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Original Article

Mean platelet volume in the differential diagnosis of tuberculous and bacterial meningitis

Carlos Rodrigo Camara-Lemarroy[1], Guillermo Delgado-Garcia[2], Juan Gilberto De La Cruz-Gonzalez[1], Hector Jorge Villarreal-Velazquez[1], Fernando Gongora-Rivera[1]

[1] Neurology Service, University Hospital "Dr. Jose E. González", Autonomous University Of Nuevo Leon, Monterrey, Nuevo Leon, Mexico
[2] Department of Internal Medicine, University Hospital "Jose E. Gonzalez", Autonomous University of Nuevo Leon, Monterrey, Nuevo Leon, Mexico

Abstract

Introduction: Mean platelet volume (MPV) has been shown to reflect the inflammatory burden in different inflammatory and autoimmune diseases. Our objective was to analyze the MPV in patients with tuberculous (TBM) and bacterial meningitis (BM).
Methodology: The demographic and clinical data of 73 consecutive patients that presented with either BM (n = 35) or TBM (n = 38) were retrospectively analyzed, as well as that of 28 age- and sex-matched controls.
Results: MPV was 8.78 ± 1.58 fL in patients with BM and 6.42 ± 1.39 fL in the TBM group ($p < 0.05$). In the control group, MPV was 7.4 ± 0.66 fL, significantly higher and lower when compared with TBM and BM, respectively. MPV was significantly associated with diagnosis (adjusted OR: 5.15, 95% CI: 1.090–23.7; $p = 0.03$). With the optimal cut-off value of 7.62 fL, MPV had 82% sensibility and 78% specificity for the differential diagnosis of TBM versus BM. Lower platelet counts, higher serum creatinine, higher white blood cell counts, and higher blood-cerebrospinal fluid glucose ratio were also predictive of BM.
Conclusions: Platelet counts were lower and MPV was higher in patients with BM compared to patients with TBM. Platelet indices, available in routine bloodwork, could be useful in the early differential diagnosis of these entities.

Key words: meningitis; mean platelet volume; inflammation; platelets; thrombocytopenia.

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Introduction

Platelet activation is an essential step in the pathophysiology of immune-mediated diseases. Mean platelet volume (MPV), a surrogate marker of the platelet function and activation, has been shown to reflect the inflammatory burden in different chronic diseases [1]. MPV is available in routine complete blood cell counts, but until recently, its diagnostic or prognostic value in the setting of acute infections had been widely ignored.

Differentiating bacterial from tuberculous meningitis remains challenging, especially in settings with a high prevalence and where molecular diagnostic techniques are not widely available. There is evidence that suggests that MPV behaves differently in bacterial infections compared to other etiologies, and that pulmonary tuberculosis is associated with changes in platelet counts and MPV [2,3]. We hypothesized that these parameters could be of use in the differential diagnosis of bacterial (BM) and tuberculous meningitis (TBM). Currently, strong diagnostic models using simple clinical and laboratory features exist for the differentiation of BM and TBM, but they have not included MPV or platelet counts [4]. To the best of our knowledge, MPV in patients with meningitis has not been previously studied.

Methodology

Patients

Patients with confirmed diagnosis of meningitis who were admitted to the University Hospital "Jose Eleuterio Gonzalez", in Monterrey, Nuevo Leon, between the years 2010 and 2015 were retrospectively enrolled in the study. Any follow-up data of the same patients over their ensuing outpatient visits to the neurology consult of the same institution were recorded. The complete medical history, clinical and biochemical evaluation, and complete blood cell count on admission and on latest follow-up with disease on remission were recorded. None of the patients had a

history of cardiovascular disease, nor were any taking anticoagulation drugs, antiplatelet agents, or aspirin. The study was approved by the ethics committee of the institution.

