

The utility of mean platelet volume delta (Δ VPM) and mean platelet volume / platelet index as predictors of mortality in patients with Sepsis and Septic Shock.

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ABSTRACT

Background. Sepsis and septic shock are the most severe clinical expressions of infection, despite having characterized several decades ago, remain as a diagnostic challenging and this can delay treatment and increasing hospital cost secondary to this pathology.

Our objective was to determine the usefulness of the mean platelet volume delta (Δ VPM) as a predictor of mortality.

Methodology. We performed an observational and descriptive study with 83 patients with Sepsis and / or septic shock criteria, from May 1, 2017 to August 1, 2017. Survival analysis was performed using Kaplan and Meier tables and was corroborated by the Long Rank test. The prognostic value through the proportional risk of Cox.

Results. Thirty-seven patients (44.6%) died because of the septic process. A univariate Cox regression analysis revealed a MPV / platelet index at admission of less than 4 was associated with a significant reduction in the risk of mortality from sepsis or septic shock at 60 days (HR, 0.236; 95% CI, 0.083-0.671; $p = 0.007$). The DVPM was not significantly associated with a reduction in the risk of mortality (HR, 0.373, 95% CI, 0.132-1.057, $p = 0.640$).

Conclusion. The platelet parameters are economical and available, providing diagnostic and prognostic results, avoiding costs, time and special tests. The VPM / PLQ index could be an effective "Alert System" in early sepsis.

Key words: Sepsis, septic shock, mean platelet volume, medium platelet volume delta.

1 BACKGROUND

Sepsis is a syndrome composed of physiological, pathological and biochemical alterations caused by an infection. In recent decades, it has been considered a public health concern that generates high costs, although the exact incidence is unknown, there are indicators that place this pathology as the main cause of mortality in critically ill patients worldwide². Since the implementation of various protocols such as early goal-directed therapy, a decrease in mortality from sepsis has been achieved, however the

risk of mortality and morbidity remains high. Which we can associate with a delay in diagnosis and treatment³⁻⁴⁻⁵.

It is not uncommon for the hematological system to be affected by the significant inflammation present in critically ill patients. Hematological profiles including hematocrit, leukocyte count and platelet count have been used in widely accepted prognostic scales such as the sequenced organ failure assessment (SOFA) and the multiple organ dysfunction scale (MODS)⁶. Within the pathophysiology we find the release of pro and anti-inflammatory cytokines generating alterations in the coagulation cascade, such as prolongation of PT (prothrombin time) and aPTT (activated thromboplastin time), in addition to a decrease in platelets⁷⁻⁸. It is important to add that there is also peripheral non-immune destruction and marrow suppression which contribute to thrombocytopenia in septic patients⁹. The marked decrease in platelets correlates with the prognosis¹⁰. Therefore, several investigations have been interested in platelet indices, such as mean platelet volume (MPV). The mean platelet volume is a platelet index available since 1970, it is an accurate measure of platelet size and platelet reactivity¹¹⁻¹². Platelets with high MPV contain a greater number of granules and prothrombotic material, which conditions greater platelet aggregation and adhesion¹³. High MPV values usually reflect compensatory bone marrow production after stress-induced destruction in sepsis¹⁴. Numerous studies suggest what changes in MPV are observed during the infectious process, sepsis, coronary artery disease, cerebrovascular disease, venous and arterial thrombosis, and chronic inflammatory diseases¹⁵⁻¹⁶.

The use of serum biomarkers has the potential to significantly improve the clinician's ability to make a diagnosis, stratify risk, and provide optimal treatment for patients with sepsis. Recent findings suggest that mean platelet volume, Δ VPM, and MPV / Platelet ratio, may be useful as a prognostic biomarker in patients with sepsis. Ho Oh et al observed a superiority of the MPV / platelet index versus MPV alone in predicting mortality at 28 days¹⁷. Likewise, Zampieri found that non-surviving patients showed higher Δ VPM levels¹⁸.

Sepsis and its clinical spectra still continue to be one of the pathologies that represents the greatest complexity for clinicians. The delay in diagnosis and treatment conditions an increase in hospital stay days, a greater risk of morbidity and mortality, and an increase in the financial burden for the hospital. The agency for research and quality of health care lists sepsis as the most expensive condition treated in hospitals in the United States, establishing a cost of more than 20 billion in 2011, with annual increases of 11.9%. This pathology continues to be the primary cause of death associated with infection despite advances in medicine. In countries like Mexico, sepsis represents 60-80% of death per year.

