

## ORIGINAL ARTICLE

## Association between Mean Platelet Volume-to-Lymphocyte Ratio and the Presence of Apical Mural Thrombus in Post-Myocardial Infarction Patients

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### Abstract

**Background:** Left ventricular apical thrombus (AT) is generally associated with ischemic and non-ischemic cardiomyopathies. The thrombo-inflammatory process plays an important role in the pathophysiology of acute coronary syndromes and post-myocardial thromboembolic complications. Mean platelet volume (MPV) has been linked to poor prognosis following myocardial infarction. Recently, platelet-to-lymphocyte ratio (PLR) has emerged as a new marker of worse outcomes linking inflammation and thrombosis.

**Objective:** We aimed to investigate the prognostic significance of the marker – mean platelet volume to lymphocyte ratio (MPVLR) in patients with AT.

**Methods:** Fifty-six patients with left ventricular AT after an anterior myocardial infarction and 51 patients without left ventricular AT after an anterior myocardial infarction were enrolled in this study retrospectively. Admission MPVLR was compared between the two groups. Logistic regression analysis was carried out to identify whether MPVLR is an independent predictor of AT. The receiver operating curve (ROC) analysis was used to show the optimal cut-off for MPVLR to predict AT. P values less than 0.05 were considered statistically significant.

**Results:** Age, gender, frequency of diabetes mellitus, hypertension and atrial fibrillation, and ejection fraction values did not differ between the groups. MPVLR was higher in patients with AT than patients without AT ( $7.91 \pm 2.5$  vs  $5.1 \pm 2.1$ ,  $p < 0.001$ ). ROC analysis revealed moderate diagnostic value in predicting the presence of AT with a MPVLR cut-off  $> 4.75$  (82.1% sensitivity and 70.2% specificity (area under the curve = 0.811, 95% confidence interval [CI]: 0.731-0.891,  $p < 0.001$ ). MPVLR was found to be an independent risk factor for the formation of AT (B:0.441,  $p < 0.001$ ).

**Conclusion:** MPVLR is a simple, cheap and easily accessible test that can predict left ventricular AT formation. (Int J Cardiovasc Sci. 2020; [online].ahead print, PP.0-0)

**Keywords:** Myocardial Infarction; Cardiomyopathies; Thrombosis/complications; Lymphocyte Ratio; Cardiac Mass.

### Introduction

One of the major complications of myocardial infarction (MI) is left ventricular apical thrombus (AT) formation, which may favor blood stasis, increased coagulability and endothelial injury.<sup>1</sup> Its incidence has reported to range between 30-40% in postmortem studies.<sup>2,3</sup> Left ventricular AT usually occurs in the presence of left ventricular aneurysm or apical akinesia after large anterior MI. Additionally, hypercoagulable or inflammatory states might accelerate thrombus formation.<sup>4,5</sup>

Platelet-to-lymphocyte ratio (PLR) has been suggested as an important and cheap prognostic factor in coronary heart disease.<sup>6</sup> It is an inflammatory marker derived from complete blood count and has been studied in various cancers,<sup>7</sup> chronic renal failures,<sup>8</sup> and coronary artery disease.<sup>9</sup>

Platelet size has been reported to reflect platelet activity. Larger size platelets are metabolically and enzymatically more active.<sup>10</sup> Mean platelet volume (MPV) is an indirect marker of platelet activity and that is readily available in clinical settings and has

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been linked to poor prognosis following ST-elevation myocardial infarction (STEMI).<sup>11</sup>

In view of the fact that platelet size reflects platelet activity more accurately than platelet count itself, the notion of replacing platelet count with MPV in the PLR to form mean platelet volume-to-lymphocyte ratio (MPVLR) seems plausible. In our study we aimed to evaluate whether MPVLR has a predictive value for the development of AT after myocardial infarction.