Diagnostic criteria

Diagnostic criteria for TBM and BM were applied to all patients. Patients were diagnosed as having TBM if *M. tuberculosis* was isolated in the cerebrospinal fluid (CSF, either by culture, Ziehl-Neelsen staining, or polymerase chain reaction testing), or if they had a clinical diagnosis of meningitis but with negative Gram stain and sterile culture and at least one of the following: proven tuberculosis in a different site, magnetic resonance imaging with basal meningeal enhancement, and a good response to anti-tuberculosis chemotherapy. Patients were diagnosed as having BM if pathogenic bacteria were isolated from CSF (either by culture or Gram stain), or if patients had a clinical diagnosis of meningitis and either a positive blood culture for a bacterial pathogen or all of the following: neutrophilic pleocytosis in the CSF, a low concentration of glucose in the CSF (< 50% of that in blood), and a full recovery without anti-tuberculosis drugs.

Control group

The control group included 28 age- and sex-matched healthy subjects (matched to BM group), whose records were obtained from the outpatient internal medicine clinic of the same institution, with complete blood cell counts as part of routine check-ups.

Other laboratory and clinical examinations

All complete blood cell counts were measured by an automatic blood counter in the central laboratory at the University Hospital. Blood was collected in potassium-ethylenediaminetetraacetic acid tubes and measured within 1 hour after venipuncture, based on institutional protocol. The range of MPV values in the laboratory was between 0 and 99 fL. All other biochemical and clinical data were obtained from medical records. Systemic inflammatory response syndrome (SIRS) on admission was defined as two or more of the following criteria: temperature >38°C (100.4°F) or < 36°C (96.8°F); heart rate > 90; respiratory rate > 20 or PaCO2 < 32 mm; and white blood cell (WBC) count > 12,000/mm3, < 4,000/mm3, or > 10% bands. Duration of illness was defined as time from first appearance of any systemic or neurological symptoms to admission. The modified Rankin scale was used to score outcome on discharge.

Validation of the Thwaites diagnostic model for TBM

Thwaites *et al.* [4,5] devised a diagnostic model after finding five factors that were independently associated with a diagnosis of TBM when compared with BM. The prediction rule gives a numerical score and suggests a diagnosis of TBM when the score is ≤ 4 and of BM when the score is > 4. The following are the factors included in this model: age $\geq$ 36 years (2 points); blood WBC count $\geq$ 15,000 10^3/mL (4 points); duration of illness $\geq$ 6 days (-5 points); CSF WBC count $\geq$ 900 (3 points); and CSF % neutrophils $\geq$ 75 (4 points). The reported sensibility and specificity of this rule to distinguish TBM from BM is 93%–100% and 73%–88%, respectively. This diagnostic model was applied to the sample to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Statistical analysis

All statistical analyses were assessed using the SPSS computer program (SPSS version 17.0; IBM, Armonk, USA). The two groups were compared by univariate analysis using either student's *t*-test or the Mann-Whitney test for quantitative variables (where appropriate) and the Chi-square test for categorical variables. Variables that were significantly different between TBM and BM were included in a logistic regression analysis, which was used to model the probability of having TBM. The best cut-off points (the value that maximizes sensitivity + specificity) were selected using the standard receiver operating characteristic (ROC) curve, and reported as area under the curve (AUC). All parameters were expressed as mean values ± standard deviation, and a p value < 0.05 was considered statistically significant.

Table 1. Demographic data, mean platelet volume (MPV) and platelet count.

	Control	BM	TBM
n	28	35	38
Male %	65	60	63
Age (mean)	42.8	40.4	39.6
Platelet count (mm^3 × 1,000)	275.5 ± 55.3	195.1 ± 71.7^{*+}	310.9 ± 122.9
MPV (fL)	7.4 ± 0.66	8.78 ± 1.58^{*+}	6.42 ± 1.39*

* $p < 0.05$ versus control; $^{+}$ $p < 0.05$ versus TBM; BM: bacterial meningitis; TBM: tuberculous bacterial meningitis.

Results

Patient characteristics

The demographic characteristics of the patients are reported in Table 1. A total of 101 patients were included in the analysis: 28 in the control group, 35 in the BM group, and 38 in the TM group. Their demographic characteristics can be found in Table 1.

MPV

The values of MPV and platelet counts are shown in Table 1. MPV was higher and platelet counts lower in BM patients compared to both the TBM and control groups. There was no difference in platelet count between patients with TBM and the control group. MPV was significantly lower in the TBM group compared to the control group. Both platelet indices were significantly different between TBM and BM groups. The AUC in the ROC curve for MPV (Figure 1) when comparing the TBM and BM groups was 0.888 (95% CI: 0.802–0.957). With the optimal cut-off value of 7.62 fL, MPV had 82% sensibility and 78% specificity for the differential diagnosis of TBM versus BM (PPV: 84% and NPV: 82%).

