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ORIGINAL ARTICLE

Relationship Between Mean Platelet Volume and Pulmonary Embolism in Patients With Deep Vein Thrombosis

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Background Mean platelet volume (MPV) has been demonstrated to be associated with deep vein thrombosis (DVT). However, its role in the prediction of pulmonary embolism (PE), which is a major complication of DVT, is still unclear. Therefore, we investigated the association of MPV values with acute PE in patients with DVT.

Method The study included three groups: patients with DVT and PE (n=98); patients with DVT without PE (n=97); and control group (No DVT, No PE, n=98). We also evaluated DVT patients according to the MPV values on admission and categorised them into two groups: MPV≤9.15 fL (n=82) and MPV>9.15 fL (n=113).

Results MPV was significantly higher in all DVT patients than controls (9.3±0.9 fL vs 7.9±0.7 fL, p<0.001) and in DVT patients with PE than DVT patients without PE (9.9±0.6 fL vs 8.7±0.7 fL, p<0.001). The rate of PE was higher in patients with DVT with MPV>9.15 fL than those with MVP≤9.15 fL (75.2% vs 15.9%, p<0.001). The presence of PE in patients with DVT was independently associated with MPV (OR: 22.19, 95%CI: 9.39–53.19, P<0.001).

Conclusion Although our findings should be considered within the limitations of the study, they suggest that MPV measures may be elevated in DVT patients and a higher MPV may be associated with PE in patients with DVT.

Keywords Mean platelet volume • Platelet activation • Platelet count • Deep vein thrombosis • Acute pulmonary embolism

Introduction

Deep vein thrombosis (DVT), a part of clinical diagnosis called venous thromboembolism (VTE), is an important cause of morbidity and mortality. Venous thromboembolism is the third most common cardiovascular disease after heart attack and stroke [1]. Pulmonary embolism (PE) along with DVT is a major clinical manifestation of VTE. In most cases PE is a major complication of DVT and shares the same predisposing factors [2]. Platelets have an important role in the pathogenesis of atherothrombosis and venous thrombosis [3,4]. Mean platelet volume (MPV) is a simple and easy marker reflecting platelet reactivity or activation [5,6]. Larger platelets have higher thrombotic potential [7]. Mean platelet

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volume is an important predictive and prognostic indicator in cardiovascular disease [8]. Increased values of MPV have been recognised as an independent risk factor for myocardial infarction (MI) and stroke [9–11]. Moreover, increased MPV has been reported to be associated with adverse outcomes such as recurrent ischaemia and MI, or death in survivors of MI, and the severity of acute ischaemic cerebrovascular events [7,8,12,13]. Increased levels of MPV observed in patients after DVT and acute PE, have been reported to be correlated with the severity of right ventricular dysfunction [14–16]. Recently, increasing levels of MPV were identified as a predictor for VTE and in particular, VTE of unprovoked origin and an independent predictor of early death in acute PE [16,17]. Therefore, these studies are supportive of platelet size as a risk factor for VTE. In the present study we investigated the relationship between MPV and the risk of developing PE in patients with DVT.

Methods

Study Population

We performed a retrospective analysis of patients admitted to the emergency department or outpatient clinic of two university hospitals, between 2005 and 2014, presenting with dyspnoea and/or swelling and pain in the legs. From a total of 18,505 patients, 453 were diagnosed with DVT or PE. However, of these only 195 DVT patients were included in the analyses fulfilling all inclusion criteria, whereas 258 patients were excluded due to incomplete medical records or on the basis of exclusion criteria. The final patient groups consisted of 98 patients with DVT and PE (48 male, mean age: 56.8 ± 12.2 years); and 97 patients with DVT without PE (48 male, mean age: 54.2 ± 14.2 years). A third group, selected as a comparative control group, consisted of 98 patients that were admitted to our outpatient clinic for suspicion of DVT but were confirmed free of DVT and PE. These patients were matched for age, gender, and body mass index (BMI), (45 males, mean age: 55 ± 8.8 years). In addition to the clinical presentation, all patients underwent physical examination and compression ultrasonographic examination for DVT. Patients with proximal or distal DVT were included in our study. Acute PE diagnosis was defined according to the European Society of Cardiology Guidelines [18]. The diagnosis of an acute PE was confirmed by an identified filling defect in the pulmonary artery system in a computed tomography pulmonary angiogram (CTPA) of the chest or positive venous ultrasound/phlebography of an extremity consistent with DVT in patients with typical symptoms of PE (chest pain or dyspnoea). In addition a positive D-Dimer or scintigraphic ventilation–perfusion (V/Q) scan read was identified, supporting a high probability for PE, as recommended in the current guidelines. All patients with PE were not symptomatic. In asymptomatic and symptomatic patients we used electrocardiography and echocardiography for diagnosis of PE. All patients of the study underwent thorax CT scan.