## Material and methods

A total of 107 patients with anterior myocardial infarction were included. Fifty-six patients with AT, 51 control subjects without AT, matched by age, sex and ejection fraction were enrolled in this study retrospectively. Data regarding individual patients were retrospectively collected from patient files. Exclusion criteria were presence of infection, cancer, nonischemic cardiomyopathy, hematological disorders, and current therapy with corticosteroid, non-steroidal anti-inflammatory drugs or oral anticoagulants. Blood samples were drawn from a large antecubital vein into Vacutainer tubes (Becton Dickinson, Rutherford, New Jersey) for determination of biochemical and hemostatic parameters (Symex K-1000, Kobe, Japan) at admission. All routine biochemical tests were performed using an auto-analyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). PLR was defined as the absolute platelet count in the peripheral blood divided by the total lymphocyte count, and MPVLR was calculated as the ratio of MPV to lymphocyte count.

All patients underwent 2D echocardiography four weeks after anterior myocardial infarction. Two-dimensional echocardiography was performed with a 3.5 MHz transducer (IE33, Philips Medical Systems, Andover, Massachusetts). Simpson's method was used to assess the left ventricular ejection fraction in two-dimensional echocardiographic apical four-chamber view, as recommended by the American Society of Echocardiography guidelines.<sup>12</sup> All images were stored and evaluated by independent cardiologist who were blinded to patients' data.

## Statistical analysis

All analyses were performed using SPSS for Windows version 18.0 (SPSS, Chicago, Illinois). Quantitative data

are presented as means  $\pm$  standard deviation (SD) for parametric variables or medians with interquartile ranges (lower and upper quartiles) for nonparametric variables.

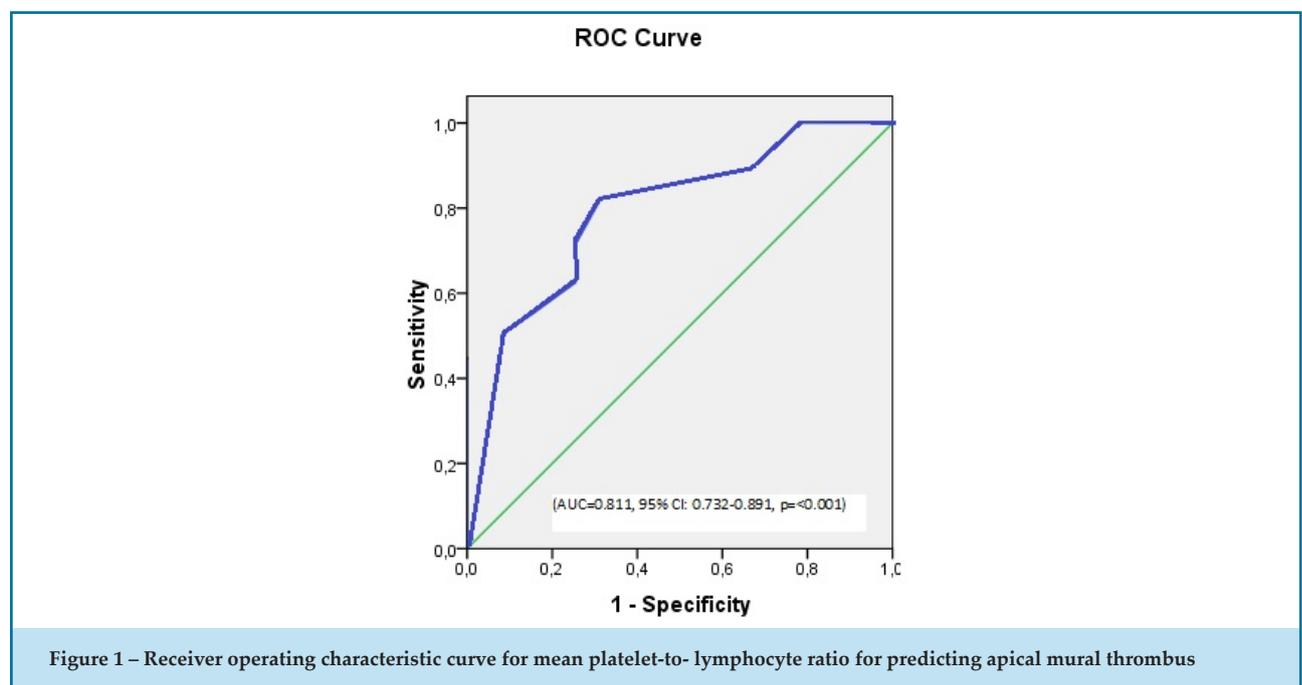
The Kolmogorov-Smirnov test was used to examine the normality of data distribution. Student's unpaired t-test was used to compare normally distributed data between the two groups and the Mann-Whitney U test was used for non-normally distributed data. The Pearson chi-square test was used for analysis of categorical variables. Logistic regression analysis was performed for parameters related to the presence of thrombus. P-values less than 0.05 were considered statistically significant. Receiver-operating characteristic (ROC) curves were estimated for MPVLR (and PLR for comparison). ROC analysis was used to determine the cut-off values of MPVLR in predicting thrombus formation. Ertem et al.,<sup>13</sup> previously demonstrated the relationship between apical mural thrombus and neutrophil-to-lymphocyte ratio in 55 patients with apical mural thrombus. In our study, we enrolled 56 patients with apical mural thrombus. According to power analysis, the power level of our study is 0.84.