Other patient variables

Besides age, sex, platelet count, and MPV, another 18 clinical and biochemical variables were included in the analysis (Table 2). After univariate analysis, only the following factors were found to be statistically different between the TBM and BM groups: creatinine level on admission, serum sodium on admission, WBC count on admission, hemoglobin level on admission, blood-CSF glucose ratio, presenting with SIRS, and duration of illness. There were, as expected, significantly more HIV-infected patients in the TBM group. These variables (as well as platelet count and MPV) were then included in a logistic regression analysis (Table 3), where only MPV, platelet count, WBC count, SIRS, and blood-CSF glucose ratio were

Figure 1. ROC curve for MPV (dark gray), Thwaites rule (dotted line) and Thwaites rule + MPV (Thw+MPV, light gray).

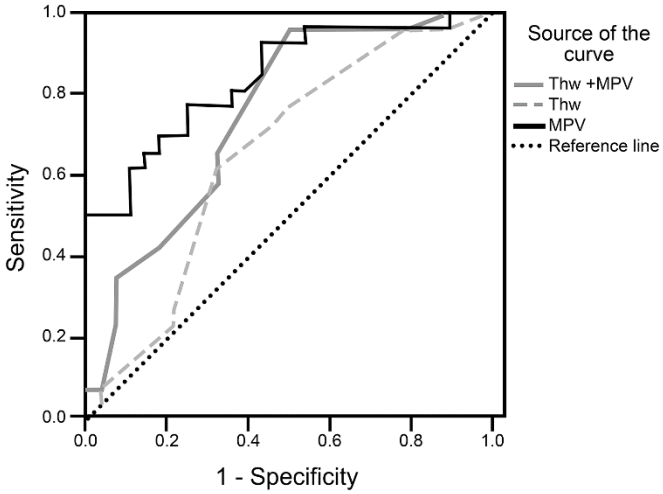

Table 2. Other biochemical and clinical variables.

	BM	TBM
Serum		
Creatinine (mg/dL)	1.33 ± 1.3	0.7 ± 0.2*
Serum albumin (g/dL)	3.3 ± 1	3.21 ± 0.8
WBC (1,000/uL)	14.5 ± 6.2	9.9 ± 4.5*
Hemoglobin (g/dL)	14 ± 2	12.5 ± 1.9*
Serum lactate (mmol/L)	2.3 ± 2.7	1.6 ± 1
Serum sodium (mmol/L)	139.3 ± 3.7	134.5 ± 6.5*
CSF		
Protein (mg/dL)	179 ± 181	358.2 ± 717
Blood-CSF glucose ratio	0.37 ± 0.2	0.23 ± 0.13*
WBC (mm^3)	337 ± 462	141 ± 169
Lactate (mmol/L)	4.8 ± 4.3	5.6 ± 2.3
Clinical		
Duration of illness	5.5 ± 4.7	12.2 ± 11.9*
HIV, n (%)	2 (6)	11 (29)*
Headache, n (%)	19 (54)	26 (68)
Fever, n (%)	26 (74)	23 (61)
Neck stiffness, n (%)	23 (66)	18 (47)
Seizures, n (%)	4 (12)	5 (13)
SIRS, n (%)	25 (71)	8 (21)*
mRS (discharge)	1.5 ± 2.1	2.1 ± 2.4

* $p < 0.05$ versus TBM; BM: bacterial meningitis; TBM: tuberculous bacterial meningitis; WBC: white blood cell; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; SIRS: systemic inflammatory response syndrome; mRS: modified Rankin Scale.

Table 3. Multivariate analysis of factors associated with the differential diagnosis between TBM and BM.

