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**ORIGINAL PAPER**

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# Evaluation of platelet indexes as potential biomarkers of suspected pulmonary embolism

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**ABSTRACT**

**Introduction.** Pulmonary embolism is one of the most frequent cardiovascular diseases, potentially leading to death. There is no validated biomarker with both high specificity and sensitivity.

**Aim**. The aim of the study was to define the diagnostic importance of platelet count (PLT), mean platelet volume (MPV) and platelet distribution width (PDW) on acute pulmonary embolism.

**Material and methods.** We retrospectively reviewed the medical records of 145 patients with clinically suspected acute pulmonary embolism admitted to the Emergency Department. Demographic data and laboratory tests were collected on admission. All patients underwent computed tomography (CT) angiography.

**Results.** The total data of 145 patients were analyzed, including 65 patients (67±17 years; 30 men/35 women) with acute pulmonary embolism confirmed with CT and 80 patients (67±19 years; 26 men/54 women) with negative CT. The MPV did not differ between the patients with acute PE and the control group (8.0 fL [IQR: 7.6-8.4] vs. 7.9 fL [IQR: 7.4-8.7], p=0.45). There were no significant differences in PLT ($220x10^3/mm^3$ [IQR: 172-274] vs. $243x10^3/mm^3$ [IQR: 186-286], p=0.12) and PDW (59.0 ± 6.9% vs. 57.2 ± 7.3%, p=0.12).

**Conclusions.** Our results suggest that platelet indexes (at a single time point) are not a reliable diagnostic biomarkers of acute pulmonary embolism.

**Keywords.** mean platelet volume, platelet count, platelet distribution width, pulmonary embolism

## Introduction

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are 2 manifestations of venous thromboembolism (VTE).[1] It is one of the most frequent cardiovascular diseases with an overall annual incidence of 110-130 per 100,000 inhabitants.[1] In most cases, PE appears as a consequence of DVT and it may be lethal, lead to chronic disease or it can remain asymptomatic.[2]

Computed tomography (CT) angiography is the method of choice for diagnosing the patients with suspected PE but it is costly and not available 24 hours a day, 7 days a week in every hospital. Moreover, it is associated with contrast-induced nephropathy and with

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radiation exposure.[3,4] D-dimer testing is sensitive but not specific for PE.[5] There is a need to disclose a reliable, noninvasive test that can precisely identify patients with PE.

Mean platelet volume (MPV) is the most commonly used measure of platelet size and a potential marker of platelet reactivity and inflammation.[6] Platelet distribution width (PDW) represents variation in platelet size.[7]

Platelets play a significant role in the pathogenesis of atherosclerosis. MPV is increased in acute coronary syndrome, mortality following myocardial infarct, restenosis following coronary angioplasty and stroke.[8-10] It was found that elevated MPV and PDW are also associated with an early phase of cerebral venous sinus thrombosis.[11] Recent pathophysiological studies indicated that etiopathogenetic mechanism in both venous and arterial thrombogenesis are similar.[12] Patients with cardiovascular risk factors for atherosclerosis have increased risk and severity of unprovoked VTE.[13]

To the present date, no validated biomarkers with both high specificity and sensitivity have been established for acute pulmonary embolism (APE).

## Aim

The aim of this study was to investigate the value of platelet indexes including platelet count (PLT), MPV and PDW as diagnostic biomarkers for APE in Emergency Department (ED).

## Material and methods

### Study population

We retrospectively reviewed the medical records of all adult patients with suspected APE who were admitted to the Emergency Department of the Clinical Hospital No. 2 in Rzeszów in the period from July 2014 to February 2017. The initial evaluation of the patients included clinical history, symptoms, physical examination, hemogram parameters, 12-lead electrocardiography and D-dimer plasma testing. The Wells score was used for the prediction of APE.[14] In patients with suspected high-risk APE (in the presence of shock or persistent hypotension) CT angiography was immediately performed. The rest of patients were tested for D-dimer plasma level and in the case of increased level – CT angiography was accomplished (in accordance with 2014 ESC Guidelines on the diagnosis and management of APE).[14]

