PROGNOSTIC VALUE OF MEAN PLATELET VOLUME AND NEUTROPHIL/LYMPHOCYTE RATIO IN PATIENTS WITH PULMONARY EMBOLISM

FULSEN BOZKUŞ1, BORA BILAL2, ANIL SAMUR3, ALİ CETINKAYA4
1Department of Chest Diseases, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras - 2Department of Anaesthesiology and Reanimation, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras - 3Department of Biostatistics, Faculty of Medicine, Akdeniz University, Antalya - 4Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey

ABSTRACT

Introduction: We compared the prognostic values of mean platelet volume (MPV) and neutrophil/lymphocyte (NLR) between surviving and nonsurviving patients with pulmonary embolism (PE).

Materials and methods: A total of 156 patients were screened by I26 code of ICD-9 and 89 patients were included as cases of confirmed PE. Admission blood counts and clinical data were obtained from hospital records. We further classified the PE patients into 2 groups: those who survived and those who died in the first 30 days. NLR and MPV were measured in serum and compared between the groups.

Results: MPV was significantly higher among patients of nonsurviving group when compared with surviving one (8.7 ± 0.1 vs 7.5 ± 0.3 fL, respectively; P < 0.001). NLR values were significantly higher in non-survivor group compared with the survivors (12.69 ± 1.87 vs 6.34 ± 0.66, respectively; P < 0.001). There was a statistically correlation between MPV and mean pulmonary arterial pressure (r = 0.50, p < 0.001) and also between MPV and right ventricle diameter (RVD) (r = 0.68, p < 0.001). In addition our result showed that a correlation between NLR and RVD (r = 0.43, p < 0.001) and also a correlation between NLR and systolic pulmonary arterial pressure (r = 0.31, p =0.003).

Discussion: Since complete blood count is a part of the routine laboratory investigation in the most hospitalised patients use and preliminary promising results of this study, NLR and MPV should be investigated in future prospective randomised trials regarding prognostic value in acute PE.

Key words: Neutrophil, lymphocyte, pulmonary embolism.

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Introduction

Pulmonary embolism (PE) is well known as an important disease with high rates of morbidity and mortality. An approximate annual incidence of 60-70 cases per 100,000 people has been reported, and it is the most common cause of sudden deaths in hospitals(1). PE along with deep venous thrombosis (DVT) is a major clinical manifestation of VTE(2). Even though surgery, trauma, hospitalization, malignancy, immobilization, pregnancy, use of estrogens and inherited thrombophilia are associated with VTE events(3,4), 30-50% of the events have no obvious predisposing factors(5).

Systemic inflammation can be measured using a variety of biochemical and haematological markers. One of these, neutrophil/lymphocyte ratio (NLR) could be an important measure of systemic inflammation as it is cost-effective, is readily available, and can be calculated easily. Since the physiological response to stress of the leukocytes in circulation leads to an increase in the number of neutrophils and a decrease in the number of lymphocytes, the ratio of these subgroups to each other is used as a marker of inflammation(6). PE is known to be associated with a leukocyte influx that occurs early after a thromboembolic event (1 day). Thrombus development is associated with pulmonary arterial and deep venous wall inflamma-
tion, marked by an early extravasation of leukocytes and an elevation in proinflammatory mediators and selectins, indicating a robust immune response following PE\(^{(7-9)}\).

Other one, platelet size, measured as mean platelet volume (MPV), is a marker of platelet function. Increased platelet volume is associated with increased platelet reactivity\(^{(10)}\), shortened bleeding time\(^{(10)}\) and increased platelet aggregation ex vivo\(^{(11)}\). Large platelets have higher thrombotic potential\(^{(12)}\) and express higher levels of P-selectin\(^{(13)}\) and glycoprotein IIb-IIIa\(^{(14)}\) than small platelets. Previous small studies evaluating the importance of MPV in patients with acute pulmonary embolism (APE) had conflicting findings related to whether it can be used as a prognostic indicator in APE\(^{(15,16)}\). Moreover, another small study evaluating platelet activity by more objective parameters showed mild elevation in APE\(^{(17)}\).

In this study, we examined prognostic values of MPV and NLR for the presence of PE events.