	Odds ratio	95% confidence interval	P
Platelet count	0.971	0.947–0.996	0.03
MPV	5.15	1.090–23.7	0.03
WBC	1.32	1.052–1.666	0.03
Blood-CSF glucose ratio	1.08	1.02–1.164	0.03
SIRS	11.4	1.520–92.7	0.04

TBM: tuberculous bacterial meningitis; BM: bacterial meningitis; MPV: mean platelet volume; WBC: white blood cells; CSF: cerebrospinal fluid; SIRS: systemic inflammatory response syndrome.

found to be significantly correlated with the differential diagnosis of TBM versus BM.

Thwaites prediction rule

Using the Thwaites model, 28 out of 38 cases were correctly classified as TBM (74%), while only 17 out of 35 cases were correctly identified as BM (48%). The PPV was 58.3% and the NPV was 66.7% (AUC: 0.652, 95% CI: 0.503–0.800). Only 3 patients in the whole sample (both with BM) had CSF WBC counts over 900. In this study, age was not different between groups. On the other hand, 13 patients predicted to have BM had a disease duration ≥ 6 days.

When the cutoff MPV value of 7.62 fL was added to the model as a dichotomic weighted variable (≥ 7.6 added 2 points to the score), the sensibility dropped to 72.4% and specificity rose to 75%. The PPV was 75% and the NPV was 72.4% (AUC: 0.732, 95% CI: 0.598–0.870). Only 6 patients predicted to have BM by the Thwaites model had an MPV value below 7.62 fL. The AUC of MPV alone was higher than either prediction rule (Figure 1).

Discussion

Platelet activation is an essential step in the pathophysiology of diseases associated with thrombosis and inflammation. MPV is one of the most widely used surrogate markers of the platelet function, reflecting the platelet production rate, activity, and stimulation [1,6]. It is generated in routine complete blood count tests. It has been shown to reflect the inflammatory burden in different chronic diseases, and large platelets are thought to indicate increased aggregability [1,6]. Additionally, overproduction of pro-inflammatory cytokines and acute phase reactants can suppress the size of platelets by interfering with megakaryopoiesis [7]. Thus, alterations in MPV could indicate both a pro-thrombotic state and an inflammatory state.

In chronic systemic inflammatory diseases, such as active rheumatoid arthritis, inflammatory bowel disease, vasculitis, and ankylosing spondylitis, MPV has been shown to be low, to correlate with disease severity, and even to increase after anti-inflammatory therapy [8-10,1]. However, in studies of acute infectious diseases, there have been conflicting results. Bacterial bloodborne infections and acute bacterial sepsis have been associated with elevated MPV, a finding with prognostic significance [2,11]. In another study of 58 cirrhotic patients with acute ascitic fluid infection also found that they had elevated MPV compared to non-infected patients [12]. However, in a study of 196 children with community-acquired pneumonia, a lower MPV was found compared to healthy controls [13], a finding later replicated in children with respiratory syncytial virus infection [14].

In our study, BM was associated with a lower platelet count and a higher MPV. These patients also had higher creatinine and WBC counts and presented more often with SIRS, which supports the above-mentioned findings in patients with bacteremia and acute bacterial sepsis [2,11]. Moreover, critical illness severity is often correlated with thrombocytopenia, and in the case of sepsis, disseminated intravascular platelet activation may occur [15]. Both thrombocytosis and thrombocytopenia are known to occur in children with meningitis. In a study involving 311 children with BM, 49% developed reactive thrombocytosis during the first week of illness, possibly due to inflammatory cytokines [16]. On the other hand, thrombocytopenia is a well-known negative prognostic factor in BM both in children and adults [16-18]. In the largest prospective study to date involving 696 episodes of bacterial meningitis in adults, the mean platelet count was 198,000 ± 100,000 [18]. Although this value fell within normal range and was similar to our findings, lower platelet counts were significantly associated with a worse prognosis.

Reactive thrombocytosis has been known to be quite common in patients with tuberculosis for some time. Thrombocytosis in tuberculosis patients also correlates well with markers of inflammation such as serum C-reactive protein and erythrocyte sedimentation rate [19]. Platelets also show increased aggregability and mediators of thrombopoiesis are increased. A study of 82 patients with pulmonary tuberculosis found an elevated MPV compared to controls and also a

correlation between MPV and radiological disease [20]. When compared to patients with bacterial pneumonia, pulmonary tuberculosis patients showed higher MPV and platelet counts [3]. However, other studies have found contrasting results. In a study of 22 patients with intestinal tuberculosis, MPV was lower than that of controls and similar to that of patients with inflammatory bowel disease [21]. Another recent study involving 82 patients with pulmonary tuberculosis found lower MPV compared to that of healthy controls, and no association between MPV and severity of radiological involvement [22]. In support of these previous findings, our patients with TBM had lower MPV and higher platelet counts compared with those of controls and BM patients.

