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Original article

Mean platelet volume is decreased in adults with active lupus disease

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ARTICLE INFO

Article history:
Received 10 June 2015
Accepted 13 December 2015
Available online 21 March 2016

Keywords:
Systemic lupus erythematosus
Mean platelet volume
Disease activity
Inflammation
Biological markers
Serum albumin

ABSTRACT

Background: Only a few biomarkers are available for assessing disease activity in systemic lupus erythematosus (SLE). Mean platelet volume (MPV) has been recently studied as an inflammatory biomarker. It is currently unclear whether MPV may also play a role as a biomarker of disease activity in adult patients with SLE.

Objective: We investigated the association between MPV and disease activity in adult patients with SLE.

Methods: In this retrospective study, we compared two groups of adult patients divided according to disease activity (36 per group). Subjects were age- and gender-matched.

Results: MPV was significantly decreased with respect to those of inactive patients (7.16 ± 1.39 *vs.* 8.16 ± 1.50, $p = 0.005$). At a cutoff level of 8.32 fL, MPV has a sensitivity of 86% and a specificity of 41% for the detection of disease activity. A modest positive correlation was found between MPV and albumin ($r = 0.407$, $p = 0.001$), which in turn is inversely associated with disease activity.

Conclusions: In summary, MPV is decreased in adult patients with active lupus disease, and positively correlated with albumin, another biomarker of disease activity. Prospective studies are needed to evaluate the prognostic value of this biomarker.

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http://dx.doi.org/10.1016/j.rbre.2016.03.003

O volume plaquetário médio está reduzido em adultos com lúpus ativo

Palavras-chave:
Lúpus Eritematoso Sistêmico
Volume plaquetário médio
Atividade da doença
Inflamação
Marcadores biológicos
Albumina sérica

RESUMO

Antecedentes: Existem poucos biomarcadores disponíveis para avaliar a atividade da doença no lúpus eritematoso sistêmico (LES). O volume plaquetário médio (VPM) foi recentemente estudado como um biomarcador inflamatório. Atualmente não está claro se o VPM também pode desempenhar um papel como um biomarcador da atividade da doença em pacientes adultos com LES.

Objetivo: Investigou-se a associação entre o VPM e a atividade da doença em pacientes adultos com LES.

Métodos: Neste estudo retrospectivo, compararam-se dois grupos de pacientes adultos divididos de acordo com a atividade da doença (36 por grupo). Os indivíduos foram pareados por idade e gênero.

Resultados: O VPM esteve significativamente diminuído nos pacientes com doença ativa em comparação com os níveis em pacientes com doença inativa ($7{,}16 \pm 1{,}39$ *versus* $8{,}16 \pm 1{,}50$, $p = 0{,}005$). Em um nível de corte de 8,32 fL, o VPM tem uma sensibilidade de 86% e uma especificidade de 41% para a detecção da atividade da doença. Encontrou-se uma correlação positiva modesta entre o VPM e a albumina ($r = 0{,}407$, $p = 0{,}001$), que por sua vez está inversamente associada à atividade da doença.

Conclusões: Em resumo, o VPM está diminuído em pacientes adultos com lúpus ativo, e positivamente correlacionado com a albumina, outro biomarcador da atividade da doença. São necessários estudos prospectivos para avaliar o valor prognóstico desse biomarcador.

Introduction

Platelet size correlates with platelet activity. Autoimmune reactions are thought to contribute to platelet activation in systemic lupus erythematosus (SLE). In fact, there is a correlation between mean platelet volume (MPV) values and active inflammatory diseases.[1,2] It has been recently reported that MPV is increased in patients with juvenile SLE. Moreover, this parameter increased in parallel with the activity index, and appears to be more accurate than erythrocyte sedimentation rate (ESR) and C3 in detecting disease activity.[3] However, it is currently unclear whether MPV may also play a role as a biomarker of disease activity in adult patients with SLE. Therefore, we conducted the present study to test this hypothesis.

Material and methods

Subjects and study design

A retrospective, cross-sectional, comparative design was used for this study. Demographic and laboratory data were obtained by reviewing medical records of all patients who had been diagnosed with SLE in our hospital. Systemic Lupus International Collaborating Clinics (SLICC) classification criteria were used for the diagnosis, except for those patients who were diagnosed before these criteria were published, in which case it was made using the American College of Rheumatology (ACR) criteria. Lupus nephritis was classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification. The inclusion criteria were as follows: age older than 16 years; diagnosis of SLE; and a Mexican Systemic Lupus Erythematosus Disease Activity Index (Mex-SLEDAI) scored in the polyclinic (inactive patients) or at admission (active patients), as recorded by a rheumatology fellow. Exclusion criteria were the following: infection, thrombocytopenia, rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), psoriasis, and incomplete medical record. Overall disease activity was assessed with Mex-SLEDAI. Patients scoring <2 were classified as inactive, while those scoring >5 were classified as active.[4,5] This study was approved by the ethics committee of the Autonomous University of Nuevo León Faculty of Medicine. Written informed consent was not required.