## Results

A total of 107 patients with anterior myocardial infarction were included in the study. The mean age of the study population was  $60.7 \pm 7$  years. Baseline demographic, clinical and echocardiographic features are summarized in Table 1. Presence of diabetes mellitus, hypertension, atrial fibrillation did not differ between patients with AT and without AT. Body mass index and rate of smoking were lower in patients with AT than without AT. Echocardiographic parameters (left ventricular ejection fraction, left atrium diameter) were not significantly different between the two groups as shown in Table 1. Medications were similar in both groups. MPV was higher in patients with AT than patients without AT ( $9.71 \pm 1.09$  vs  $8.84 \pm 0.61$  fL,  $p < 0.001$ ). Lymphocyte count was lower in patients with AT than patients without AT ( $1.37 \pm 0.48$  vs  $2.0 \pm 0.77$   $10^3/\text{mm}^3$ ,  $p < 0.001$ ). While PLR did not differ between the two groups ( $p = 0.068$ ), MPVLR was higher in patients with AT than patients without AT ( $7.91 \pm 2.5$  vs  $5.1 \pm 2.1$ ,  $p < 0.001$ ). The ROC analysis yielded a cut-off value of 4.75 for the MPVLR to predict AT, with a sensitivity of 82.1% and specificity of 70.2% (Area under the curve = 0.811, 95% confidence interval [CI]: 0.731-0.891,  $p < 0.001$ ) (Figure 1).

**Table 1 – Demographical, echocardiographic and biochemical characteristics of study subjects and controls**

| Variables                                | Thrombus (+) patients<br>(n:56) | Thrombus (-) patients<br>(n:51) | p value |
|--|---------------------------------|---------------------------------|---------|
| Gender (female) (n, %)                   | 17(30%)                         | 8(15%)                          | 0.048   |
| Age (years±SD)                           | 65.3 ± 7.1                      | 56 ± 7.9                        | 0.001   |
| Diabetes mellitus (n,%)                  | 31(55%)                         | 18(35%)                         | 0.38    |
| Hypertension (n,%)                       | 33(58%)                         | 29(56%)                         | 0.831   |
| Body mass index, kg/m <sup>2</sup>       | 25.7 ± 2.2                      | 27.4 ± 2.7                      | 0.001   |
| Coronary heart disease (n,%)             | 51(91%)                         | 49(96%)                         | 0.298   |
| Percutaneous coronary intervention (n,%) | 53(94%)                         | 49(96%)                         | 0.727   |
| Coronary artery bypass grafting (n,%)    | 4(7%)                           | 2(3%)                           | 0.472   |
| Stroke (n,%)                             | 6(10%)                          | 2(3%)                           | 0.184   |
| Atrial fibrillation (n,%)                | 3(5%)                           | 1(2%)                           | 0.360   |
| Heart failure (n,%)                      | 56(100%)                        | 51(100%)                        | 1       |
| Current smokers (n,%)                    | 28(50%)                         | 38(74%)                         | 0.009   |
| ACE blockers (n,%)                       | 53(94%)                         | 49(96%)                         | 0.727   |
| Aldosterone antagonists (n,%)            | 52(92%)                         | 47(92%)                         | 0.891   |
| Betablockers (n,%)                       | 56                              | 51                              | 1       |
| Aspirin (n,%)                            | 50(89%)                         | 45(88%)                         | 0.864   |
| Clopidogrel (n,%)                        | 48(85%)                         | 44(86%)                         | 0.934   |
| Anticoagulants (n,%)                     | 6(10%)                          | 2(3%)                           | 0.184   |
| Statins (n,%)                            | 56                              | 51                              | 1       |



