET imaging between August 2011 and September 2013 who had a history of ischemic cardiomyopathy were evaluated. All patients had a history of myocardial infarction. The time from myocardial infarction to PET changed from 3 to 38 months. PET imaging was performed in order to determine the presence of viable myocardium for stable angina pectoris after coronary angiography for all patients. Complete blood count (CBC) and CRP levels within 30 days of imaging were retrospectively evaluated. Patients were included in the present study after the following exclusions: patients with hepatic and hemolytic disorders, concomitant inflammatory diseases and neoplastic diseases, patients taking steroids, immunosuppressive drugs, or non-steroidal anti-inflammatory drugs -except for low-dose aspirin- were also excluded from the study. 122 patients, 107 males and 15 females, were included in the study. The patients were dichotomized depending on the presence of transmural scar. Group 1 consisted of 21 patients who had transmural scar tissue, only (19 males and 2 females). Group 2 consisted of 101 patients who had hibernation and/or non-transmural scar (88 males and 13 females). 40 patients had hibernation, only. 64 patients had hibernation and non-transmural scar; 3 patients had non-transmural scar, only. Histories, demographics, risk factors, biochemical results, PET imaging findings of all patients were reviewed and noted.

*Myocardial perfusion SPECT imaging*

All patients scheduled for 18F-FDG PET/CT for ischemic cardiomyopathy should also undergo myocardial perfusion assessment. Patients underwent Tc-99m MIBI myocardial perfusion scintigraphy with a two-day protocol. The treadmill exercise or pharmacological stress with dipyridamole was used. The treadmill test was performed using Bruce protocol. 20 mCi Tc-99m MIBI was injected at peak exercise level and the patients continued the exercise at least for 90 seconds. For the dipyridamole stress test, 0.56 mg/kg dipyridamole was infused intravenously over 4 min. Tc-99m MIBI (20 mCi) was injected 8 min. after the beginning of injection of dipyridamole infusion. Tc-99m MIBI ECG gated SPECT imaging was performed 1 hour after the 20 mCi tracer injection at stress and rest.
**Myocardial F-18 FDG PET imaging**

The baseline blood sugar level was checked in the morning at least 6 hours of fasting. 50-100 g. of glucose was loaded and after 45-60 min., the injection blood sugar level was rechecked. 444 MBq (12 mCi) of 18F-FDG was injected if the sugar level was lower than 140 mg/dL. 2, 3 and 5 U of insulin was injected for 140–160, 160–180, and 180–200 mg/dL of blood glucose, respectively, if the sugar level was higher than 140 mg/dL. About 45–60 min. after 18F-FDG injection, myocardial 18F-FDG PET study was performed in a PET scanner in 3-D mode (Siemens Biograph 2 LSO DUO PET/CT, Germany). PET acquisition parameters were as follows: myocardium was covered in one bed position with a slice thickness of 5 mm, 10 minutes of emission time, 128 matrix, zoom 2.0, iterative reconstruction (4 iterations, 8 subsets). Attenuation correction was performed by CT.

PET images were analyzed by two nuclear medicine specialists. Perfusion and 18F-FDG PET images are interpreted side-by-side using a conventional Siemens cardiac display software and a comparison of myocardial perfusion to myocardial metabolism is included. Three major patterns were reported: a. A reduced myocardial perfusion with preserved FDG uptake, mismatch pattern, representing hibernating myocardium. b. An absent myocardial perfusion with an absent FDG uptake, match pattern, representing transmural scar. c. A partially reduced myocardial perfusion with concordant FDG uptake, non-transmural match pattern, representing non-transmural scar. The presence of the hibernation and/or non-transmural scar were accepted as the presence of viability. An example pattern of transmural scar is displayed in Figure 1 (Figure 1). Since PET imaging was not performed with ECG gated and additional quantification was not available on the current software, we did not measure the extent or amount of metabolic defects.

**Biochemical and Hematological parameters**

The blood was collected from the antecubital vein. Complete blood count (CBC) analysis was performed using a Beckman Coulter HMX-AL (Brea, CA, USA), and CRP was measured in serum by enzyme immunoassay (EIA) (Immage CRP EIA Kit; Beckman Coulter Inc, Brea, CA). WBC, neutrophil, lymphocyte, platelet, hemoglobin, RDW, MPV were recorded and NLR, PLR were derived from these parameters.