Early detection and timely treatment of sepsis have an enormous impact on the prognosis of patients, which is why numerous investigations have tried to establish one or more biomarkers that can improve the outcome of sepsis.

For this reason, it was considered in our study that the use of these platelet indices can be used as predictors of mortality in patients with sepsis and septic shock. In this way, we provide a reliable, accessible tool to carry out timely detection of patients with a higher risk of complications, with the aim of carrying out timely interventions that increase their probability of survival. It is important to emphasize that the availability of biomarkers that support the stratification of patients with sepsis is scarce in our hospital environment and not always accessible, which is why it is considered of vital importance to establish the reliability of tools such as Δ VPM and MPV / platelet index, which are constantly available to the clinician 24 hours a day without the need for special blood sampling. Establishing these types of tools in the management of sepsis represents a significant cost containment, when compared with the costs produced by the use of other biomarkers such as lactate and procacyltonin.

The objective of this study was to determine the usefulness of the Mean Platelet Volume delta (Δ VPM) and the MPV / Platelet index as predictors of mortality in patients with Sepsis and Shock.

2 PATIENTS AND STUDY DESIGN.

An observational, longitudinal, prospective and descriptive study was carried out, with data obtained from patients with a diagnosis of Sepsis and septic shock, according to the third definition of Sepsis, admitted to the Regional General Hospital No. 1 “Lic. Ignacio García Téllez”. This study was reviewed and approved by the Local Research and Ethics Committee in Health Research, Hospital General Regional Numero 1, Yucatán.

Eighty-three patients older than 18 years admitted to the emergency department, internal medicine and intensive care in the period from May 1 to August 1, 2017, with a non-probabilistic sampling technique were included. A blood sample was taken from all patients for processing of hematic biometry and biochemical parameters at hospital admission and 72 hours. Thus, information was also collected from the clinical record, laboratory results, measured hemodynamic parameters, and the SOFA and APACHE II scale score was calculated. With the results of MPV and platelets at admission and at 72 hours, the Δ VPM and MPV / platelet index were calculated. Sepsis was defined as life-threatening organ dysfunction, caused by an alteration in the host's response to infection, always emphasizing a non-homeostatic response to infection. Septic shock was defined as a subset of sepsis in which underlying abnormalities are found in circulation and cellular metabolism, which can be objectively characterized as persistent hypotension with mean arterial pressure values < 65 mmHg and / or hyperlactatemia > 2 mmol a despite the use of vasopressors and adequate fluid resuscitation. The Δ VPM and MPV / Platelet index were defined as the percentage of change in MPV in the first 72 hours after admission (Δ MPV = $[(72 \text{ hrs MPV} - \text{admission MPV}) / \text{admission MPV}] \times 100$) and MPV / Platelet index as $[\text{VPM} / \text{Platelet} (\text{count} / 1000)] \times 100$, respectively.

3 STATISTIC ANALYSIS

In the statistical analysis, it was performed in means, modes, medians, minimum and maximum ranges, as well as standard deviations for continuous variables, while categorical variables were expressed with numbers and percentages. Mortality was assessed as the primary outcome. The comparison of the parameters obtained between the groups of survivors and non-survivors was performed using the Mann Whitney U test for continuous variables and chi square for categorical variables. The correlation between Δ VPM, MPV, MPV / Platelet index at admission, APACHE II score and SOFA were processed using a Spearman correlation analysis. Survival was analyzed using Kaplan and Meyer graphs and corroborated using the Long Rank test. The prognostic value of Δ VPM and MPV / Platelet index at admission and 72 hours was evaluated using the Cox proportional hazard expressed in Hazard Ratios (HR) with a confidence interval of 95%. The value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS for Windows version 22.0 (IBM corporation).

4 RESULTS

The mean age of the patients studied was 64.89 years (+ 13.93 years). 50.6% (42 patients) were female and 49.4% (41 patients) were male. Of the total of patients recruited, 55.4% (46 patients) were censored; on the contrary, 44.6% (37 patients) died as a direct cause of the septic process. The main etiology of the septic process was pulmonary infection with 28.9% (24 cases), followed by urinary tract infections with 26.5% (22 cases), abdominal infections with 25.3% (21 cases) and finally soft tissue infections with 19.3% (16 cases).

