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Utility of cytometric parameters and indices as predictors of mortality in patients with sepsis

Jorge Luis Vélez-Páez[1,2], Andrea Carolina Armendáriz-Carvajal[1], Fernando Enrique Rueda-Barragán[1], Evelyn Elizabeth Castro-Reyes[1], Ana Cristina Escola-Brito[1], Diego Chambergo-Michilot[3,4], Sergio A. Castillo-Sancho[5], Maryori M. Hilario-Gomez[6,4], Joshuan J. Barboza[7,4,*]

Abstract

Introduction: A comprehensive cytometry assessment in the critical ill patient shows modifications in cell lines that estimate severity and mortality in sepsis. The objective of this study is to determine the utility of different cytometric parameters and indices as predictors of mortality in septic patients.

Materials and Methods: Retrospective cohort study of adults with sepsis (SEPSIS Criteria 3) hospitalized in an Intensive Unit Care (Quito, Ecuador). Patients with neoplasms or immunodeficiency states were excluded. Different cytometric parameters have been assessed and logistic regression models were used to stablish the predictive range of mortality for each parameter and areas under the curve (AUC) for sensitivity analysis.

Results: Over 159 patients, the mortality was 25%. In non-survivors, the median of the APACHE II was 25.20 points, and the median of the SOFA was 11.18, 10.44, 10.15 points at the time of admission, 48, and 72 hours respectively. About the sensitivity analysis for mortality, the cut-off point of EDW was 14.5% (AUC 0.708), and it presented an adjusted OR of 5.25 (95%CI: 1.64-16.76, p: 0.005). The cut-off point of MPV was 8.45 fL (AUC 0.666), and it had an adjusted OR of 5.28 (95%CI: 1.72-16.21, p 0.004).

Conclusions: EDW and MPV are independent predictors of mortality, and they must be used with scales or biomarkers to optimize the management and therapy of patients with sepsis. They would be an alternative in centers where only blood cytometry is available as an analytical test.

Keywords: cytometry, sepsis, mortality, biomarkers (Source: MeSH NLM).

Utilidad de los parámetros e índices citométricos como predictores de la mortalidad en pacientes con sepsis.

Resumen

Introducción: Una evaluación completa de citometría en el paciente enfermo crítico muestra modificaciones en las líneas celulares que estiman la gravedad y la mortalidad en la sepsis. El objetivo de este estudio es determinar la utilidad de diferentes parámetros e índices citométricos como predictores de la mortalidad en pacientes sépticos.

Materiales y métodos: Estudio retrospectivo de cohortes de adultos con sepsis (Criterio 3 de la SEPSIS) hospitalizados en una Unidad de Cuidados Intensivos (Quito, Ecuador). Se excluyeron los pacientes con neoplasias o estados de inmunodeficiencia. Se evaluaron diferentes parámetros citométricos y se utilizaron modelos de regresión logística para establecer el rango predictivo de la mortalidad para cada parámetro y las áreas bajo la curva (AUC) para el análisis de sensibilidad.

Resultados: En más de 159 pacientes, la mortalidad fue del 25%. En los no supervivientes, la mediana del APACHE II fue de 25,20 puntos, y la mediana del SOFA fue de 11,18, 10,44 y 10,15 puntos en el momento del ingreso, 48 y 72 horas respectivamente. En cuanto al análisis de sensibilidad para la mortalidad, el punto de corte del EDW fue 14,5% (AUC 0,708), y presentó un OR ajustado de 5,25 (IC 95%: 1,64-16,76, p: 0,005). El punto de corte de MPV fue de 8,45 fL (AUC 0,666), y presentó un OR ajustado de 5,28 (95%CI: 1,72-16,21, p 0,004).

Conclusiones. EDW y MPV son predictores independientes de mortalidad, y deben ser utilizados con escalas o biomarcadores para optimizar el manejo y la terapia de los pacientes con sepsis. Serían una alternativa en los centros donde sólo se dispone de citometría de sangre como prueba analítica.