**Statistical analysis**
Statistical analyses were performed using SPSS 17.0 (Chicago). The Kolmogorov-Smirnov test was used to analyze the normality of the data. The continuous data was expressed as mean ± standard deviation (SD) and the categorical data was expressed as percentages. The Chi-square test was used to assess the differences in categorical variables between the groups. The relationships among the parameters were assessed using Pearson’s or Spearman’s correlation analysis according to the normality of the data. Multiple logistic regression analysis was used to identify the independent predictors of viable myocardium. All variables showing significance values of less than 0.25 on univariate analysis (age, dyslipidemia, hypertension, NLR, RDW and MPV) were included in the model. The differences between patient subgroups were tested using Mann–Whitney U or Student's T testing where appropriate P-value <0.05 was considered statistically significant.

RESULTS
122 patients with ischemic cardiomyopathy having myocardial PET were evaluated. Group 1 consisted of 21 patients with transmural scar in myocardium which were accepted as the group having non-viable myocardium. Group 2 consisted of 101 patients with non-transmural scar and/or hybernation in myocardium that were accepted as the group having viable myocardium.

The baseline characteristics of the groups are presented in Table 1 (Table 1). There were no differences between these two groups in terms of age, hypertension, diabetes mellitus and dyslipidemia. In addition, no significant difference was observed regarding the double antiplatelet therapy (DAPT), beta-blocker, angiotensin converting enzyme (ACE) inhibitor, and mineralocorticoid receptor antagonist (MRA) use. There were no significant differences between the two groups regarding WBC, neutrophil, lymphocyte, platelet, hemoglobin, RDW, NLR, PLR, and CRP. Patients with viable myocardium have significantly lower levels of MPV (p=0.002) (Table 2, Figure 2). In multiple logistic regression analysis - MPV [odds ratio (OR)=0.373, 95% confidence interval (CI) 0.20 - 0.69, p=0.002] - was identified as an independent predictor of myocardial viability (Table 3). In ROC analysis, a cut-point of 8.19 identified the patients with viable myocardium (area under curve (AUC) =0.72, 95% CI 0.60-0.84)(Figure 3). MPV value of less than 8.19 demonstrated a sensitivity of 76%, with a specificity of 55%.

DISCUSSION
This study revealed that MPV is independently associated with the presence of viable myocardium. Our study showed that a cut-off value of MPV below 8.19 could predict the presence of a viable myocardium in ischemic cardiomyopathy.

The outcomes depend on the presence of viable myocardium in patients with ischemic cardiomyopathy. The studies showed better prognosis, both in medically treated and revascularized patients with viable myocardium compared to non-viable one (6). Although many different imaging techniques were proposed, including an echocardiography, SPECT, PET, and MRI. 18F-fluorodeoxyglucose (18F-FDG) PET is the most sensitive imaging modality for detecting viable myocardium. A meta-analysis of 24 studies reported a weighted sensitivity and specificity of 92% and 63%, respectively, with a positive and negative predictive value of 74% and 87%, respectively, for the diagnosis of hibernating myocardium and the prediction of patient outcomes (6).

MPV is a marker of platelet activity. Large platelets have denser granules, containing mediators that play a role in the inflammation, atherosclerosis and eventually cardiac syndromes. Higher MPV is associated with increased mortality after both ST segment elevation myocardial infarction (STEMI) and non-STEMI (7,8). Higher MPV correlates with the reperfusion failure in STEMI (8,9). Higher MPV level may be associated with an impaired microvascular perfusion, even in successfully reperfused patients (10,11). Fabregat-Andrés Ó et al. showed the association of high MPV level with larger infarct size in STEMI by using a cardiac MRI which is a very sensitive tool for the myocardial infarct assessment (11). Another study found a significant correlation with a degree of systolic depression and MPV in STEMI patients (12,13). MPV level predicts transmural involvement of myocardium in patients with STEMI (14). Beside these studies, long-term patency of infarct related artery in follow-up is less in patients with higher MPV (15). LAD involvement is associated with high MPV level in patients with non-STEMI and this may be another factor causing large infarct size in addition to the microvascular obstruction (16). Although contradictory data exists, some studies showed a correlation of MPV with severity of coronary artery disease (17,18). Sarikaya S. et al. showed MPV levels were higher in diabetic patients with myocardial perfusion defects than in those without (5). Thus, more extensive micro and macrovascular diseases may result in a less perfused and less viable myocardium.