The mean MPV / platelet index at admission was 7.5 and 12.7 at 72 hours in the group of non-survivors and in the survivors it was 4.6 and 5.5 respectively ($p < 0.001$ and $p < 0.001$). Regarding the Δ VPM, it was 8.0 fL in the survivors, increasing considerably to 8.6 fL in the non-survivors ($p < 0.001$) Table 1.

The Kaplan and Meier graphs described the probability of survival at 60 days, finding greater survival in patients with Δ VPM < 3 fL ($p < 0.049$). Patients with an MPV / platelet index at admission and 72 hours < 4 fL showed greater survival ($p < 0.007$). Spearman's correlation analysis revealed a significantly positive correlation between the MPV / platelet index at admission and at 72 hours ($r = 0.719$; $p < 0.001$). Likewise, the MPV / platelets index at 72 hours showed a significantly positive correlation with the SOFA score at admission ($r = 0.320$; $p = 0.004$). In contrast, the Δ VPM did not have a significant correlation with any of the variables. A univariate Cox regression analysis revealed that an MPV / platelet index on admission < 4 was associated with a significant reduction in the risk of mortality from sepsis or septic shock at 60 days (HR, 0.236; 95% CI, 0.083-0.671; $p = 0.007$). In addition, the

MPV / platelet index at 72 hours < 4 was also associated with a significant reduction in the risk of mortality from sepsis or septic shock at 60 days (HR, 0.190; 95% CI, 0.058-0.625; $p = 0.006$). Δ VPM was not significantly associated with a reduction in the risk of mortality from sepsis or septic shock at 60 days (HR, 0.373; 95% CI, 0.132-1.057; $p = 0.640$). In a multivariate analysis, the MPV / platelet index on admission revealed to be a significant risk factor for mortality from sepsis or septic shock when adjusted for age, sex, APACHE II score, SOFA score, degree of acute kidney injury, and origin. of the infectious site (HR, 2.919; 95% CI, 1.254-6.797; $p = 0.013$). Additionally, the MPV / platelets index at 72 hours was similarly shown to be a significant risk factor when adjusted with the same variables (HR, 7.289; 95% CI, 1.784-29.786; $p = 0.006$).

5 DISCUSSION

Due to the impact of septic processes, it is necessary to establish accessible prognostic markers to discriminate severity in patients with sepsis and septic shock. There is ample literature in which an attempt has been made to document the relevance of platelet parameters in patients diagnosed with sepsis. Among the parameters studied are MPV, platelet index, platelet distribution width, delta MPV, MPV / Platelet index, among others. This study was carried out with the intention of establishing the correlation between MPV / Platelet index and MPV delta with mortality in patients diagnosed with sepsis and septic shock. Venkata et al. Found an association between thrombocytopenia and mortality, as well as a higher incidence of acute renal failure in contrast to patients who do not present thrombocytopenia; however, despite this, they did not find an association with the isolated platelet count at admission as a prognostic factor in patients with sepsis¹⁹. The platelet count in our population of survivors and non-survivors did have a significant difference both at admission and at 72 hours. Regarding MPV values at admission and at 72 hours, we also found a significant difference between both groups. On the other hand, the MPV delta did not show a significant difference between both groups, although it showed a relationship with mortality when figures greater than 3 fL were presented, the risk ratio was not significant. In the same way, the MPV / Platelet index at admission and 72 hours showed an association with an increase in mortality when figures greater than 4 fL were obtained, with a significant risk ratio for both the index obtained at admission and at 72 hours.

In contrast to our results, Kim et al demonstrated that both the platelet count and the MPV value in non-surviving patients with sepsis and septic shock were higher than in the survivors during the first 72 hours²⁰. Now the increase in baseline MPV levels had tried to establish it as an independent risk factor for mortality, seeking to establish this. Oh et al found that both MPV and platelet count alone do not predict 28-day mortality in patients with sepsis¹⁷. Although the follow-up in our study was not as long, higher levels were evidenced in non-survivors, however it was not possible to establish a

prognostic factor for mortality. Kim et al found that MPV delta was a significantly useful marker for predicting 28-day mortality²⁰. Contrary to what was observed in our study, where no utility was shown to predict mortality from the MPV delta.