Assays

Blood samples were taken by from both plain and EDTA tubes. The latter were used for complete blood count (CBC). Most routine CBC were done with a Cell-Dyn Ruby analyzer (Abbott Diagnostics, USA), while most clinical chemistry parameters (creatinine, blood urea nitrogen and serum albumin) were measured using a DxC800 Synchron analyzer (Beckman Coulter, USA). ESR determinations were performed by the Wintrobe method, whose upper normal limit was 20 mm/h.

Statistics

Based on a previous report on MPV in juvenile SLE,[3] sample size was calculated using comparisons of means. Calculation was performed using $\alpha = 0.05$, $\beta = 0.20$, and two tails. A total sample size of 60 (30 in each group) would be required to demonstrate a statistically significant difference between groups. Data were first analyzed for normality

using Shapiro–Wilk test. Comparisons between groups were performed by using chi-square test, Student's *t*-test or Mann–Whitney *U* test, as appropriate. Associations between the variables were explored using the Pearson product-moment correlation coefficient or Spearman's rho. A receiver operating characteristic (ROC) curve was generated to determine the cutoff value in the MPV (and other inflammatory biomarkers) with the highest level of accuracy in identifying patients with disease activity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Unless indicated otherwise, all results are expressed as mean ± SD or median (25–75%). Statistical analyses were conducted using SigmaStat (v. 3.5, Erkrath, Germany) or MedCalc (v. 14.12.0, Ostend, Belgium), and a *p*-value below 0.05 ($p < 0.05$) was considered significant.

Results

A total of 72 patients were included in this study, 36 patients were classified as having active disease (34 females, aged 18–64 years), and 36 patients as having inactive disease (35 females, aged 20–53 years). The age and gender distributions were similar in the two groups ($p = 0.83$ and $p = 0.55$, respectively). 10 active patients (27%) were diagnosed during their first hospitalization, so years since diagnosis were significantly different between groups (1 [0–15] *vs.* 5 [1–23], $p \leq 0.001$). The percentage of a previous diabetes diagnosis did not differ by disease activity ([1, $n = 70$] = 2.57, $p = 0.108$, Yates' *p*-value). Patients with active disease were more likely to have a previous hypertension diagnosis than those with inactive disease (38.2% *vs.* 2.7%, [1, $n = 70$] = 13.74, $p \leq 0.001$). Ten (27.7%) of the active patients had biopsy-proven lupus nephritis (LN). Of these, 40% had ISN/RPS class III LN, 30% had class IV LN, 20% had class V LN, and 10% had class II LN.

Hemoglobin, absolute lymphocyte count (LYM), MPV, and albumin of active patients were significantly decreased with respect to those of inactive patients, whereas ESR was comparatively increased in the former group. Platelet count and creatinine were not significantly different between groups (Table 1). A modest positive correlation was found for MPV and albumin in active patients ($r = 0.407$, $p = 0.001$). There were no significant relationships between MPV and ESR ($p = 0.26$). The ROC curve analysis for MPV showed an area under the curve (AUC) of 0.685 (95% CI 0.565–0.790, $p = 0.003$) with an optimal cutoff value of 8.32 fL (Fig. 1). Sensitivity, specificity, PPV, and NPV were 86%, 41%, 59%, and 75%, respectively. The AUC for predicting disease activity was 0.658 (95% CI 0.537–0.766, $p = 0.015$) for ESR (Fig. 1). At a cutoff level of 37 mm/h, sensitivity, specificity, PPV, and NPV were 44%, 86%, 76%, and 60%, respectively. The AUC for albumin, with a cutoff point of 3.2 g/dL, was 0.845 (95% CI 0.737–0.922, $p \leq 0.001$) (Fig. 1).

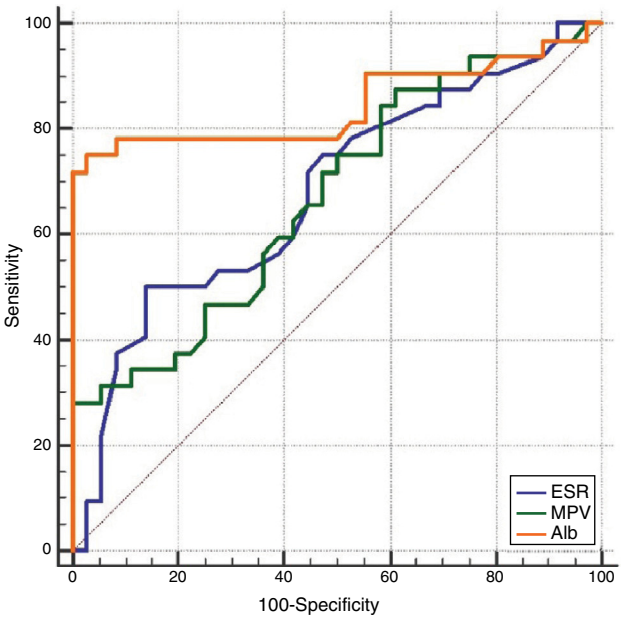

Fig. 1 – Receiver-operating characteristics (ROC) curve analysis for the diagnostic performance of ESR (blue line), MPV (green line) and albumin (Alb, orange line).