We calculated the cut-off point of 9.15 fL for MPV to estimate the presence of PE with a sensitivity of 86% and a specificity of 82% (area under curve = 0.93, $p<0.001$) by using the receiver-operating curves (ROC). Accordingly, patients with DVT were categorised into two groups: MPV≤9.15 fL (n=82) and MPV>9.15 fL (n=113). Clinical information was obtained by review of patient medical records. For each patient, BMI was calculated by the formula of weight (kg)/height $(m)^2$. Obesity was considered for BMI ≥30 kg/m^2. Definitions for other risk factors were made based on the current guidelines. However, patients who were smoking before hospitalisation were allocated to a sole smoker category. Exclusion criteria were left ventricular systolic dysfunction (ejection fraction < 50%), history of coronary artery disease, acute coronary syndromes, atrial fibrillation, history of renal or hepatic disease, haematological disorders, acute or chronic infection, cancer and stroke. The institutional ethics committee approved the study and all participants provided written informed consent.

Biochemical Measurements

Blood samples were drawn from the antecubital vein by careful venipuncture using a 21-gauge needle attached to sterile syringe without stasis at 8.00 to 10.00 AM, after a fasting period of 12 hours. Glucose, creatinine, and lipid profiles were determined by standard methods. An automatic blood counter (Beckman-Coulter Co, Miami, FL, USA) was used for whole blood counts. Mean platelet volume was measured in a blood sample collected in dipotassium EDTA tubes within two hours after sampling.

Statistical Analysis

Data were analysed with the SPSS software version 15.0 for Windows (SPSS Inc, Chicago, III, USA). Continuous variables were presented as mean ± standard deviation and categorical variables as percentages. To compare continuous variables, the Student t test or Mann-Whitney U test were used where appropriate. Categorical variables were compared with the chi-square test. The values were statistically analysed using the one-way ANOVA and post hoc Tukey multiple comparison tests. We used a ROC analysis with area under the curve and MPV cut-off point for prediction of PE. In addition, a Spearman correlation analysis was performed to identify the relationship of MPV with other variables. Thereafter, a multivariate logistic regression analysis was undertaken to identify the independent variables associated with PE in DVT patients. The confounders, which had importance at a level of P 0.10 or less, were entered into this regression analysis. $P < 0.05$ was considered significant.

Results

There were no statistically significant differences among the three groups according to gender, age, BMI, comorbidities such as hypertension, diabetes mellitus and cholesterol levels. Table 1 summarises the demographic, clinical and laboratory

Table 1 Baseline Clinical and Laboratory Characteristics of patients with DVT and PE, patients with DVT without PE and control groups.

	DVT patients PE (+) n=98	DVT Patients PE (-) n=97	Controls n=98	P Value
Age, years	56.8 ± 12.2	54.2 ± 14.2	55 ± 8.8	0.29
Sex (M/F)	48/50	48/49	45/53	0.86
BMI (kg/m^2)	30.3 ± 3.7‡	29.6 ± 2.7	29.2 ± 3.1	0.07
SBP (mmHg)	123.3 ± 10.3	121.2 ± 7.6	121.5 ± 8.9	0.86
DBP (mmHg)	77.9 ± 8	76.6 ± 6.3	76 ± 6.3	0.35
Hypertension (%)	25 (25.5%)	24 (24.7%)	19 (19.4%)	0.54
Diabetes Mellitus (%)	7 (7.1%)	9 (9.3%)	6 (6.1%)	0.69
Smoking (%)	22 (22.4%)	21 (21.6%)	17 (17.3%)	0.64
Glucose, mg/dL	105 ± 18.2	101.6 ± 21.1	103.9 ± 22.6	0.50
Creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	0.20
Total cholesterol, mg/dL	185.7 ± 39.4	180.1 ± 25.2	175.3 ± 37.5	0.12
Triglycerides, mg/dL	142.4 ± 72.3	127 ± 63.6	142.1 ± 79.4	0.24
LDL-cholesterol, mg/dL	109.5 ± 30.8	104.8 ± 26.5	100.8 ± 31.3	0.14
HDL-cholesterol, mg/dL	46.5 ± 12.2	48.5 ± 11.2	46.1 ± 14.7	0.37
WBC (x10^3 cells/μL)	9.7 ± 3.9*	9.2 ± 1.7*	7.4 ± 1.3	<0.001
Haemoglobin, g/dL	13.4 ± 2	13.7 ± 2.1	14.2 ± 1.5	0.13
Platelet count (x10^3 cells/μL)	232.5 ± 66.9*	261.5 ± 73.4*	326 ± 135.6	<0.001
MPV, fL	9.9 ± 0.6*†	8.7 ± 0.7*	7.9 ± 0.7	<0.001