Within the literature, there is less evidence regarding the MPV / Platelet index, Azab et al were the first to establish superiority of the MPV / Platelet Index over MPV alone, as a prognostic factor in patients with AMI without ST elevation²¹. Once this relationship with the level of inflammation present in other pathologies has been established, in our study, a univariate analysis revealed that an MPV / Platelet index at admission and 72 hours < 4 fL are useful as predictors of survival at 60 days. On the contrary, when performing a multivariate analysis adjusted to different confounders, it was found that MPV / Platelet index > 4 fL both at admission and 72 hours were related to an increase in mortality at 60 days in patients with sepsis and septic shock. Similarly, a high correlation was observed between the MPV / Platelets index at admission and 72 hours with the SOFA scale, MPV levels and platelet counts.

This study has several limitations, firstly, the recruited population was from a single hospital, and secondly, there were variants that were not taken into consideration, such as the smoking habit of the patients, the intake of drugs such as antiplatelet agents and non-steroidal anti-inflammatory drugs 7-10 days prior to admission, since these drugs can modify MPV values.

6 CONCLUSIONS

In contrast to other Δ VPM studies, our study showed that it is not useful for predicting mortality, however, in patients with sepsis and septic shock an MPV / Platelet index greater than 4 fL did prove useful as a predictor of mortality both when admission as at 72 hours, indicating the potential need for more intensive monitoring and management due to its close association with early mortality.

The platelet count as well as its indices are inexpensive and are available in routine laboratories, so serial measurements could be performed in patients with sepsis and septic shock, providing results for both diagnosis and severity, avoiding costs, long times and special tests. additionally, for all this the MPV / Platelet index could be an effective "Alert System" in early stages of sepsis.

A greater number of studies are required in the future to validate the usefulness of platelet indices as prognostic markers in patients with sepsis, in addition to establishing reference values for MPV, as well as the association of these values with the etiological agent of infectious processes.

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Table 1. Clinical characteristics and biochemical variables

Variable	Total (n= 83)	Survivors (n= 46)	Non survivors (n= 37)	Value of P
Demographic data				
Age	64.89 ± 13.93	64.22 ± 13.92	65.46 ± 13.67	0.851
APACHE II	17.21 ± 6.24	16.43 ± 6.62	17.82 ± 5.48	0.258
SOFA	8.06 ± 2.52	7.51 ± 2.60	8.63 ± 2.36	0.007
Hematic cytometry data				
Leukocytes (x 10 ³ / mm ³)	19.23 ± 7.66	17.98 ± 7.46	19.79 ± 7.84	0.313
Hemoglobin (g/dL)	10.24 ± 2.27	10.21 ± 2.35	10.58 ± 2.36	0.531
Platelets admission (x10 ³ / mm ³)	218.71 ± 117.20	254.78 ± 118.08	174.13 ± 103.44	0.002
Platelets 72 hrs (x10 ³ / mm ³)	173.48 ± 107.80	222.92 ± 115.96	122.23 ± 67.35	< 0.001
MPV admission (fL)	8.88 ± 0.84	8.63 ± 0.85	9.18 ± 0.79	0.014
MPV 72 hrs (fL)	9.03 ± 1.03	8.49 ± 0.94	9.66 ± 0.75	< 0.001
Δ MPV (fL)	8.63 ± 6.34	8.09 ± 7.01	8.67 ± 5.16	0.515
MPV/Platelets admission	5.85 ± 5.08	4.64 ± 3.78	7.58 ± 6.24	0.001
MPV/Platelets 72 hrs.	8.98 ± 11.14	5.5 ± 4.89	12.78 ± 14.6	< 0.001
Data are means and standard deviations. APACHE II Acute Physiology and Chronic Health Evaluation II; SOFA Sequential Organ Failure assessment; Mean Platelet Volume MPV.				
The value of P compares between survivors and non-survivors.				

Figure 1. Kapla-Meier. Probability of survival at 60 days.