Materials and methods

**Study population and study design**

This is a retrospective study that included adult patients admitted to a state hospital with diagnosis of PE between March 2012 and September 2013. PE cases were screened by ICD-9 code of I26 from the electronic database of the hospital. A total of 156 patients were screened and 89 patients were determined as having a confirmed PE by pulmonary computed tomography (CT). There were 22 patients who were prediagnosed with PE but whose diagnosis was not proven by spiral CT; they were excluded. In addition, patients with haematological disorders (White blood cell (WBC) <3.0 x 10^9 /L or >20.0x10^9/L), infectious and inflammatory diseases, serious renal and liver disease as well as current use of immunosuppressant drugs (including steroids) were excluded from the study. Patients whose hospital records were incomplete, who were under the age of 18 or who were diagnosed with PE using methods other than spiral CT were also excluded. We classified the PE patients into 2 groups: those who survived 30 days after PE and those who died in the first 30 days. The Local Ethical Committee approved the study.

**Laboratory and radiologic analyses**

Complete blood counts and differentials were studied for the peripheral venous blood samples taken on admission to the various outpatient departments. Blood counts were studied by an auto-analyser (Abbott Cell-Dyn 3700 Hematology Analyzer, USA). Whole blood count, white blood cell (WBC) count, neutrophil, lymphocyte, NLR, MPV, D-dimer and other routine laboratory parameters were recorded by using electronic database of the hospital. Echocardiography and lower extremity venous Doppler ultrasound were also performed.

**Statistical analyses**

The software package Statistical Package for the Social Sciences (SPSS) for Windows version 12.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables from the study groups were reported as mean + standard deviation and categorical variables as percentages. To compare continuous variables, the Student t test or Mann-Whitney U test was used where appropriate. Correlation analysis for nonparametric variables was conducted using Spearman Rho test. To compare categorical variables, Chi-Square test was used. The level of statistical significance was set at \(p<0.05\).

**Results**

Demographic and clinical characteristics of the surviving and non-surviving patients are depicted in Table I.

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>Survivors (n = 78)</th>
<th>Non-survivors (n = 11)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.88 ± 11.70</td>
<td>74.63 ± 6.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>53.8/46.2</td>
<td>63.6/36.4</td>
<td>0.748</td>
</tr>
<tr>
<td>Malignancy, n (%)</td>
<td>5(6.4)</td>
<td>2(18.2)</td>
<td>0.207</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>13(16.7)</td>
<td>4(36.4)</td>
<td>0.211</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>27(34.6)</td>
<td>5(45.5)</td>
<td>0.515</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10(12.8)</td>
<td>2(18.2)</td>
<td>0.640</td>
</tr>
<tr>
<td>COPD n (%)</td>
<td>10(12.8)</td>
<td>2(18.2)</td>
<td>0.640</td>
</tr>
<tr>
<td>Deep vein thrombosis, n (%)</td>
<td>15(19.2)</td>
<td>2(18.2)</td>
<td>0.900</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>9(11.5)</td>
<td>2(18.2)</td>
<td>0.621</td>
</tr>
</tbody>
</table>

Table I: Comparison of demographic features between survivor and nonsurvivor of the patients with pulmonary embolism.  
CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident.
The mean age of the patients with survivors and the nonsurvivors group were 56.8 ± 11.7 years and 74.6 ± 6.54 years, respectively. There was significant difference between the groups in terms of age (p < 0.05). In total, 11 (12%) patients died in hospital, of which 8 (72%) occurred because of massive PE, 3 (27%) because of submassive PE. None of the patients died after discharge to the ward. All patients were treated with low molecular weight heparin and 11 (12%) patients with massive and submassive PE received additional tissue plasminogen activator. All patients also received warfarin throughout the follow-up.

There were no statistical differences between the surviving and nonsurviving groups with respect to comorbidity and history of the patients. The most common cause of comorbidity was hypertension (27 cases, 34.6%), followed by coronary arterial disease (13 cases, 16.7%) and DVT (15 cases, 19.2%).

The vital signs and laboratory findings for the survivors, nonsurvivors are presented in Table II.

There were no statistically significant differences between the 2 groups with respect to gender, heart rate and levels of haemoglobin and platelet count. MPV was significantly higher among patients of nonsurviving when compared with surviving group (8.7 ± 0.1vs 7.5 ± 0.3 fL, respectively; P < 0.001). NLR values were significantly higher in nonsurvivor group compared with the survivors (12.69 ± 1.87 vs 6.34 ± 0.66, respectively; P < 0.001). In addition to this, significant increases in WBC and neutrophil counts and decreases in lymphocyte counts were also observed. The mean serum D-dimer levels, pulmonary arterial pressure, systolic blood pressure, diastolic blood pressure and arterial O2 saturation were significantly higher in the nonsurviving group than in the surviving one (p < 0.0001, p < 0.0001, p < 0.0001 and p < 0.0001, respectively). All of the nonsurviving patients had right ventricle overload on echocardiography, as expected. There was a statistically correlation between MPV and mean pulmonary arterial pressure (r = 0.50, p < 0.001, Fig. 1) and also between MPV and right ventricle diameter (RVD) (r = 0.68, p < 0.001). There was a statistically correlation between NLR and RVD (r = 0.43, p < 0.001) and also a correlation between NLR and systolic pulmonary arterial pressure (r = 0.31, p =0.003). In addition our result showed that a correlation between NLR and MPV (p=0.001, r=0.510, Fig. 2).