Smoking was defined as the inhalation of the smoke of burning tobacco in the amount of at least one cigarette per day. Diabetes mellitus was defined in accordance with the European Association for the Study of Diabetes criteria.[15] Arterial hypertension was defined as a systolic/diastolic blood pressure ≥ 140/90 mmHg or current use of antihypertensive treatment.[16] Family history of VTE was defined as a confirmed VTE episode in a first-degree relative. Obesity was defined as body mass index (BMI) ≥ 30 kg/m$^2$. Immobilization was defined as a bed rest ≥ 2 days. Hospitalization was defined as a hospital stay during the last 30 days.

### Blood samples

Blood samples were collected from an antecubital vein on admission. EDTA- tubes were used for automatic blood count. The blood count was measured by a Siemens high volume hematology analyzer ADVIA 2120i (Siemens Healthcare Diagnostics, Eschborn, Germany). Sodium citrate tube and ACL TOP 500 analyzer (Beckman Coulter, Brea, CA, USA) were used for quantitative D-dimer measurement. Age adjusted cut-off values (age × 10 ng/ml) for patients over 50 years of age and 500 ng/ml for other patients were set. As a hospital policy, platelet indexes were measured within 1 hour after sampling.

### Computed tomography

Multi-detector CT angiography was performed with the use of GE Revolution 256-slice scanner (General Electric Company, Boston, MA, USA) and GE Discover CT750 (General Electric Company, Boston, MA, USA).

### Statistical analysis

Data were analyzed using SPSS software ver. 19.0 for Windows (SPSS Inc., Chicago, IL, USA). In order to identify the normal distribution, the Kolomogorov-Smirnov and Shapiro-Wilk tests were applied. Categorical variables were analyzed using the chi-square test or the Fisher's exact test (as appropriate). Student's t-test was used for variables with normal distribution and the values were presented as mean ± standard deviation (SD). Continuous variables without normal distribution were analyzed using the Mann-Whitney U test and the obtained values were presented as median (50$^{th}$) values and interquartile ranges (25$^{th}$ and 75$^{th}$). The Pearson correlation test (Pearson's r) were calculated for correlation of parametric variables and the Spearman's rank correlation test was used for nonparametric variables. The level of significance for the two-tailed p-value was set below 0.05 and confidence intervals (CI) were 95%.

## Results

The baseline characteristics and laboratory measurements of patients are compared in Table 1. There were no intergroup differences in demographic or clinical variables. 145 patients were included in this study, with an average age 67 ± 18 years, 61% women. The average age of patients was similar in both of the groups (67 ± 17 vs. 67 ± 19; p=0.613). CT angiography was positive in 45% of cases (32.5% women vs. 54% men). APE was diagnosed with similar frequency in the female (54%) and the male sex (46%).

There were no significant differences in PLT (220 ×10$^3$/mm$^3$ [172-274] vs. 243 × 10$^3$/mm$^3$ [186-286],