According to the cut-off > 4.75 for MPVLR, patients were divided into two groups; patients with a MPVLR > 4.75 were older, had a higher prevalence of female gender, and a lower frequency of smoking compared with the MPVLR ≤ 4.75 group (Table 2).

In multivariate logistic regression analysis, MPVLR (odds ratio [OR]: 1.406, 95% CI: 1.156-1.711, P ¼.0.001), MPV (OR: 2.293, 95% CI: 1.306-4.028, P ¼ .004), and smoking ((OR: 2.388, 95% CI: 0.886-6.434, P ¼ .020) were independent predictors of AT (Table 3).

**Table 2 – Demographical, echocardiographic and biochemical characteristics of study subjects and controls according to mean platelet volume to lymphocyte ratio (MPVLR) cut-off value**

| Variables                                       | MPVLR ≤ 4.75<br>(n:45) | MPVLR > 4.75<br>(n:62) | p-value |
|---|------------------------|------------------------|---------|
| Gender (female) (n, %)                          | 6 (15%)                | 20 (32%)               | 0.023   |
| Age (years ± SD)                                | 57.3 ± 8.9             | 60.1 ± 7.6             | < 0.001 |
| Diabetes mellitus (n, %)                        | 26(55%)                | 23(35%)                | 0.378   |
| Hypertension (n, %)                             | 23(58%)                | 39(56%)                | 0.415   |
| Body mass index, kg/m <sup>2</sup>              | 27.4±2.6               | 26.4±2.4               | 0.04    |
| Percutaneous coronary intervention (n, %)       | 43(94%)                | 59(96%)                | 0.727   |
| Coronary artery bypass grafting (n, %)          | 2(7%)                  | 4(3%)                  | 0.472   |
| Stroke (n, %)                                   | 5(11%)                 | 3(5%)                  | 0.047   |
| Atrial fibrillation (n, %)                      | 0(0%)                  | 4(6%)                  | 0.084   |
| Heart failure (n, %)                            | 56(100%)               | 51(100%)               | 1       |
| Current smokers (n, %)                          | 34(75%)                | 32(51%)                | 0.012   |
| ACE blockers (n, %)                             | 42(94%)                | 60(96%)                | 0.407   |
| Aldosterone antagonists (n, %)                  | 41(92%)                | 58(92%)                | 0.638   |
| Betablockers (n, %)                             | 45(100%)               | 62(100%)               | 1       |
| Aspirin (n, %)                                  | 41(89%)                | 54(88%)                | 0.518   |
| Clopidogrel (n, %)                              | 41(85%)                | 51(86%)                | 0.199   |
| Anticoagulants (n, %)                           | 1(10%)                 | 7(03%)                 | 0.080   |
| Statin (n, %)                                   | 45(100%)               | 62(100%)               | 1       |
| Diuretics (loop diuretic) (n, %)                | 42(92%)                | 58(94%)                | 0.969   |
| Glucose (mg/dl±SD)                              | 134 ± 61               | 156 ± 71               | 0.037   |
| Creatinine (mg/dl±SD)                           | 1.08 ± 0.21            | 1.09 ± 0.19            | 0.788   |
| Total cholesterol (mg/dl±SD)                    | 270 ± 58               | 290 ± 71               | 0.241   |
| LDL cholesterol (mg/dl±SD)                      | 139 ± 21               | 141 ± 26               | 0.535   |
| HDL cholesterol (mg/dl±SD)                      | 32 ± 8                 | 34 ± 6                 | 0.685   |
| Triglyceride (mg/dl±SD)                         | 208 ± 63               | 225 ± 67               | 0.102   |
| Hemoglobin (g/l±SD)                             | 11.7 ± 1.3             | 11.8 ± 1.7             | 0.681   |
| White blood cell (10 <sup>3</sup> /μL±SD)       | 11.4 ± 3.9             | 10.19 ± 3.6            | 0.79    |
| Platelet (10 <sup>3</sup> /mm <sup>3</sup> ±SD) | 208 ± 77               | 194 ± 71               | 0.356   |
| Lymphocyte count, (/mm <sup>3</sup> )           | 2.2 ± 0.5              | 1.2 ± 0.4              | < 0.001 |
| Left ventricular ejection fraction, (%±SD)      | 31 ± 5                 | 29 ± 5                 | 0.082   |