Table II: Comparison of haemodynamic parameters and laboratory findings of patients according to the survival status.

<table>
<thead>
<tr>
<th>Haemodynamic parameters</th>
<th>Survivors (n = 78)</th>
<th>Non-survivors (n = 11)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>116.37 ± 9.29</td>
<td>80.45 ± 6.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73.72 ± 8.54</td>
<td>52.27 ± 7.19</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>91.23 ± 5.65</td>
<td>89.64 ± 5.93</td>
<td>0.667</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>89.5 ± 2.79</td>
<td>79.0 ± 6.30</td>
<td>0.001</td>
</tr>
<tr>
<td>RV dilatation n (%)</td>
<td>11(14.1)</td>
<td>11(100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell (10⁹/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (10⁹/L)</td>
<td>7.70 ± 0.41</td>
<td>12.48 ± 0.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphocytes (10⁹/L)</td>
<td>1.22 ± 0.12</td>
<td>1.00 ± 0.161</td>
<td>0.001</td>
</tr>
<tr>
<td>NLR</td>
<td>6.34 ±0.66</td>
<td>12.69 ± 1.87</td>
<td>0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.88 ± 0.32</td>
<td>13.1 ± 0.68</td>
<td>0.313</td>
</tr>
<tr>
<td>Platelets (10⁹/L)</td>
<td>254.65 ± 50.63</td>
<td>258.91 ± 26.71</td>
<td>0.587</td>
</tr>
<tr>
<td>MPV</td>
<td>7.59 ± 0.15</td>
<td>8.78 ± 0.19</td>
<td>0.001</td>
</tr>
<tr>
<td>PAP-systolic (mmHg)</td>
<td>37.10 ± 10.62</td>
<td>75.91 ± 6.96</td>
<td>0.001</td>
</tr>
<tr>
<td>Ddimer</td>
<td>7.16 ± 1.08</td>
<td>14.56 ± 0.95</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 1: Comparison of MPV among the survivors, nonsurvivors.

Fig. 2: Comparison of NLR among the survivors, nonsurvivors.
Discussion

The present study examined the prognostic value of NLR and MPV at hospital admission in patients with PE. Our study showed that NLR and MPV were significantly increased in non-survivor group compared with survivor one. The findings of the present study indicated for the first time that NLR and MPV are independent predictor of acute mortality in patients with PE. Our results encourage the use of these as a powerful and inexpensive parameter for the risk stratification of patients with PE.

Recent studies showed the role of NLR as an independent predictor of early mortality in various cardiovascular diseases (18-20). These studies demonstrated that increased NLR was due to an increase in neutrophil count and a decrease in lymphocyte count. It has been proposed that elevated serum cortisol levels due to increased sympathetic system activity in acute coronary syndrome and acute decompensated heart failure may account for the alterations in neutrophil and lymphocyte counts in these patients (21). This ratio, which can be calculated easily, may be used as an independent prognostic factor in PE.

In the present study, a correlation was found between NLR and mortality due to PE. Age, systolic blood pressure, heart rate, comorbid conditions and vital signs at presentation have been shown to be significant prognostic factors to predict 30-day mortality (22). Kayrak et al. (23) found that, survivors were older, had lower systolic BP and higher heart rates compared with non-survivor group. In contrast, we found that nonsurvivors were older, had lower systolic BP compared with survivor group.

We know that PE is associated with a leukocyte influx that occurs early after PE. Thrombus development is associated with deep venous and pulmonary arterial wall inflammation marked by an early extravasation of leukocytes and an elevation in proinflammatory mediators and selectins, indicating that a robust immune response occurred with right ventricle damage following PE.

In particular, neutrophils are the first leukocytes to be found in the damaged pulmonary area. Procoagulants are secreted locally by leukocytes that contribute to oxidative and proteolytic injury (24-25). It is well known that right ventricular damage contributes to poor clinical outcome after PE, and one study reported that neutrophils contribute to right ventricular dysfunction in PE (26).

