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Mean platelet volume as a prognostic factor for venous thromboembolic disease

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ABSTRACT

Background: *Mean platelet volume (MPV) is a risk factor for cardiovascular and inflammatory diseases.* ***Aim****: To evaluate the association between high MPV and 90-day mortality after an episode of venous thromboembolism (VTE).* ***Material and Methods****: Retrospective cohort of 594 patients with a median age of 73 years (58% women) with a first episode VTE, included in an institutional Thromboembolic Disease registry between 2014 and 2015. MPV values were obtained from the automated blood cell count measured at the moment of VTE diagnosis. Volumes ≥ 11 fL were classified as high. All patients were followed for 90 days to assess survival.* ***Results****: The main comorbidities were cancer in 221 patients (37%), sepsis in 172 (29%) and coronary artery disease in 107 (18%). Median MPV was 8 fl (8-9), brain natriuretic peptide 2,000 pg/ml (1,025-3,900) and troponin 40 pg/ml (19.5-75). Overall mortality was 20% (121/594) during the 90 days of follow-up. Thirty three deaths occurred within 7 days and 43 within the first month. The loss of patients from follow-up was 5% (28/594) at 90 days. Mortality among patients with high MP was 36% (23/63). The crude mortality hazard ratio (HR) for high MPV was 2.2 (95% confidence intervals (CI) 1.4-3.5).When adjusted for sepsis, oncological disease, heart disease, kidney failure and surgery, the mortality HR of high MPV was 2.4 (CI95% 1.5-3.9) in the VTE group, 2.3 (CI95% 1.5-4.4) in the deep venous thrombosis group, and 2.9 (CI95% 1.6 -5.6) in the pulmonary embolism group.* ***Conclusions****: High MPV is an independent risk factor for mortality following an episode of VTE.*

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Key words: *Mean Platelet Volume; Venous Thromboembolism; Thromboembolism.*

Volumen plaquetario medio como factor pronóstico de la enfermedad tromboembólica venosa

Antecedentes*: El volumen plaquetario medio (VPM) es un factor de riesgo de complicaciones cardiovasculares y enfermedades inflamatorias.* ***Objetivo****: Evaluar la asociación entre VPM alto y la mortalidad a los 90 días después de un episodio de tromboembolismo venoso (ETV).* ***Material y Métodos****: Cohorte retrospectiva de 594 pacientes adultos con una edad media de 73 años (58%*

mujeres) con un primer episodio de ETV incluidos en un registro de enfermedad tromboembólica institucional entre 2014 y 2015. Se obtuvieron valores de VPM desde el hemograma tomado en el momento del diagnóstico de ETV y un volumen ≥ 11 fL fue clasificado como alto. Todos los pacientes fueron seguidos durante 90 días para determinar sobrevida. ***Resultados****: Las comorbilidades fueron cáncer en 221 pacientes (37%), sepsis en 172 (29%) y enfermedad coronaria en 107 (18%). La mediana de VPM fue 8 fl (89), el péptido natriurético cerebral fue de 2.000 pg/ml (1.025-3.900) y la troponina fue de 40 pg/ml (19,5-75).La mortalidad global a 90 días fue 20% (121/594). Treinta y tres muertes ocurrieron dentro de los 7 días y 43 en el primer mes. La pérdida de seguimiento de pacientes fue de 5% (28/594) a los 90 días. La mortalidad en el grupo con VPM alto fue 36% (23/63). La razón de riesgo (HR) cruda de la mortalidad para un VPM alto fue de 2,2 (intervalos de confianza (IC) de 95% 1,4-3,5). Cuando se ajustó por sepsis, enfermedad oncológica, enfermedad cardíaca, insuficiencia renal y cirugía, la HR de muerte para un VPM alto fue de 2,4 (IC95% 1,5-3,9) en el grupo de ETV; 2,3 (IC95% 1,5-4,4) en el grupo de trombosis venosa profunda; y 2,9 (CI95% 1,6 -5,6) en el grupo de embolia pulmonar.* ***Conclusiones:*** *Un VPM alto es un factor de riesgo independiente de mortalidad después de un episodio de ETV.*

Palabras clave: *Tromboembolia; Tromboembolia Venosa; Volumen Plaquetario Medio.*

Thromboembolic disease (VTE) whose clinical manifestations are pulmonary embolism (PE) and deep vein thrombosis (DVT) is a prevalent disease with severe complications in the short and long run, and a high potential for morbidity and mortality[1]. The PE is responsible for 5-10% of hospital mortality in general[2], and can be increased up to 30% if not diagnosed and treated early, adding a 5% mortality caused by recurrence[3]. Some studies have shown that the high values of ProBNP, serum troponins, hyponatremia and lactate are associated with an increased mortality in patients with a thromboembolic event, just as a right ventricular dysfunction and the coexistence of PE with DVT[2,4,5]. The platelet size, measured as mean platelet volume (MPV), is a marker of platelet reactivity[5,6], where larger platelets are hemostatically more reactive than normal sized platelets[1,5]. The association was demonstrated with platelet activity indicators, including the expression of glycoprotein Ib, glycoprotein receptor IIb/IIIa and the expression of higher levels of P-selectin[6,7].