**Table 1.** Characteristics of the studied groups

| | Positive CT angiography (n=65) | Negative CT angiography (n=80) | p-values |
|---|---|---|---|
| Age, y | 67 ± 17 | 67 ± 19 | 0.613 |
| Male gender, n (%) | 30 (46%) | 26 (32.5%) | 0.093 |
| Body mass index, kg/m$^2$ | 26.98 ± 3.25 | 27.46 ± 3.75 | 0.415 |
| Risk factors and comorbidities, n (%) | | | |
| Smoking | 18 (28%) | 17 (21%) | 0.367 |
| Oral contraceptives or HRT | 0 | 0 | 1 |
| Arterial hypertension | 22 (34%) | 31 (39%) | 0.542 |
| Family history of VTE | 7 (11%) | 4 (5%) | 0.192 |
| Diabetes mellitus | 11 (17%) | 13 (16%) | 0.914 |
| Obesity | 15 (23%) | 16 (20%) | 0.653 |
| Known malignancy | 8 (12%) | 4 (5%) | 0.112 |
| Immobilization | 3 (5%) | 1 (1%) | 0.219 |
| Hospitalization | 6 (9%) | 3 (4%) | 0.174 |
| Pregnancy or postpartum period | 2 (3%) | 0 (0%) | 0.199 |
| Laboratory parameters | | | |
| PLT [$10^3$/mm$^3$] | 220 (172-274) | 243 (186-286) | 0.122 |
| MPV [fL] | 8.0 (7.6-8.4) | 7.9 (7.4-8.7) | 0.447 |
| PDW [%] mean ± SD | 59.0 ± 6.9 | 57.2 ±7.3 | 0.119 |
| Hemoglobin [g/dL] | 13.7 (12.1-14.4) | 12.9 (11.7-14.0) | 0.057 |
| WBC [$10^3$/mm$^3$] | 9.39 (7.8-13) | 9.07 (7.19-12.73) | 0.472 |
| Creatinine [mg/dL] | 0.90 (0.74-1.09) | 0.89 (0.75-1.26) | 0.905 |
| NT-pro-BNP [pg/mL] | 1434 (242-5460) | no data | - |
| Troponin T [pg/mL], cut-off value 14 pg/mL | 27 (9-61) | no data | - |
| D-dimer [ng/mL] | 7483 (3202-16878) | 4874 (1935-16727) | 0.17 |

Data are shown as median (interquartile range), mean ± standard deviation or number (percentage).
Abbreviations: HRT, hormone replacement therapy; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; MPV, mean platelet volume; PDW, platelet distribution width; PLT, platelet count; WBC, white blood cells;

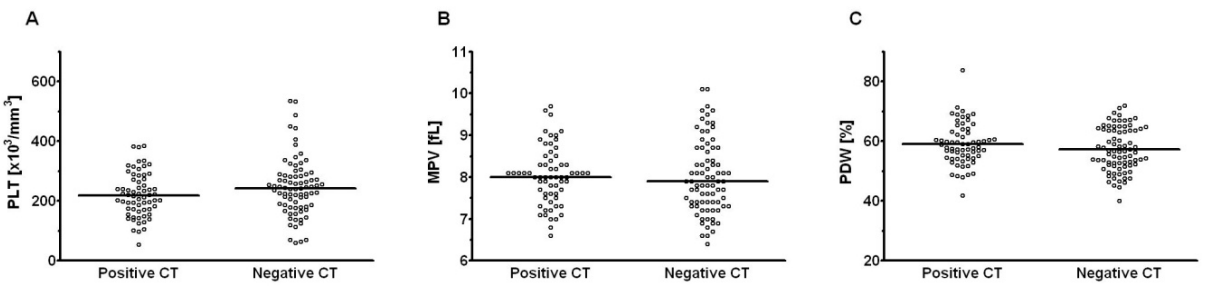


**Fig. 1.** Comparison of selected parameters in the studied groups. Horizontal lines represent medians (PLT and MPV) or means (only PDW) of each groups

p=0.122)(Fig.1A) and MPV (8.0 fL [7.6-8.4] vs. 7.9 fL [7.4-8.7], p=0.447)(Fig.1B).

The PDW did not differ between the patients with APE and the control group (59.0% ± 6.9 vs. 57.2 ± 7.3%, p=0.119)(Fig.1C).

No differences between the groups were found in other hematological parameters. Hemoglobin levels were similar (13.7 g/dL [12.1-14.4] vs. 12.9 g/dL [11.7-14.0], p=0.057). White blood cell (WBC) levels did not differ between the groups (9.39 × $10^3$/mm$^3$ [7.8-13] vs. 9.07 × $10^3$/mm$^3$ [7.19-12.73], p= 0.472)(Table 1).

Patients with positive CT angiography had an elevated level of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (1434 pg/mL [242-5460]) and T-troponin (27 pg/mL [9-61]; High-sensitive assay; cut-off value 14 pg/mL).