Palabras clave: Citometría, sepsis, mortalidad, biomarcadores

1 Unidad de Terapia Intensiva, Hospital Pablo Arturo Suarez, Quito, Ecuador;
2 Facultad de Ciencias Medicas, Universidad Central del Ecuador, Quito, Ecuador;
3 Facultad de Medicina Humana, Universidad Científica del Sur, Lima, Peru;
4 Tau-Relaped Group;
5 Facultad de Medicina, Universidad Nacional San Agustin, Arequipa, Peru;
6 Facultad de Medicina, Universidad Nacional Mayor de San Marcos, Lima, Peru;
7 Escuela de Medicina, Universidad Señor de Sipan, Chiclayo, Peru.
* Autor para correspondencia.
Correo electrónico: jbarbozameca@relaped.com
Juan del Corral 937. El Bosque. Trujillo. Peru

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Introduction

Sepsis is a clinical syndrome currently defined in the Sepsis-3 consensus[1] as "a life-threatening organ dysfunction caused by a dysregulated host response to infection", moreover its mortality varies from 20% to 50%[2].

According to the World Health Organization Bulletin 2019, sepsis affects more than 30 million people each year, causing about 6 million deaths (2,3). In economic terms, in the United States, sepsis and septic shock are reported to cost $16,000 and $38,000 annually, respectively, resulting in 13% of the hospital budget[4]. In Ecuador, the picture is no different from global reality[5].

The severity and mortality of sepsis can be predicted and estimated with validated scales, such as the SOFA and Logistic System of Organic Dysfunction (LODS)[5,6]; or by biological markers such as procalcitonin[7], interleukin 6[8-9], C-reactive protein[10], among others. The infrastructure required and the high economic cost make many centers unable to use these tools routinely. It has motivated the search for simple and accessible alternatives; one of them is the comprehensive blood biometry, whose cell lines express modifications that could estimate the severity of the pathology, and generate therapeutic approaches that modify the course of the disease[11].

The systemic inflammatory impact on sepsis affects all hematological cell lines. The red series experiences a decrease in hematocrit, hemoglobin, and global infection, the erythrocytes maintain a constant volume, but morphologically they become spherical and rigid affecting their capacity for deformation and microcirculatory functionality. The erythrocyte distribution width (EDW) is a parameter of anisocytosis that tends to increase in sepsis, these changes have been detected in the first six hours of evolution according to experimental models, and have shown an association with mortality[12].

The mean platelet volume, which reflects platelet activity, has been associated with unfavorable outcomes in several studies, such as mortality in sepsis, suggesting that platelets represent therapeutic targets in sepsis by combining their mechanisms of inflammation and coagulation[13].

Other markers are the indices neutrophil/lymphocyte, monocyte/lymphocyte, platelet/lymphocyte, mean platelet volume/platelet count, which have shown diverse results, however, their values tend to increase in non-survivors, and some of them have shown to be prognostic markers of mortality[14].

Based on this premise, this study aimed to determine the utility of different cytometric parameters and indices as predictors of mortality in septic patients.

Materials and methods

General description of the study

The study design consisted on a retrospective cohort. It was a census of all patients with sepsis from different infectious sites, who were admitted to the Intensive Care Unit of the Pablo Arturo Suárez Hospital in Quito (Ecuador) over a 2-year period.

Selection criteria

We included adult patients (older than 18 years of age) diagnosed with sepsis using the SEPSIS criteria 3 (1). The sites of infection were abdominal, lung, urinary, soft tissue, central nervous system. We excluded patients with neoplasms or previous immunodeficiency states.

Variables

On admission, 48 and 72 hours of hospitalization in the Intensive Care Unit, the cytometric parameters of the hemograms were recorded. These were erythrocyte distribution width, platelet mean volume, platelet count, neutrophil count, lymphocyte count, neutrophil/lymphocyte index (division between the absolute number of neutrophils and the absolute number of lymphocytes) and MPV/platelet ratio (a division of platelet mean volume and the absolute number of platelets). The hemograms were performed by impedance in a Mindray BC-6800 equipment. We collected other parameters: lactate in mmol/L, central venous oxygen saturation in %, and procalcitonin in ng/ml. Finally, the days of hospitalization in the Intensive Care Unit and the status of the discharge as alive or deceased were recorded.

Statistical Analysis

The analyses were carried out with the IBM SPSS version 25 statistical package, for which descriptive statistics were used, using tables and representing the absolute and relative values of the qualitative variables, as well as measures of central tendency and variability for the quantitative variables.