There are reports which describe that the MPV increases in the acute myocardial infarction, and this is a risk factor independent for poor prognosis in myocardial infarction and in cerebrovascular accident[8-11]. Additionally, platelet activation in patients after an acute thromboembolic event, determines higher MPV values, that are significantly associated with the severity of the VTE[1]. However, we have not found evidence of the association between the MPV and mortality in patients with VTE[1].

The aim of this study was to evaluate the association between MPV and the high risk of death in patients with acute VTE.

Materials and Methods

We conducted a retrospective cohort study of adult patients with confirmed diagnosis of a first episode of PE and/or DVT. Patients included were captured from the Institutional Thromboembolism Disease Registry (IRTD) (Institutional Registry of Thromboembolic.- Home ClinicalTrials.gov, NCT01372514) which prospectively includes all cases of PE or DVT documented and diagnosed in all areas of Hospital Italiano de Buenos Aires. We included patients recruited in the IRTD during the period of January 2014 to December 2015.

We included all consecutive patients with a diagnosis of symptomatic first episode of pulmonary embolism confirmed by Computed Tomography Multislice or ventilation/perfusion scintigraphy and/or DVT defined as acute/subacute of the deep venous system (deep and superficial femoral veins, popliteal, and deep venous system

of the upper limbs) confirmed by a Doppler ultrasound. We excluded pregnant patients, episodes of recurrent PE, and those who refused to participate in the process of informed consent for the IRTD.

All IRTD assessments were performed prospectively and diagnoses were confirmed by the reviewing of electronic health records. The Hospital Italiano is a high complexity referral center of the Autonomous City of Buenos Aires that has a single repository of information of all patients treated at the hospital, centralized in the Electronic Health Record (EHR). The problems, comorbidities, medication, procedures, and any patient information is stored and encrypted using a controlled vocabulary.

All variables were collected by the systematic review of both the EHR and the IRTD structured database. Patients were stratified at baseline according to the European Guidelines of the Society of Cardiology on the diagnosis and management of VTE, which considers clinical parameters, biomarkers and echocardiographic parameters. The values for ultrasensitive troponin (UST) and ProBNP were obtained at the diagnosis for PE, considering positive values to ≥ 20 pg/mL and 300 pg/mL, respectively. Information on echocardiographic prognostic parameters (dilation and hypokinesia of the right ventricle) was collected. We evaluated the presence of sepsis, active cancer, oncohematologic diseases, coronary heart disease, kidney disease and stroke. Pharmacological prophylaxis was considered receiving unfractionated heparin (up to a maximum of 15,000 IU per day), enoxaparin (up to a maximum of 60 mg per day), dabigatran, rivaroxaban or apixaban.

MPV values were obtained at diagnosis of PE and DVT. Patients whose values were ≥ 11 fL were categorized as high MPV values, and the rest (between 7.0 and 11.0 fL, according to laboratory range) were categorized as normal MPV. The blood sample was taken in a tube with EDTA anticoagulant, the time that takes between sample taking and processing is less than 2 hours. The MPV is calculated by the automated hemogram during routine cell count (Beckman Coulter DxH-800, CA, USA) and revised by blood smear.

Follow up began from the day of VTE diagnosis, the end follow up date was defined as the date of death or 90 days after diagnosis (including intra and extra-hospital follow-up). We assessed mortality from all causes as a primary event. Events of death were detected through the EHR and systematic telephone follow registry.

Survival was calculated with Cox Proportional Hazards regression with a sample size 594, with an alpha 0.05 (two sided), SD 0.5 and effect size HR 0.2, the estimates power was 1. Continuous variables with mean and standard deviation or median and interquartile range (IQR) are described according to the observed distribution and categorical variables as proportions. Survival (CI 95%) at 7, 30 and 90 days for both normal and high MPV was estimated with the Kaplan Meier (KM) estimator. A Cox proportional hazard model was built with clinical and statistical variables to predict 90 days mortality. Variables included in the model were baseline characteristics, clinical, laboratory (ProBNP, UST, and MPV) and ventricular dysfunction. The Hazard Ratio (HR) crude and adjusted are presented for each predictor with a 95% confidence interval. The analysis was performed using the entire cohort and repeated in subgroups with DVT alone and PE alone. The statistical analysis was performed using Stata 13 software.