Abbreviations: M/F: male to female, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disease, LDL-cholesterol: low density lipoprotein cholesterol, HDL-cholesterol: high-density lipoprotein cholesterol, WBC: white blood cells, MPV: mean platelet volume, DVT: deep vein thrombosis, PE: pulmonary embolism. P value is for comparison between control and study population overall.
*P<0.001 versus group controls; ‡P<0.05 versus group controls; †p<0.001 versus group DVT Patients PE (-).

characteristics of the three groups. The differences in levels of MPV, platelet count and white blood cells were found to be statistically significant (one-way ANOVA; p<0.001). Mean platelet volume was significantly higher in all enrolled patients with DVT than controls (9.3 ± 0.9 fL vs 7.9 ± 0.7 fL, p<0.001). Mean platelet volume values were significantly higher in DVT patients with and without PE than controls (9.9 ± 0.6 fL and 8.7 ± 0.7 fL vs 7.9 ± 0.7 fL respectively, p< 0.001 for both). Mean platelet volume values were also significantly higher in DVT patients with PE than DVT patients without PE (9.9 ± 0.6 fL vs 8.7 ± 0.7 fL respectively, p< 0.001). In contrast, patients with DVT had lower platelet count than control group (Table 1). Intergroup comparison showed that BMI was higher in DVT patients with PE than control group (p=0.043). Compared with control group, WBC was higher in DVT patients with and without PE groups (p<0.01 and p<0.01) (Table 1). The frequency of asymptomatic PE is 31.6% in patients with DVT who had PE. Table 2 shows the comparison of the patients with DVT with MPV ≤9.15 fL and MPV >9.15 fL. Clinical and other laboratory characteristics were similar between these two groups. However, platelet count was significantly higher in patients with DVT with MPV ≤9.15 fL than in patients with DVT with MPV >9.15 fL (263 ± 70.3 vs 235.3 ± 70.4, respectively, p = 0.007). The incidence of PE was greater in patients with DVT with MPV >9.15 fL than those with MVP ≤9.15 fL (75.2% vs 15.9%, p<0 .001).

In the correlation analysis, MPV was positively correlated with symptomatic PE (r= 0.66, P < .001). The ROC analysis to identify the presence of PE shows an area under the curve of 0.93, p<0.001 and a cut-off value for MPV of 9.15 fL. The sensitivity, specificity, positive and negative predictive values were calculated as 86, 82, 75, and 59%, respectively (Figure 1). In logistic regression analysis, the presence of PE in patients with DVT was independently associated with MPV (OR: 22.19, 95% CI: 9.39–53.19, P<0.001).

Discussion

In the present study, we found that MPV was significantly increased in patients with DVT with and without PE than age-, gender- and risk factor matched controls. Moreover, the higher MPV was associated with PE in patients with DVT. Platelets activated by abnormal venous blood flow, may interact with erythrocytes, endothelial cells, neutrophils and monocytes and released fibrinogen, and other tissue factors resulting in venous thrombosis [19]. Platelet size, measured as MPV, may be a marker of platelet function as it is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A_2, platelet factor 4, and β-thromboglobulin [9,20]. Notably, larger platelets are haemostatically more reactive and prone to the

Table 2 Comparison of the Clinical and Laboratory Characteristics of the DVT Patients With MPV ≤9,15 fL and MPV >9.15 fL.