D-dimer level was increased in all individuals but there was no difference between the groups (7483ng/mL (3202-16878) vs. 4874ng/mL (1935-16727), p=0.17)(Table 1).

There was a positive correlation between MPV and PDW (r=0.638, p<0.001) likewise the creatinine level and age (r=0.345, p<0.05). Negative correlation was found between PLT and MPV (r= -0.334, p<0.001) and between PLT and PDW (r= -0.308, p<0.001).

In the group of patients with confirmed APE 7 (11%) patients met the criteria for high-risk PE and 4 patients died (6%). We found no differences with regard to the platelet indexes between high-risk PE patients and others, as well as between survivors and non-survivors.

During the collection of blood samples, none of the patients had international normalized ratio (INR) > 1.2 (data not shown) and none of them declared ongoing anticoagulant treatment.

## Discussion

In this study we investigated the platelet indexes among patients with suspected APE in ED. However, we did not observe any differences between the APE group and others regarding to these parameters.

Recent publications showed the discrepancies in results concerning the role of MPV in APE and DVT at diagnosis. Varol et al. showed that MPV was increased among patients with APE whereas Lippi et al. supported an inverse association between MPV and the risk of VTE.[17,18] There were differences in the rules of inclusion criteria and control group between those studies. According to the *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS) in our research the spectrum of patients included those, who will eventually receive a new diagnostic test in practice (patients with suspected APE in ED).[19] Moreover, we measured platelet indexes within 1 hour after sampling. It is important because delaying this test may influence the MPV when EDTA is used. There is a study which revealed that MPV can be accurately measured by both methods of anticoagulation (EDTA and sodium citrate) if analysis is performed within 1 hour after sampling.[20] Failure to comply with these rules may be the cause of existing differences.

Recently, platelets to lymphocyte ratio (PLR) was found to be a predictor of VTE and proved to be associated with the severity and long-term outcomes in patients with APE.[21-23] Further studies on larger populations are necessary.

In our study we found a negative correlation between PLT and MPV (r= -0.334, p<0.001). Platelets are involved in thrombus formation. Large platelets are immature, more adhesive and likely to aggregate than small ones.[24] Their number increase in case of platelets consumption and good bone marrow compensatory function. MPV is a parameter of volume and regeneration of platelets.

Among patients with positive CT we found elevated troponin and NT-pro-BNP. It can be associated with the right ventricular dysfunction among patients with an APE and it was found to be a significant predictor of mortality in the above-mentioned individuals.[25]

Positive predictive value of elevated D-dimer is low and it is not useful for confirmation of APE. In this study we confirmed the low specificity of D-dimer in APE diagnosing. There was no significant difference between the group with positive and negative CT angiography (p=0.17). Pulmonary embolism is pathophysiological pulmonary circulation disorder syndrome caused by partial or complete occlusion of the pulmonary artery and it is commonly a consequence of deep vein thrombosis. The main cause of death in severe stage is acute right ventricle failure due to pressure overload. Thrombosis begins with the aggregation of erythrocytes, fibrin and platelets. D-dimer is a sensitive marker of acute thrombosis because of simultaneous activation of coagulation and fibrynolysis.[14] The specificity of D-dimer is poor because fibrin is produced in a variety of conditions such as cancer, trauma, inflammation, pregnancy and infection. [14]

Our study has several limitations. Not all of the comorbidities and environmental factors that might have affected platelet count and functions were taken into account. MPV is believed to be a marker of platelet activity but it is not specific. It was a single-center, retrospective study and included a relatively small sample size.

## Conclusion

To conclude our results, it can be noted that platelet indexes (at a single time point) are not a reliable indicator for the diagnosis of APE in the Emergency Department. Further studies in this matter are necessary.