By analyzing the ROC curve, the cut-off point for the parameters of blood cytometry was determined; the areas under the ROC curve, sensitivity, specificity, PPV and NPV, and Odds Ratio (OR) were determined.

Bivariate analysis was performed to compare the clinical characteristics and blood cytometry parameters with the discharge condition of patients with sepsis. For categorical variables, the Chi-square test was applied for quantitative variables as they did not present normality, and the Mann-Whitney test of independent samples was used to compare means.

Multivariate logistic regression analysis with Wald's test was used to determine the predictors of mortality in patients with sepsis using the cut-off points of blood cytometry parameters.

Statistical significance for comparing ratios and means was established for p-value <0.05; the Odds Ratio was considered significant, observing the limits of the 95% confidence interval.

Ethical aspects: Secondary data from the hemograms were routine, so it was not necessary to apply informed consent.

Results

We analyzed 159 patients with sepsis, of which 25.16% (40 patients) had died at discharge; the average age of all patients was 59.47 years; regarding the location of infection, there are no significant differences between the groups (p=0.496); SOFA presented significant differences between non-survivors and survivors with p-value 0.000. On the other hand, differences were observed in the initial APACHE II values with a p-value of 0.000 (Table 1).

With regard to blood cytometry parameters, significant differences were observed for the erythrocyte distribution width (EDW), the MPV, platelets, and the MPV/ platelet ratio with p-values <0.05 when compared to the discharge condition of patients with sepsis. Baseline MPV, platelets/mm^3, MPV/ platelets, neutrophils/mm^3, lymphocytes/mm^3, and other parameters are different between the groups. (Table 2)

For the blood cytometry parameters that presented statistical significance in the bivariate analysis with the exit condition, mortality cut-off points were determined using the ROC curve (Figure 1)

Table 1. Clinical characteristics of patients with sepsis by discharge condition.

Clinical features	Total	Discharge condition		p-value
		Non-survival (n=40)	Survival (n=119)	
Age (mean (SD)) years	59,47 (19,09)	61,97 (19,63)	58,66 (18,93)	0,321
SOFA (mean (SD))				
Initial	8,52 (4,45)	11,18 (3,92)	7,62 (4,27)	0,000*
48 hours	5,82 (3,60)	10,44 (2,99)	5,08 (3,11)	0,000*
72 hours	4,92 (3,60)	10,15 (3,13)	4,08 (2,9)	0,000*
APACHE II initial (mean (SD))	18,36 (8,41)	25,20 (8,94)	16,07 (6,87)	0,000*
Location of infection (n (%))				
Abdominal	66 (41,77)	15 (22,73)	51 (77,27)	0,496
Pulmonary	52 (32,91)	16 (30,77)	36 (69,23)	
Urinary	29 (18,35)	5 (17,24)	24 (82,76)	
Soft parts	7 (4,43)	2 (28,57)	5 (71,43)	
Nervous-central system	4 (2,53)	2 (50,00)	2 (50,00)	
Length of hospitalization mean (SD))	4,75 (4,53)	4,70 (6,81)	4,76 (3,48)	0,938

SD: Standard deviation.
SOFA: Sequential organ failure assessment.
APACHE: Acute physiology and chronic health evaluation II.

The estimate of the area under the curve was significant in predicting mortality with p-values <0.05, for EDW at baseline (0.708) and 48 (0.696) hours, WMV at baseline (0.666), 48 (0.699) and 72 (0.728) hours, and for the WMV/platelet ratio at 48 (0.651) hours. (Table 3)

The cut-off points were determined on the ROC curve using the Youden index; for the EDW at baseline and at 48 hours the cut-off point was ≥14,50%, where the sensitivity was 62.50% at baseline and 69.57% at 48 hours, specificity 61.34% at baseline and 58.93% at 48 hours, PPV 32.21% at baseline and 25, 81% at 48 hours, NPV 82.95% at baseline and 90.41% at 48 hours, plus patients with baseline or 48-hour EDW ≥14,50% are 2.65 and 3.68 times more likely to fail to survive than those with <14.50% values. The MPV at baseline, 48 and 72 hours presented a cut-off point of ≥8,45fL, where the sensitivity was 67.50% at baseline, 78.26% at 48 hours and 72.22% at 72 hours, specificity 65.55% at baseline, 57.14% at 48 hours and 59.22% at 72 hours, PPV 39.71% at baseline, 27, 27% at 48 hours and 23.64% at 72 hours, NPV 85.71% at baseline, 92.75% at 48 hours and 92.42% at 72 hours, plus patients with baseline, 48 or 72 hour MPV ≥8,45fL are 3.95, 4.80 and 3.78 times more likely to not survive than those with <8.45 fL values. Finally, the ratio WMP/platelet presented a cut-off point at ≥4,75, with sensitivity of 60.87%, specificity 64.29%, PPV 25.93%, NPV 88.89%, where patients with WMP/ platelet ≥4,75 are 2.80 times more likely to not survive than those with values <4.75. (Table 4)