	MPV≤9.15 fL (n = 82)	MPV >9.15 fL (n = 113)	P Value
Age, years	55.4 ± 13.8	55.6 ± 12.8	0.90
Sex (M/F)	43/39	53/60	0.44
BMI (kg/m^2)	29.8 ± 3	30 ± 3.5	0.71
SBP (mmHg)	121.2 ± 8.3	121.8 ± 9.9	0.63
DBP (mmHg)	76.1 ± 6.8	77.7 ± 7.6	0.13
Hypertension (%)	19 (23.2%)	30 (26.5%)	0.59
Diabetes Mellitus (%)	5 (6.1%)	11 (9.7%)	0.36
Smoking (%)	19 (23.2%)	24 (21.2%)	0.75
Glucose, mg/dL	100.8 ± 19.5	105.1 ± 19.7	0.14
Creatinine, mg/dL	0.9 ± 0.1	0.9 ± 0.2	0.87
Total cholesterol, mg/dL	184.2 ± 29.8	182 ± 35.5	0.65
Triglycerides, mg/dL	133.2 ± 69.5	135.8 ± 67.7	0.80
LDL-cholesterol, mg/dL	106.8 ± 29.8	107.4 ± 28.1	0.90
HDL-cholesterol, mg/dL	48.5 ± 11	46.7 ± 12.2	0.28
WBC (x10^3 cells/μL)	9.2 ± 2.8	9.6 ± 3.2	0.35
Haemoglobin, g/dL	13.8 ± 2.1	13.7 ± 1.8	0.58
Platelet count (x10^3 cells/μL)	263 ± 70.3	235.3 ± 70.4	0.007
DVT patients PE (+)	13 (15.9%)	85 (75.2%)	<0.001

Abbreviations: M/F: male to female, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disease, LDL-cholesterol: low density lipoprotein cholesterol, HDL-cholesterol: high-density lipoprotein cholesterol, WBC: white blood cells, DVT: deep vein thrombosis, PE: pulmonary embolism, MPV: mean platelet volume. P value is for comparison between low MPV group (MPV≤9.15 fL) and high MPV group (MPV >9.15 fL).

development of thrombosis than platelets of normal size [21,22]. Investigators have consistently reported that increased MPV may be associated with the risk of short- and long-term adverse cardiovascular outcomes such as MI, recurrent ischaemia or death and overall vascular mortality in the general population [7,8,10,12,23–25]. We evaluated the platelet reactivity by measuring MPV in patients with DVT. Support for the role of platelet abnormalities contributing to the pathophysiology of VTE is evident from reports of increased MPV in VTE such as DVT and PE [4,14–17].

Our study suggests that a higher MPV may be an independent predictor of PE in DVT patients. Similar results regarding the role of MPV as a predictor have been reported in various cardiovascular diseases and VTE [16,17,23,24]. Recently, Braekkan et al. have reported that increased MPV may be a predictor for VTE of unprovoked origin [16]. Varol et al. reported that MPV values were increased in patients with acute PE, and such incidence also correlated with RV diameter. Notably, platelet count was decreased in patients with acute PE [14]. Kostrubiec et al. demonstrated that MPV is an independent predictor of early death in acute PE and was associated with right ventricular dysfunction and myocardial injury [17]. This significant positive association between MPV level and these data on the predictor role of MPV support our hypothesis that the higher MPV value is associated with the development of PE in patients with DVT. Venous thrombosis and its recurrence have been reported to be associated with platelet activation [4]. Recently, increased levels of P-selectin, expressed by large, activated platelets, have been measured in VTE patients, with high levels of circulating P-selectin being associated with increased risk of recurrent VTE [26–28]. Chung et al. have proposed that chronic elevation of soluble P-selectin for six or more months may predispose platelet activation in the initiation of PE [29]. Although our study did not measure P-selectin due to the retrospective design, our findings are generally accordant with other previous studies, and add strong support for a role of increased MPV being linked to the initiation of PE in DVT patients. Interestingly, common pathophysiological links between VTE and atherothrombosis are identified in patients with a significantly higher incidence of acute coronary syndromes and stroke following an episode of VTE [30,31]. Thus, increased MPV may reflect more aggressive platelet behaviour, with larger, hyperactive platelets accelerating the formation and propagation of thrombus, leading to the occurrence of PE.