The study was conducted using secondary data bases de-identified, in full accordance with the Declaration of Helsinki and was approved by the Ethics Committee of research protocols. The IRTD is financed by the medical clinic service of the Hospital Italiano de Buenos Aires in its totality.

Results

During the study period, 594 patients with VTE were included, of which 49.32% (293) had DVT, 31.14% (185) PE, and 19.52% (116) DVT/PE.

The median age was 72.9 years (IQR 62.9-82.3) and 58% (347) were women. Comorbidities where present in 37% (221) with oncological disease, 29% (172) with sepsis, 18% (107) with coronary heart disease, and 12% (70) with stroke.

At baseline we observed a MPV median of 8 fL (IQR 8-9); 10% (63) of patients presented a high MPV, while the rest portrayed normal MPV values. Basal description of comorbidities and laboratory by MPV groups are presented in Table 1.

The overall mortality for the entire cohort was 20.3% (121/594) during the 90 days of follow-up: 33 deaths occurred within 7 days and 43 within the first month. The loss of patients to follow up was 4.7% (28/594) at 90 days. Mortality for the

Table 1. Baseline characteristics of both normal and high mean platelet volume (MPV) groups

	High MPV n = 63	Normal MPV n = 528	p-value
Concomitant disease			
Active cancer	28% (18)	38% (203)	0.13
Active oncohematological disease	7.9% (5)	5.3% (28)	0.34
Sepsis	36.5% (23)	27.8 % (147)	0.15
Stroke	15.8% (10)	11.1% (59)	0.27
Kidney failure	41.2% (26)	28.2% (149)	0.03
Surgery	36.5% (23)	37.3% (197)	0.90
Immobilization	68% (43)	56.8% (300)	0.08
Therapeutic intervention			
Thromboprophylaxis	68% (43)	45% (238)	< 0.001
Anticoagulation	93% (59)	88% (466)	0.20
Fibrinolytics	7.9% (5)	2.6% (14)	0.02
Thromboembolic disease			
Deep venous thrombosis	67% (42)	69% (366)	0.49
Pulmonary thromboembolism	65% (41)	49% (258)	0.01

Table 2. Risk characteristics for death in patients with Pulmonary Embolism according to the European Guide Society of Cardiology

	High MPV n = 63	Normal MPV n = 528	p-value
ProBNP, pg/mL	2,000 (IIC 1,025-3,900)	700 (IIC 199-2,036)	< 0.001
Ultra-sensitive troponin, pg/dL	40 (IIC 19.5-75)	20 (IIC 11-43)	0.003
Right ventricular dysfunction	39% (16)	26.9% (66)	0.11

Abbreviations: IIC, interval interquartile; MPV, mean platelet volume.

high MPV group was 36% (23/63) compared to 18.5% (98/531) in normal MPV group (p 0.001).

The estimated survival at 7, 30 and 90 days for both groups are shown in Table 3. The difference in the KM survival estimate between groups was statistically significant ($p < 0.001$) as observed in Figure 1.

As for risk stratification parameters for mortality, higher ProBNP and UST values were observed in the high MPV group; 2,000 (IQR: 1025-3900) and 40 (IQR: 19.5-75.0) respectively, with p-values significantly different compared to the normal MPV group. The parameters of risk stratification in patients with PE are shown in Table 2.

The HR for mortality in patients with high MPV versus normal MPV was 2.22 (95%CI 1.41-3.49, $p < 0.001$) for VTE; 2.45 (95% CI 1.44-4.17, $p < 0.001$) in the subgroup with only DVT and 2.08 (95% CI 1.14-3.80, $p = 0.016$) in the subgroup with only PE. Age (HR: 1, $p = 0.44$), female gender (HR: 0.930, $p = 0.69$), coronary heart disease (HR: 1.07, $p = 0.74$) were not significantly associated with death in any of the events. Conversely, mortality was associated with sepsis with a HR of 2.16 (95%CI 1.51-3.10, $p < 0,001$), oncological disease with a HR of 3.04 (95%CI 2.11-4.39, $p < 0.001$);

Table 3. Estimated survival with 95% confidence interval at 7, 30 and 90 days for both normal and high mean platelet volume (MPV)