## References

1. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.
2. Kearon C. Natural History of Venous Thromboembolism. *Circulation*. 2003;107(90231):22I-30.
3. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique--comparison with pulmonary angiography. *Radiology*. 1992;185(2):381-387.
4. Turedi S, Erdem E, Karaca Y, et al. The High Risk of Contrast-induced Nephropathy in Patients with Suspected Pulmonary Embolism Despite Three Different Prophylaxis: A Randomized Controlled Trial. Runyon MS, ed. *Acad Emerg Med*. 2016;23(10):1136-1145.
5. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-Dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost*. 2008;6(7):1059-1071.
6. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8(1):148-156.

7. Yılmaz F, Köklü E, Kizilirmak Yilmaz F, Sarıönder Gencer E, Alparslan AŞ, Yıldırımtürk Ö. Evaluation of mean platelet volume and platelet distribution width in patients with asymptomatic intermediate carotid artery plaque. *Kardiol Pol*. 2017;75(1):35-41.
8. Budzianowski J, Pieszko K, Burchardt P, Rzeźniczak J, Hiczkiewicz J. The Role of Hematological Indices in Patients with Acute Coronary Syndrome. *Dis Markers*. 2017;2017:1-9.
9. Varasteh-Ravan HR, Ali-Hassan-Sayegh S, Shokraneh S, Mozayan MR, Karimi-Bondarabadi AA. Relationship of admission mean platelet volume, platelet distribution width and white blood cells with ST resolution in patients with acute ST segment elevation myocardial infarction treated with streptokinase without history of previous cardiovascular surgery. *Perspect Clin Res*. 2013;4(2):125-129.
10. Wan J-L, Ma Z-W. The Value of Mean Platelet Volume for Prognosis of Patients with Acute Cerebral Infarction. *Clin Lab*. 2017;63(11):1801-1807.
11. Kamisli O, Kamisli S, Kablan Y, Gonullu S, Ozcan C. The prognostic value of an increased mean platelet volume and platelet distribution width in the early phase of cerebral venous sinus thrombosis. *Clin Appl Thromb Hemost*. 2013;19(1):29-32.
12. Poredoš P. Interrelationship between venous and arterial thrombosis. *Int Angiol*. 2017;36(4):295-298.
13. Gaertner S, Cordeanu E-M, Mirea C, et al. Increased risk and severity of unprovoked venous thromboembolism with clustering cardiovascular risk factors for atherosclerosis: Results of the REMOTEV registry. *Int J Cardiol*. 2018;252:169-174.
14. Zamorano JL, Achenbach S, Baumgartner H, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033-3073.
15. Authors/Task Force Members, Rydén L, Grant PJ, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2013;34(39):3035-3087.
16. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;34(28):2159-2219.
17. Varol E, Icli A, Uysal BA, Ozaydin M. Platelet indices in patients with acute pulmonary embolism. *Scand J Clin Lab Invest*. 2011;71(2):163-167.
18. Lippi G, Buonocore R, Cervellin G. The Mean Platelet Volume Is Decreased in Patients Diagnosed with Venous Thromboembolism in the Emergency Department. *Semin Thromb Hemost*. 2016;42(6):632-635.
19. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3(1):25.
20. Dastjerdi MS, Emami T, Najafian A, Amini M. Mean platelet volume measurement, EDTA or citrate? *Hematology*. 2006;11(5-6):317-319.
21. Kundi H, Balun A, Cicekcioglu H, et al. The relation between platelet-to-lymphocyte ratio and Pulmonary Embolism Severity Index in acute pulmonary embolism. *Hear Lung*. 2015;44(4):340-343.
22. Grilz E, Posch F, Königsbrügge O, et al. Association of Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio with the Risk of Thromboembolism and Mortality in Patients with Cancer. *Thromb Haemost*. 2018;118(11):1875-1884.
23. Ozcan Cetin EH, Cetin MS, Canpolat U, et al. Platelet--to-lymphocyte ratio as a novel marker of in-hospital and long-term adverse outcomes among patients with acute pulmonary embolism: A single center large-scale study. *Thromb Res*. 2017;150:33-40.
24. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. *Platelets*. 2002;13(5-6):301-306.
25. Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. *Intensive Care Med*. 2008;34(12):2147-2156.