In the Tromso study, they divided three DVT patient groups according to MPV values, and they found discrimination at MPV 9.5 with RR of 1.3 for any DVT and 1.5 for unprovoked VTE compared with MPV < 8.5 [16]. Their findings showed much smaller relative risks than our present study. This may be due to differences in patients' characteristics and the prospective design of the Tromso study. However, we found the cut-off point of 9.15 for MPV to predict the presence of PE with a sensitivity of 86% and specificity of 82%.

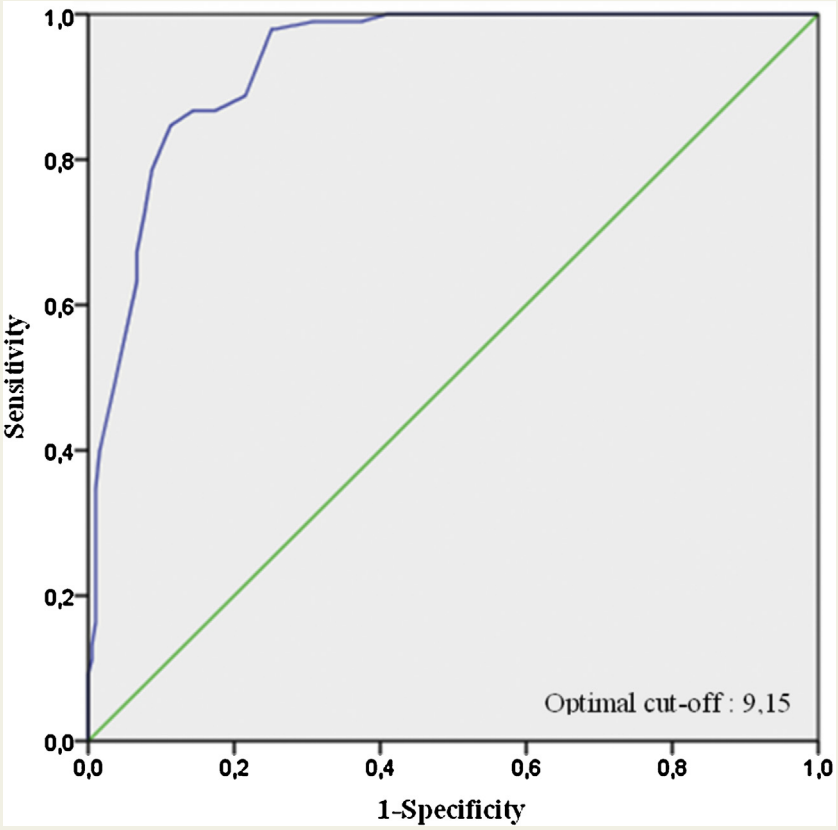

Figure 1 ROC curve with calculated area under the curve and optimal cut-off point for MPV to identify the presence of PE. Optimal cut-off point is 9,15 fL. AUC is calculated at 0.93. Abbreviations: ROC: receiver–operating curve, MPV: mean platelet volume, PE: pulmonary embolism, AUC: area under curve.

In our study, platelet count was significantly lower among DVT patients with and without PE when compared with control group. Mean platelet volume has been shown to inversely correlate with the total platelet count, suggesting consumption of small platelets and a compensatory production of larger reticulated platelets [22,32]. We also found that WBC values were elevated in DVT patients with PE. It has been proposed that a modest leukocytosis may accompany, and possibly be caused by, PE itself [33].

Study limitations

Firstly, this is a retrospective cross-sectional case-control type study, which can have subject selection bias compared to prospective studies. Also we measured only admission MPV values, but did not make follow-up measurements. Limited information was available regarding time-dependent MPV changes in EDTA tubes, however, our university hospital whole blood count including MPV is generally measured within one hour after sampling. Addition of MPV to current risk markers may further improve the prognostic evaluation in such patients. However, different cut-off points for this marker have been reported highlighting the uncertainty of a useful range or cut-off point for MPV in clinical practice. Also we did not measure P-selectin or other potential novel molecular markers that might be indicative of cell function associated with MPV changes.

Conclusions

Our findings suggest that MPV are elevated in patients with DVT, and the higher MPV may be associated with PE in this group of patients. Further prospective studies, are needed to clarify and validate the predictive value of MPV levels, and the measure of novel cell-specific molecular markers of functional activity with outcomes in DVT patients.

Declaration of Interests

The authors report no conflicts of interest. All authors are responsible for the content and writing of the paper.

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