	High MPV n = 63	Normal MPV n = 528
7 days	93% (84-97)	96% (94-98)
30 days	77% (65-86)	89% (86-92)
90 days	63% (50-74)	81% (77-84)

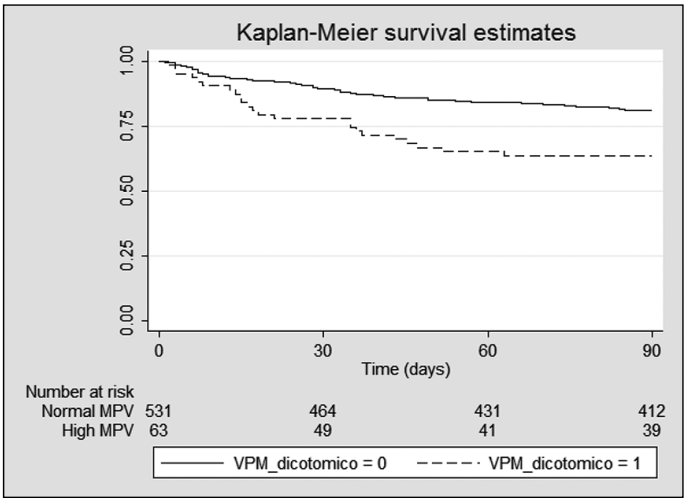

Figure 1. Estimated survival by KM method for both high and normal MPV (n = 591).

this association was significant for the VTE group and the PE or DVT subgroups; whereas renal disease with HR 1.51 (95% CI 1.05-2.18, p = 0.02) showed significant association with mortality only considering VTE.

Prognostic laboratory parameters: ProBNP > 300 pg/mL and UST > 20 pg/dL had a HR of 1 (95% CI 0.99-1, p = 0.05) and 0.99 (95% CI 0.99-1 p = 0.96), respectively.

The HR of high MPV adjusted for sepsis, oncological disease, heart disease, kidney failure and previous surgery was 2.42 (95% CI 1.54-3.85, p < 0.001) for VTE; 2.25 (95% CI 1.48-4.38, p < 0.001) in the subgroup only with DVT; and 2.97 (95% CI 1.58-5.57, p 0.001) in the subgroup only with PE as presented in Table 4.

Table 4. Characteristics associated with 90-day mortality

	Thromboembolic disease (n = 591)		Deep vein thrombosis (n = 407)		Pulmonary embolism (n = 300)	
	HR (CI)	p-value	HR (CI)	p-value	HR (CI)	p-value
Age	1 (0.99-1.01)	0.44	1 (0.99-1.02)	0.29	1 (0.98-1.01)	0.97
Feminine gender	0.93 (0.65-1.33)	0.69	1.04 (0.68-1.59)	0.83	0.86 (0.51-1.44)	0.57
Sepsis	2.16 (1.51-3.10)	< 0.001	2.15 (1.41-3.26)	< 0.001	1.75 (0.96-3.18)	0.06
Active cancer	3.04 (2.11-4.39)	< 0.001	3.05 (2 -4.65)	< 0.001	3.59 (2.05-6.30)	< 0.001
CHD	1.07 (0.68-1.69)	0.74	1.16 (0.67-1.99)	0.58	1.24 (0.67-2.29)	0.48
Kidney failure	1.51 (1.05-2.18)	0.02	1.48 (0.97-2.26)	0.06	1.37 (0.73-2.58)	0.32
Previous surgery	0.5 (0.33-0.76)	0.001	0.57 (0.35-0.93)	0.02	0.5 (0.28-0.89)	0.02
ProBNP (pg/mL)	1 (0.99-1)	0.05	1 (0.99-1)	0.08	1 (0.99-1)	0.05
UST (pg/dL)	0.99 (0.99-1)	0.96	0.99 (0.99-1)	0.67	0.99 (0.99-1)	0.96
Ventricular dysfunction	1 (0.58-1.89)	0.85	0.68 (0.25-1.83)	0.44	1 (0.58-1.89)	0.85
Crude high MPV	2.22 (1.41-3.49)	0.001	2.48 (1.46-4.21)	0.001	2.08 (1.14-3.78)	0.016
Adjusted high MPV	2.45 (1.54-3.89)*	0.001	2.65 (1.54-4.55)†	0.001	2.73 (1.48-5.04)†	0.001

*Adjusted for sepsis. cancer. coronary heart disease. kidney failure and previous surgery. †Adjusted for sepsis. cancer. coronary heart disease and previous surgery. Abbreviations: CHD,Coronary heart disease; CI, confidence interval; HR, hazard ratio; MPV, mean platelet volume; UST, Ultra-Sensitive Troponin. DVT and PE groups are not mutually exclusive.