The multivariate logistic regression model was used to determine the relationships with mortality using the cut-off points of the blood cytometry parameters. The results obtained showed that the initial EDW with p-value 0.005 and the initial MPV with p-value 0.004 are predictors of mortality, where for initial EDW ≥14,5, the probability of not surviving was increased by 5.25 times, while for MPV ≥8,45 fL the probability of not surviving was increased by 5,28 times. (Table 5)

Discussion

In our study, we evaluated the predictive usefulness of cytometric indicators for mortality in critically ill patients with sepsis; EDW, MPV, platelet count, MPV/platelet ratio were associated with mortality, while neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio were not significant. In the multivariate model with logistic regression, the measurement of EDW and MPV at admission were independent predictors of mortality, i.e., an EDW value greater than or equal to 14.5% and an MPV greater than 8.45 fL, are 5.25 and 5.28 times more likely, respectively, to not survive.

The variability in the size of erythrocytes or anisocytosis is assessed by the EDW; its normal ranges are 12 to 13%. The causal relationship of increased EDW is not well understood, but it is a prognosis of clinical severity and death in different acute and chronic diseases, sepsis among them[11].

Table 2. Comparison of blood cytometry parameters of patients with sepsis by discharge condition.

Blood cytometry parameters	Total	Discharge condition		p-value
		Non- survival(n=40)	Survival (n=119)	
EDW(mean (SD))[1/] %				
Initial	14,66 (2,19)	15,76 (2,44)	14,29 (1,97)	0,001*
48 hours	14,63 (2,36)	15,97 (3,27)	14,37 (2,05)	0,004*
MPV (mean (SD))[1/] fL				
initial	8,38 (1,35)	13,59 (20,45)	8,17 (1,24)	0,001*
48 hours	8,71 (1,34)	9,58 (1,63)	8,53 (1,21)	0,002*
72 hours	8,59 (1,36)	9,46 (1,41)	8,44 (1,3)	0,002*
platelets/mm3 (mean (SD))[1/]				
initial	275843 (149705)	225575 (140855)	292739 (149355)	0,014*
48 hours	250830 (145697)	201913 (136086)	260875 (146144)	0,048*
MPV/platelets (mean (SD))[1/]				
Day 1	5,47 (9,50)	11,56 (17,53)	3,42 (1,57)	0,001*
Day 2	5,85 (13,56)	13,62 (31,93)	4,25 (2,24)	0,014*
Neutrophils/mm3 (mean (SD))[1/]				
initial	11834 (8449)	11845 (8314)	11830 (8528)	0,976
48 hours	10900 (7397)	11487 (8662)	10780 (7148)	0,935
Lymphocytes/mm3 (mean (SD))[1/]				
initial	11834 (8450)	1117 (924)	1208 (1167)	0,645
48 hours	10900 (7397)	1580 (3010)	1231 (1270)	0,306
Neutrophils-Lymphocytes (mean (SD))[1/]				
initial	15,70 (16,30)	17 (18,67)	15,27 (15,51)	0,894
48 hours	17,79 (34,16)	20,59 (22,88)	17,21 (36,1)	0,231
Other parameters				
lactate (mean (SD))[1/] mmol/L	3,31 (3,04)	5,4 (3,99)	2,63 (2,3)	0,000*
initial SatO2VC(mean (SD))[1/] %	69,32 (11,15)	65 (16,43)	70,85 (8,27)	0,259
Procalcitonin (mean SD))[1/]ng/ml	29,80 (44,78)	34,11 (42,08)	28,29 (45,79)	0,139

MPV: Mean platelet volume.
SD: Standard deviation.
EDW: Erythrocyte ditribution width.