With respect to a possible mechanism explaining our findings, both BM and TBM are associated with an intense inflammatory state (increased oxidative stress, pro-inflammatory cytokine production, and inflammatory cell activation) as well as with a pro-thrombotic state (endothelial dysfunction, vasculitis, and pro-coagulant mediators) [23-26]. Longer disease duration in TBM could result in an altered megakaryopoiesis due to chronic exposure to an inflammatory environment. Further studies are needed to establish if other mediators, specific to bacterial or tuberculous infection, could also play a significant role.

In our study, hyponatremia was much more common in TBM than in BM, but did not reach statistical significance on multivariate logistic regression analysis. The association between hyponatremia and TBM has been established for some time, with over 50% of patients presenting with hyponatremia and evidence of syndrome of inappropriate secretion of antidiuretic hormone in both adult and pediatric series [27,28]. Other proposed mechanisms are adrenal insufficiency and cerebral salt-wasting. In a comparative study of over 500 patients with either TBM or BM, serum sodium levels were found to be lower in the TBM group, and to be independently predictive of a TBM diagnosis [29].

Thwaites *et al*. developed a prediction rule with over 90% of sensitivity and sensibility; this was obtained for differentiating tuberculous from other types of meningitis, including BM, based on clinical and laboratory features [4,5]. Five features were predictive of a diagnosis of tuberculous meningitis: age, length of history (duration of illness), WBC count, total CSF white-cell count, and CSF neutrophil proportion. Several studies have confirmed these findings [30] and added other discriminating features such as protein count, headache [31], and focal deficit [32]. In our series, of these factors, only length of history and WBC count were significantly different between groups.

Platelet count and MPV had the lowest p values on univariate analysis and the largest areas under the curve on ROC of all the features studied. Furthermore, we found other significant differences, such as SIRS, creatinine level, and blood-CSF glucose ratio. When we applied the Thwaites prediction rule to our sample, the sensitivity and sensibility was much lower than the figures reported originally. This can be explained by the differences between the factors we identified as significant in our study and those identified by Thwaites *et al*., as well as by other epidemiological factors that could be specific to our population. Another possible confounding factor is the prevalence of HIV infection in our sample, but studies on MPV in this setting are controversial as well. In a study of 234 patients with HIV infection, MPV was lower compared with that of healthy controls [33], whereas they were found to be elevated in asymptomatic HIV-infected and treatment-naive patients [34]. None of the findings in this paper were significantly modified if we excluded HIV-positive cases (data not shown). Of note, in our series, age was not a useful discriminating factor, which is consistent with later findings by other groups [32]. The sensibility and specificity of the Thwaites prediction rule was only mildly improved in accuracy when we included MPV values into the rule as a dichotomic variable using the optimal cut-off value. The Thwaites prediction rule was of limited value in our population.

This study has several limitations commonly shared by retrospective studies. The sample size was small. We also did not investigate inflammatory markers or other markers of platelet function or aggregability, nor mediators such as platelet activating factor, thromboxane, or thrombomodulin.

Conclusions

Platelet counts are lower and MPV is higher in patients with BM as opposed to those with TBM. Platelet indices, available in simple, inexpensive, and routine bloodwork, could be useful in the early differential diagnosis of these entities, particularly if combined with other established predictors.

Authors' contributions

CRCL designed research and wrote the paper; GDG and JGDCG performed research; HJVV and FGR analyzed data and approved the final manuscript

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Corresponding author
Carlos Rodrigo Cámara-Lemarroy
Servicio de Neurología. Hospital Universitario "Dr. José E. González"
Universidad Autónoma de Nuevo León. Monterrey, N.L. México
Madero y Gonzalitos S/N, Monterrey NL. 64700 México
Phone/Fax: +52 (81) 8333-7798.
Email: crcamara83@hotmail.com

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