In our study we found that a weak correlation between NLR and RVD \((r = 0.43, p < 0.001)\) and also a weak correlation between NLR and systolic pulmonary arterial pressure \((r = 0.31, p = 0.003)\).

In a rat model of pulmonary embolism it was shown that there was severe right ventricular dysfunction in the group with early mortality due to acute PE. Significant neutrophil infiltration in the right ventricle microscopically was proposed as a cause of severe right ventricular dysfunction (27). In our study show that, all of the nonsurviving PE patients had right ventricular dysfunction (100%) as compared to surviving patients, may lend support to the latter hypothesis.

A few studies show that role of inflammation in acute PE. One of these, Huang et al. (28) found that WBC >11,000 mm3 was an independent predictor of mortality among patients who presented with acute PE. In our study we found that statistically higher WBC levels in nonsurviving PE patients group compared with surviving \((15.2 \pm 1.02 \text{ vs } 11.48 \pm 1.09, \text{ respectively; } P < 0.001)\). Other one, Kaya et al. (29) demonstrated that soluble CD40 ligand was elevated in acute PE. CD40 ligand is an important marker of vascular thrombosis and inflammation. Moreover increased levels of this marker in acute PE may support the role of inflammation in acute PE.

In addition to coagulation factors, circulating anucleated disc-shaped cells called platelets are critical in the initiation of thrombosis, thrombus propagation, vasoconstriction, and inflammation. Platelet size, measured as MPV, is a marker of its function and is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A2, platelet factor 4 and b-thromboglobulin (30-31). Increased platelet activation in patients with PE has been demonstrated in the previous studies (15,16,32). Mechanism of this activation has not been clearly explained (32). In the literature, there are limited studies evaluating MPV levels in patients with acute PE (15,33). Varol et al. (34) determined the increased MPV levels in patients with acute PE compared with controls. They showed a correlation between increased levels of MPV and right ventricular diameters. Kostrubiec et al. (15) found that MPV levels were similar in control subjects and PE patients. However, MPV values were differed between low and intermediate or high risk. In contrast Ermis et al. (35) found that there was no difference in both the intermediate and high-risk APE groups’ MPV compared with healthy people that could not be explained. The remarkable finding in their study was a higher MPV in nonsurviving patients, as compared to survivors.
In our study, similar to that of Erms et al., we found statistically higher MPV levels in nonsurviving PE patients group compared with surviving. Erms et al., found a weak correlation between MPV and RVD \((r = 0.11, p = 0.045)\) and also a weak correlation between MPV and systolic pulmonary arterial pressure \((r = 0.25, p < 0.001)\). In our study, similar to that Erms et al., we found a correlation between MPV and RVD \((r = 0.68, p < 0.001)\) and also a correlation between MPV and systolic pulmonary arterial pressure \((r = 0.50, p < 0.001)\).

It is well known that advanced age and D-dimer levels, although nonspecific, have prognostic value and have high sensitivity in PE. The majority of PE patients were reported to be between the ages of 60 and 70 years in clinical studies and between the ages of 70 and 80 years in autopsy series. In our study, there was significant difference between the groups in terms of age \((p < 0.05)\). However, in terms of age distribution, our results were comparable with the literature.

In a study by Galle et al., the plasma D-dimer level was reported to be directly proportional to the severity of PE. In most PE patients, D-dimer levels are high, but D-dimer levels may also rise in the presence of advanced age, inflammatory conditions, trauma, pregnancy, infection, and malignity and in the postoperative period. One or more of these conditions, causing an increase in D-dimer levels, may coexist in patients diagnosed with PE. Therefore, it is proposed that D-dimer should be used to exclude the diagnosis of PE, not as a marker of prognosis. Cavus et al., found that a significant relationship was found between D-dimer and the diagnosis of PE, but no significant relation was revealed between D-dimer levels and mortality. In our study, a significant relationship was found between D-dimer and the mortality of PE.

There are some limitations of this study that should be concerned. Main limitation of this study was retrospective design. Another important limitation was the small number of patients with PE. Additionally, our analysis was based on a simple baseline determination that may not reflect the patient status over long periods. Moreover, further prospective studies including larger participants are needed to confirm and explore these results.

In conclusion, we have shown that NLR and MPV were significantly elevated in nonsurviving patients with PE compared to surviving group. The present study examined the prognostic value of NLR and MPV in patients with PE.

In this clinical setting, WBC counts were not only increased but also significant alterations occurred in the composition of leucocyte subtypes and MPV as potential markers of platelet activation can be used in the determination of disease severity for PE patients.

References