ACE: angiotensin converting enzyme; LDL: low-density lipoprotein, HDL: high-density lipoprotein

**Table 3 – Univariate and multivariate predictors of apical mural thrombus**

| Variables                                 | Univariate |                   | Multivariate |              |
|---|------------|-------------------|--------------|--------------|
|   | r          | p                 | B            | p            |
| Age                                       | 0.166      | 0.087             | -0,028       | 0.782        |
| Sex                                       | 0.192      | <b>0.048</b>      | -0.056       | 0.584        |
| Current smoker                            | -0.252     | <b>0.009</b>      | -0.195       | <b>0.020</b> |
| Body mass index                           | -0.322     | <b>0.001</b>      | -0.136       | 0.102        |
| Diabetes mellitus                         | 0.201      | <b>0.038</b>      | 0.121        | 0.553        |
| Ejection fraction                         | -0.176     | 0.070             | -0.050       | 0.585        |
| Glucose                                   | 0.241      | <b>0.012</b>      | 0.010        | 0.960        |
| Platelet count                            | -0.198     | <b>0.041</b>      | -0.290       | 0.213        |
| Lymphocyte count                          | -0.431     | <b>&lt; 0.001</b> | -0.301       | 0.179        |
| Platelet-to-lymphocyte ratio              | 0.177      | 0.068             | 0.230        | 0.452        |
| Neutrophil-to-lymphocyte ratio            | 0.408      | <b>&lt; 0.001</b> | 0.210        | 0.068        |
| Mean platelet volume                      | 0.440      | <b>&lt; 0.001</b> | 0.350        | <b>0.004</b> |
| Mean platelet volume-to- lymphocyte ratio | 0.501      | <b>&lt; 0.001</b> | 0.441        | <b>0.001</b> |

## Discussion

In this study, we showed that MPVLR was significantly higher in patients with AT after anterior myocardial infarction than without AT. To the best of our knowledge, this is the first study to determine the clinical utility of MPVLR in predicting AT after a myocardial infarction.

Left ventricular AT formation is known to occur in patients with acute anterior MI and dilated cardiomyopathy as a result of low flow and inflammatory states.<sup>3</sup> AT can also be found in patients with severe congestive heart failure.<sup>14,15</sup> Reportedly, the incidence of LV apical thrombi was approximately 60% in patients with acute anterior MI particularly in the pre-thrombolytic era.<sup>16,17</sup> The formation of an LV apical thrombus was associated with reduced LVEF ( $\leq 35\%$ ) and presence of apical aneurysms.<sup>18</sup> Recently, percutaneous coronary intervention has replaced thrombolytic therapy and caused a decrease in the incidence of LV apical thrombi. A study by Choi et al.,<sup>19</sup> showed an incidence of LV apical thrombi of 3.3% (34 of 1,045) in patients with acute anterior MI.<sup>19</sup>