Discussion

Our study shows that the increased platelet size is a prognostic factor for early mortality in patients with VTE.

It is described that the increase in MPV is associated with higher mortality and severity in patients with arterial and vascular diseases such as acute coronary syndrome and ischemic cerebrovascular events, even though there are few reports that assess the association between MPV and mortality in patients with VTE[9-11].

Kostrubiec et al. described the MPV as a marker of platelet activation and as an important predictor of premature death in a single-center prospective study of 192 patients with PE[2]. Among the most marked differences with our study, this study included younger patients (mean age of 64 years, SD18) with a much lower percentage of cancer (between 14 and 8%). The 30-day mortality was 7% in the group with normal MPV versus 18% in the high MPV group. Baseline differences between the two populations may explain to a certain extent the lower mortality compared to our study for both groups.

The study by Hillal et al did not found an association between the MPV and the severity of PE in 209 consecutive patients[1]. However, it was noted that the MPV was significantly higher in patients who did not survive the PE event. Our findings are consistent for both PE and DVT subgroups.

The increase in platelet size is related to the platelet adhesiveness and reactivity. This biological mechanism may be associated with the increase in mortality[2]. Previous studies have shown that MPV is a marker of platelet function and it is positively associated with the other markers of platelet activity[3-5]. Situations such as hypoxemia, ventricular dysfunction and impaired cardiac output are potent stimuli for platelet activation, promoting the release of vasoactive mediators, which play a key role in the increase of pulmonary vascular resistance, ischemia and myocardial damage Virchow's triad –hypercoagulability, endothelial injury and venous stasis– is essential in the pathogenesis of VTE, activating the coagulation pathway and the active participation of platelets in the thrombus formation. This clinically translates as impairment for contractility and dilation of the right cavities and as an increase in serum biomarkers[12,13]. The use of UST and ProBNP for risk stratification of patients with PE, which are mediated by mechanisms of myocardial damage and ventricular dysfunction, is described in the bibliography[14].

We studied the MPV as a prognostic factor of mortality in VTE, including patients with PE and DVT. We observed that the increase in platelet volume is associated with higher mortality in patients with PE and patients with DVT. This finding confirms that this factor is independent of the clinical presentation and comorbidities presented by patients, including oncological disease, coronary heart disease and sepsis, among others.

Likewise, high MPV has a statistically significant association with elevated biomarkers such as UST and ProBNP, demonstrating a more severe disease. UST, proBNP and right ventricular dysfunction by echocardiography are indicators of acute hemodynamic compromise and relate to mortality or severity of the acute VTE event. In our study, serological biomarkers (UST and ProBNP) were not associated with increased mortality. Our interpretation is that this manuscript describes global mortality and not PE mortality. For that final point, and being patients with a high burden of morbidity, particularly active cancer and sepsis, we think that global mortality is not influenced by biomarkers.

The MPV could represent a more consistent global marker of platelet activation and could be related to longer-term mortality, capable of being a prognostic marker of the severity of the VTE episode.

The MPV measurement in our study was obtained at diagnosis of VTE, not taking into account the values previous to the PE or DVT episode, nor the monitoring throughout the clinical evolution. This is consistent with measurements of other risk stratification markers like UST and ProBNP, in which a single measurement at the moment of diagnosis proved helpful in prognosis[15].

Solid cancer and hematological neoplasm were present in more than one third (37%) of the enrolled population, it is likely that cancer deaths might have strongly influenced analysis. It has been reported that chemotherapy might cause in vivo platelet activation and decreased platelet size. Although all patients had active cancer, chemotherapy data was not available. We can hypothesize that this might explain the higher rate of cancer in the "normal" MPV group.

Unlike the use of UST and ProBNP measurements, which have a low availability and have high cost, the MPV measurement is easily obtained because it is automatically calculated during a routine blood count, therefore, economically accessible. The MPV is potentially a useful tool for prognosis of overall mortality of VTE patients with high availability that should be further studied in prospective studies.

Conclusion

We studied the MPV as a prognostic factor of mortality in VTE and observed that high platelet volume is associated with higher mortality. This finding confirms that this factor is independent of the clinical presentation and comorbidities.

Although there are well known biomarkers of mortality for VTE, the MPV is potentially a useful tool for prognosis of overall mortality of VTE patients with high availability that should be further studied in prospective studies

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ARTE Y FOTOGRAFÍA

El Viejo y El Mar. Isla de Procida. Dr. Francisco Cordero Anfossi