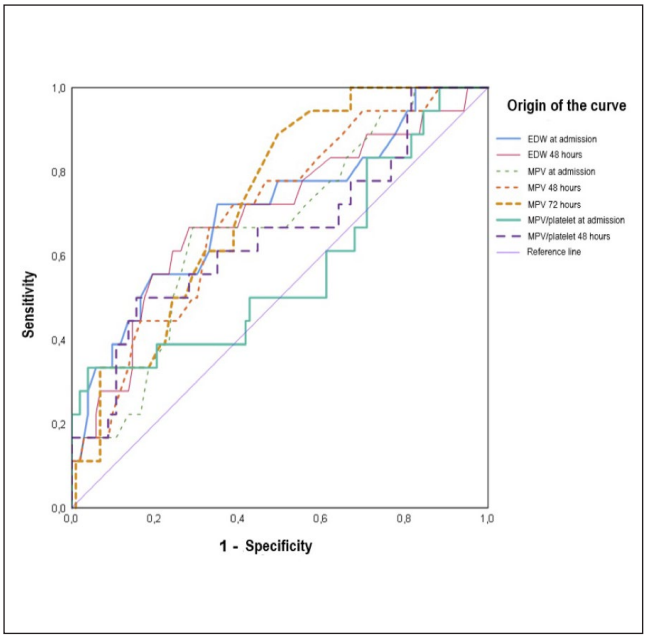

Figure 1. ROC curve for blood cytometry parameters of patients with sepsis to predict mortality.

The MPV is a marker of severity in sepsis; when proinflammatory cytokines are increased, platelets change morphologically from discoid to spherical with pseudopodia, increase their size[15] and can express receptors for immunoglobulin G (IgG), that is to say, they participate in adaptive immunity[16] and Toll type for molecular pattern recognition to pathogens (PAMPs)[11]. Young platelets are larger than old platelets, are more metabolic and enzymatic functional, and have a greater prothrombotic effect due to increased synthesis of thromboxane A2, p-selectin, and glycoprotein IIIa.[17,26] Nishimura et al.[18] identified poor prognosis when platelets are young and large, due to a lower organization of their microtubules.

Regarding the EDW, several studies have determined the association and prediction of mortality. Wang et al.[19] in 602 critical patients with a cut-off point of 14.8%; Cavusoglu et al.[20] in the United States with data collected from critical patients with sepsis in 10 years with a cut-off point of 14.4%; Braun et al.[21] in community pneumonia with a cut-off point of 14.5%, and finally Hunziker et al.[22], in 17922 critically ill patients demonstrated that it is an independent predictor of mortality and by associating it with the Simplified Acute Physiology

Table 3. Test for the area of the ROC curve to predict mortality in patients with sepsis according to blood cytometry parameters

Blood cytometry parameters	area	p-value[a]	IC-95%	
			LI	LS
EDW(mean (SD))[1/] %				
initial	0,708	0,005*	0,569	0,848
48 hours	0,696	0,008*	0,555	0,838
MPV(mean (SD))[1/] fL				
initial	0,666	0,025*	0,535	0,798
48 hours	0,699	0,007*	0,574	0,825
72 hours	0,728	0,002*	0,622	0,835
MPV/platelets (mean (SD))[1/]				
initial	0,573	0,322	0,412	0,735
48 hours	0,651	0,041*	0,501	0,801

EDW: Erythrocyte distribution width. MPM : Mean platelet volume.
SD: Standard deviation.

Score (SPAS II), it improved its prognostic performance and stratification capacity, bringing the area under the curve (AUC) from 0.746 to 0.774 (p < 0.001) for hospital mortality and 0.793 to 0.805 (p < 0.001) for ICU mortality. In our results, the EDW at admission and at 48 hours was significantly associated with mortality and with a cut-off point similar to the studies cited of 14.5% (AUC 0.708 CI 0.569-0.848 p: 0.005) and, at admission, was an independent predictor of mortality with an ORadj of 5.25 (p: 0.005).