Besides the low LVEF, inflammatory states play an important role in thrombotic process. Erythrocyte sedimentation rate (ESR), c-reactive protein (CRP),

PLR and neutrophil-to-lymphocyte ratio (NLR) have been studied in a large number of epidemiological studies as indicators of systemic inflammation.<sup>20,21</sup> Lymphocytes are known to play a crucial role for a complete inflammatory response, and reduced lymphocyte counts induced by apoptosis may increase inflammatory damage.<sup>22,23</sup> PLR has been reported to reflect hyperactive inflammatory pathways.<sup>6</sup> High platelet counts reflect underlying inflammation, because many inflammatory mediators stimulate megakaryocyte proliferation and lead to relative thrombocytosis.<sup>6</sup> Higher cytokine levels may lead to the production of large size platelets in the bone marrow.<sup>24</sup> The platelet size shows platelet activity more accurately than the platelet count.<sup>25</sup> MPVLR, which was calculated using MPV instead of platelet count in PLR, was claimed to be a more plausible index of platelet activity.<sup>25</sup> Several studies have shown that a high MPV is associated with cardiovascular events.<sup>26,27</sup> The mechanism mediating the relationship between high MPV and cardiovascular disease is not obvious. One of the reasons for increased number of larger platelets is cytokines released from ischemic tissues.<sup>28</sup> On the other hand, lymphocytes are involved the mechanisms of cell death caused by inflammation.<sup>29</sup>

Some studies have claimed that lymphocyte-mediated apoptosis is the most important type of cell death in ischemic myocardial tissue.<sup>30</sup> Increased physiologic stress can cause the release of cortisol and catecholamines during acute coronary syndrome.<sup>31</sup> In this situation, redistribution of lymphocytes to lymphatic organs results in apoptosis, which leads to lymphopenia,<sup>32</sup> and lower lymphocyte count.

In previous studies, researchers showed that higher PLR levels were associated with adverse events in various cardiovascular diseases.<sup>29, 30, 33</sup> Ertem et al.,<sup>13</sup> reported that PLR-like inflammatory marker, NLR, was associated with AT. Studies evaluating MPVLR in cardiac conditions are limited. Hudzik et al.,<sup>34</sup> reported that MPVLR was associated with high coronary thrombus burden and late mortality in STEMI patients. MPVLR was also found to be higher in patients with poor coronary collaterals.<sup>35</sup> In the present study, we found that MPVLR was strongly associated with AT. In response to increased inflammatory and thrombotic status, both higher MPV levels and lower lymphocyte counts may be associated with newly developed AT after a myocardial infarction. Taken together, the MPVLR is a simple and readily available biomarker that combines the predictive risk of MPV and lymphocyte counts into a single risk factor. According to our data, we suggest that the MPVLR is a better predictor than NLR, MPV, and PLR for AT.

### Study limitation

The limitations of this study are that this is a single center study, with a small cohort and retrospective design, which may affect the strength of the results. Platelet count would be better assessed with peripheral blood smear, but peripheral blood smear samples were not available in this study population. Additionally, MPVLR was measure only on admission; it would be worthy to see whether follow-up measurements of MPVLR could have prognostic value. Finally,

antiplatelet drugs and statins may affect MPV and lymphocyte count.<sup>36</sup> However, to the authors' knowledge, this is the first study in the literature to show an association between MPVLR and AT. It is believed that further studies are needed to confirm our findings.

### Conclusions

MPVLR is an easily calculated and efficient index that can be considered a powerful and independent predictor of AT in anterior MI patients. The authors suggest that it can be a useful adjunct to standard tests in the diagnosis of AT.

### Author contributions

Conception and design of the research: Koseoglu C. Analysis and interpretation of the data: Kurmus O. Statistical analysis: Koseoglu C. Writing of the manuscript: Koseoglu C. Critical revision of the manuscript for intellectual content: Kurmus O.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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