Table 1 – Paraclinical comparison between groups.

Parameter	Active ($n = 36$)	Inactive ($n = 36$)	*p*	Test
Hb (g/dL)	10.9 ± 1.97	12.69 ± 1.2	<0.001	ST
WBC (10^9/L)	6.46 ± 2.73	6.28 ± 2.76	0.781	ST
NEU (10^9/L)	4.81 ± 2.36[a]	4.12 ± 2.49	0.237	ST
LYM (10^9/L)	1.12 ± 0.74[a]	1.58 ± 0.67	0.008	ST
PLT (10^9/L)	269.88 ± 870.02	271.72 ± 698.07	0.922	ST
MPV (fL)	7.16 ± 1.39	8.16 ± 1.50	0.005	ST
ESR (mm/h)	31 (21.5–45)	22.5 (14.5–34.5)	0.021	MWU
Crea (mg/dL)	0.61 (0.57–0.89)[a]	0.64 (0.53–0.72)	0.60	MWU
BUN (mg/dL)	13.4 (10–22.75)[a]	12 (10–14)	0.12	MWU
Alb (g/dL)	2.73 ± 0.81[b]	3.7 ± 0.27	<0.001	ST

Hb, hemoglobin; WBC, white blood cell count; NEU, absolute neutrophil count; LYM, absolute lymphocyte count; PLT, platelet count; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; Crea, creatinine; BUN, blood urea nitrogen; Alb, albumin; ST, Student's *t*-test; MWU, Mann–Whitney *U* test.
All results are expressed as mean ± SD or median (25–75%).
[a] $n = 35$.
[b] $n = 32$.

Sensitivity, specificity, PPV, and NPV were 75%, 97.2%, 96%, and 81%, respectively. The pairwise comparison among the ROC curves showed no statistical difference ($p = 0.054$ and $p = 0.947$, respectively).

Discussion

Contrary to previously reported findings in juvenile SLE,[3] in this study the MPV was found to be significantly lower in adult patients with active disease compared to those classified as having inactive disease. Although several reports have indicated the potential link between higher MPV values and active inflammatory disease, the opposite has been found in other studies.[1,2] In the largest sample to date, MPV was decreased in adult patients with active RA, and increased after treatment.[6] A recent review did not include this report.[7] In a small retrospective study of 30 adult patients with active AS, MPV was decreased when initial tests were performed, and increased after treatment.[8] Notwithstanding, this finding was not reproduced in a larger study.[9] Adult patients with IBD (both in active and remission stages) also have a lower MPV when compared to control group.[10] Likewise, in children with acute rheumatic fever, MPV has been reported as decreased, and increased after treatment.[11]

Platelet activation is observed in patients with SLE, and its pathophysiology could include inflammatory cytokines and complement.[12,13] One plausible mechanism to explain the association between decreased MPV and disease activity could be the consumption of large activated platelets in extravascular sites of inflammation.[1] However, while platelet activation is enhanced in patients with SLE, these patients have normal values for platelet mean life-span,[14] suggesting that platelet consumption is minimal. More studies are needed in order to further elucidate the cause of this reduction in platelet size.

Serum albumin was comparatively lower in those with active disease. A modest positive correlation was found between MPV and albumin, which in turn is inversely associated with disease activity.[15] ESR was significantly elevated in patients with active disease. This is in line with existing literature, since ESR elevations have been associated with overall disease activity.[16] Interestingly, we found no correlation between ESR and MPV. Even though both parameters might evaluate disease activity, this lack of correlation could be, in part, because these biomarkers may reflect two separate biological processes.

Only a few biomarkers are available for assessing disease activity in SLE. An ideal biomarker must be easily measured, reproducible and sensitive to changes in disease activity.[17] In this study, there was no significant difference in overall accuracy between MPV and ESR for detection of disease activity. Besides being a widely available test, MPV is also cost-effective. At a cutoff level of 8.32 fL, MPV has a high sensitivity (86%) for the detection of disease activity. A highly sensitive test is chiefly important when it is used to identify a serious but treatable condition (as a lupus flare).

This is the first study, to our knowledge, to specifically examine the relationship between MPV and disease activity in adult patients with SLE. Various authors have identified a previous study that found decreased MPV in adult patients with SLE.[1,3] Nonetheless, the aforementioned study was not intended to demonstrate that MPV is associated with disease activity, since its truly aim was to compare the performance of two automated cell counters.[18]

The time delay between sampling and processing was not controlled in our study. However, we found a decreased MPV in adult patients with active disease, and MPV increases (not decreases) over time in EDTA tubes.[2] Phlebotomists and laboratory technicians were blind to the clinical status of the patient, thus rationally excluding bias. Also, the diagnosis of hypertension was more frequent in patients with active disease, yet this would most likely not affect our results, because hypertension is associated with an increased MPV, and not with its decrease.[19,20]

In summary, MPV is decreased in adult patients with active lupus disease, and positively correlated with serum albumin, another biomarker of disease activity. Prospective studies are needed to evaluate the prognostic value of this biomarker.

Conflicts of interest

The authors declare no conflicts of interest.

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