We did not observe any correlation between NLR, PLR and CRP with myocardial viability. Evidently, low-grade inflammation contributes to the progression of atherosclerosis in all stages. Since our study included patients with stable coronary artery disease with prior myocardial infarctions, it is plausible that the inflammatory parameters like NLR and CRP are
all alike between the groups. Besides, platelet aggregation is an important stage that have a significant influence on the outcomes. Platelet aggregation ultimately determines the infarct size, transmurality of infarct, and systolic functions. Aurigemma C. et al. showed an increased persistence of platelet activity one month after in patients with STEMI and microvascular obstruction (19). Kiris T et al. compared MPV levels of non-STEMI patients on admission and on the 24th hour, they found an association between total mortality and an early increase in MPV (20). The increased platelet activity after coronary events continues for a long period. Thus, more severely affected myocardium may be the result of the more persistent, extensive, and severe platelet activation. MPV was significantly higher in both ischemic and non-ischemic cardiomyopathy patients, compared with healthy controls in another study; this study demonstrated not only the correlation between high MPV levels and a decreased ejection fraction, but also the relationship between the high tromboembolic risk in cardiomyopathies with high MPV levels (21). Since MPV is affected by several factors such as increased levels of interleukins in cardiomyopathies, there may be a non-causal relationship between MPV and these factors. MPV may be a marker that may reflect all stages of the atherosclerotic and thrombotic pathologies.

Limitations of the study
The retrospective nature of the study is the major limitation. A small number of patients are another limitation. Additionally, unavailability of quantitative data of PET patterns is a significant restriction. Findings of the study is yet not to be generalized across all patients in a clinical practice.

CONCLUSIONS
The present study showed that MPV is an inexpensive, clinical and routinely measurable parameter that is associated with the presence of viable myocardium in ischemic cardiomyopathy.

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References


**Table 1:** Baseline characteristics; EF - ejection fraction (calculated with SPECT); DAPT - dual antiplatelet therapy; ACE/ARB inh. - angiotensin converting enzyme / angiotensin receptor blocker inhibitor; MRA - mineralocorticoid receptor antagonist

**Table 2:** Hematological parameters of groups; WBC - white blood cell; RDW - red cell distribution width; NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; CRP - C-reactive protein

**Table 3:** Multivariate analyses of viable myocardium; NLR - neutrophil-to-lymphocyte ratio; RDW- red cell distribution width; MPV – mean platelet volume

**Figure 1:** A patient with apical transmural scar. A. Aperfusion both at rest and stress. B. Absence of FDG uptake.

**Figure 2:** MPV values of groups; 1. Non-viable; 2. Viable.

**Figure 3:** Diagnostic accuracy of MPV in prediction of viable myocardium.
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<tbody>
<tr>
<td>Age</td>
<td>60,6±10,6</td>
<td>57,7±8,8</td>
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<tr>
<td>Sex, Male</td>
<td>88(%87,1)</td>
<td>19(%90,5)</td>
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<td>24(%23,8)</td>
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<td>9(%42,9)</td>
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<td>DAPT</td>
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<td>Beta Blocker</td>
<td>97(%96)</td>
<td>21(%100)</td>
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<td>ACE inh./ARB</td>
<td>92(%91,1)</td>
<td>20(%95,2)</td>
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<td>MRA</td>
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<td>9(%42,9)</td>
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<tr>
<td>Test</td>
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<td>Non-Viable Group n:21</td>
<td>p value</td>
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<tr>
<td>-----------</td>
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<tr>
<td>WBC</td>
<td>7977±2019</td>
<td>7789±1520</td>
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<td>Neutrophil</td>
<td>5085±1482</td>
<td>4816±1227</td>
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<tr>
<td>Lymphocyte</td>
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<tr>
<td>PLR</td>
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<td>116±34</td>
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<td>Hemoglobin</td>
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AUC: 0.72, 95% CI (0.60-0.84)