Several studies have demonstrated the predictive usefulness of MPV in sepsis, including one by Kim et al.[23], which found it to be an independent predictor of mortality at 28 days in 345 critical patients, and Zampieri et al.[24], which found it to be a strong predictor of mortality at 72 hours in 84 patients; Vardon-Bounes F., et al.[25], who studied the kinetics of MPV and determined the significance of 90-day survival of MPV with HR 3.79 and two meta-analyses, one performed by Tajarernmuang P. et al.[26], in 11 studies (n=3724), which aimed to determine whether there is an association between MPV and mortality in critically ill patients, found a significant association with day three values and identical results were replicated in the meta-analysis by Vélez JL et al.[27], where they analyzed ten studies (n: 1845) with critically ill patients diagnosed with sepsis. In our study, we found an association with mortality of WMV from admission to 72 hours, but in the multivariate model of logistic regression, only MPV > 8.45 fL of admission had an independent predictive value for mortality with an ORa of 5.28. An interesting fact is that in the current SARS-Cov2 pandemic, the MPV / platelet count ratio has been shown to be a useful index to predict severity of viral pneumonia[28].

Other cytometric indicators such as the absolute number of neutrophils and lymphocytes and their neutrophil/lymphocyte ratio, the latter promising under the physiopathological reasoning that in bacterial sepsis the neutrophil count increases and the lymphocyte count decreases, therefore the value of the same increases the greater the severity of the picture, were not useful in predicting mortality, this contrasts with some studies[29-31] and coincides with the results of a previous study by the same authors[32].

The strengths of this study are the concordance of its results with the world literature and that it starts from a low-cost analytical examination to obtain its results; in addition to the low probability of measurement bias by using the same equipment to measure the variables used in the cytometric parameters and indices, but, being single-centered and with a relatively small sample makes it necessary to carry out studies with a greater number of patients to determine if the results are replicable.

In ocnclusion, as our research has demonstrated, cytometric parameters and indices are a tool to determine severity and mortality in sepsis; our study determines that and positions the EDW and initial MPV as independent predictors of mortality; they should be used in association with scales and other validated biomarkers to optimize management and therapy of patients with sepsis and would be an alternative in centers where only blood cytometry is available as an analytical test. The clinical significance of our results relies on cytometry as an alternative in centers where only blood cytometry is available as an analytical test.

Table 4. Statistical predictors of mortality in patients with sepsis by cut-off points of blood cytometry parameters.

Statistics	Blood cytometry parameters					
	EDW initial	EDW 48 hours	MPV initial	MPV 48 hours	MPV 72 hours	MPV/platelets 48 hours
Cut-off points	≥14,5%	≥14,5%	≥8,45 fL	≥8,45 fL	≥8,45 fL	≥4,75
Sensibility	62,50%	69,57%	67,50%	78,26%	72,22%	60,87%
Specificity	61,34%	58,93%	65,55%	57,14%	59,22%	64,29%
PPV	35,21%	25,81%	39,71%	27,27%	23,64%	25,93%
NPV	82,95%	90,41%	85,71%	92,75%	92,42%	88,89%
OR (CI-95%)	2,65* (1,26-5,54)	3,28* (1,25-861)	3,95* (1,84-8,47)	4,80* (1,66-13,84)	3,78* (1,25-11,39)	2,80* (1,11-7,04)

PPV: Positive predictive value. NPV: Negative predictive value.
OR: Odds ratio. CI: Confidence interval.
MPV: Mean platelet volume. EDW: Erythrocyte distribution width.

Table 5. Multivariate relationship to predict mortality in patients with sepsis by cut-off points of blood cytometry parameters.

Variables	B	Wald	p-value	OR	IC-OR 95%	
					Li	Ls
In the model						
EDW (mean SD)[1/] %						
initial ≥14,5%	1,66	7,83	0,005*	5,25**	1,64	16,76
MPV (mean SD)[1/] fL						
initial ≥8,45 fL	1,66	8,44	0,004*	5,28**	1,72	16,21
Excluded from model						
EDW (mean SD)[1/] %						
48 hours ≥14,5%		0,01	0,918			
MPV (mean SD)[1/] fL						
48 hours ≥8,45 fL		1,77	0,184			
72 hours ≥8,45 fL		3,78	0,052			
MPV/platelets (mean SD)[1/]						
48 hours ≥4,75		2,26	0,133			

EDW: Erythrocyte distribution width.
MPV: Mean platelet volume. SD: Standard deviation.

Ethical disclosures

Protection of human and animal subjects. This research was approved by the Institutional Review Board.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this article.

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