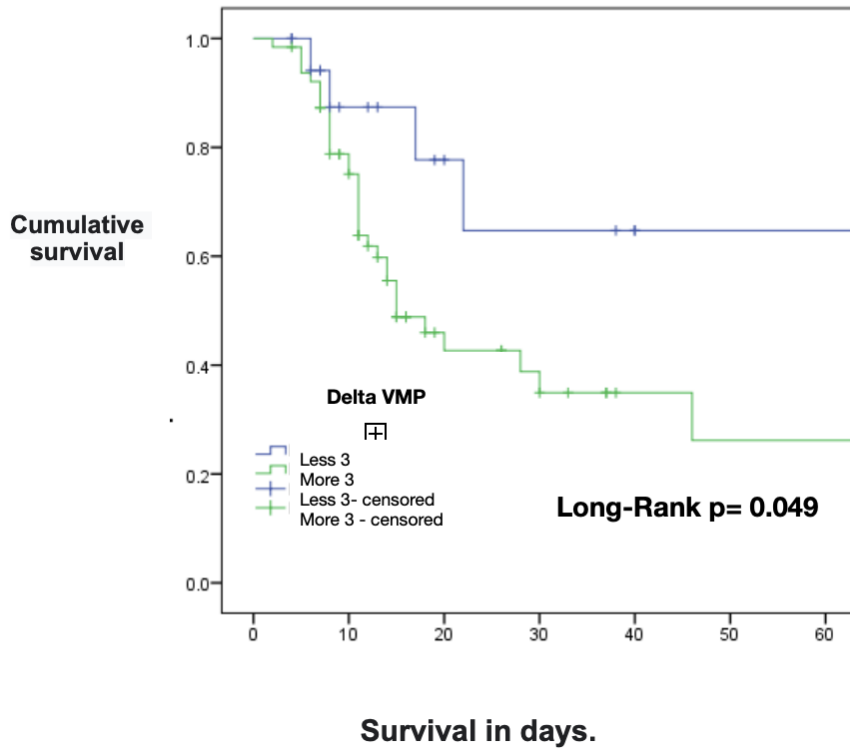


Figure 2. Kapla-Meier. Probability of survival at 60 days.

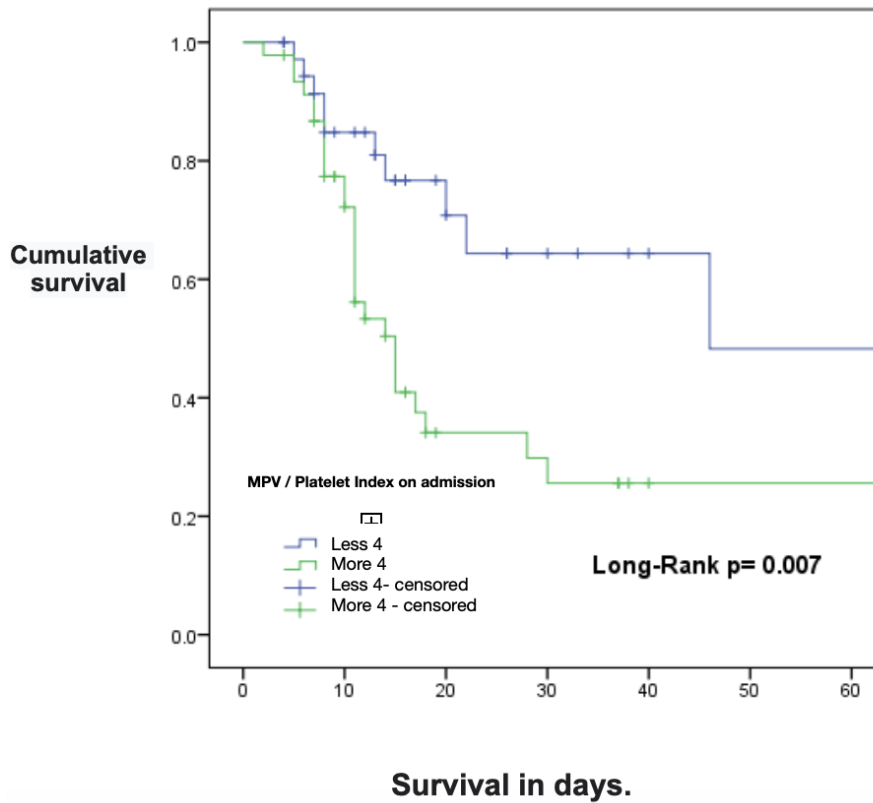


Figure 3. Kapla-Meier. Probability of survival at 60 days.

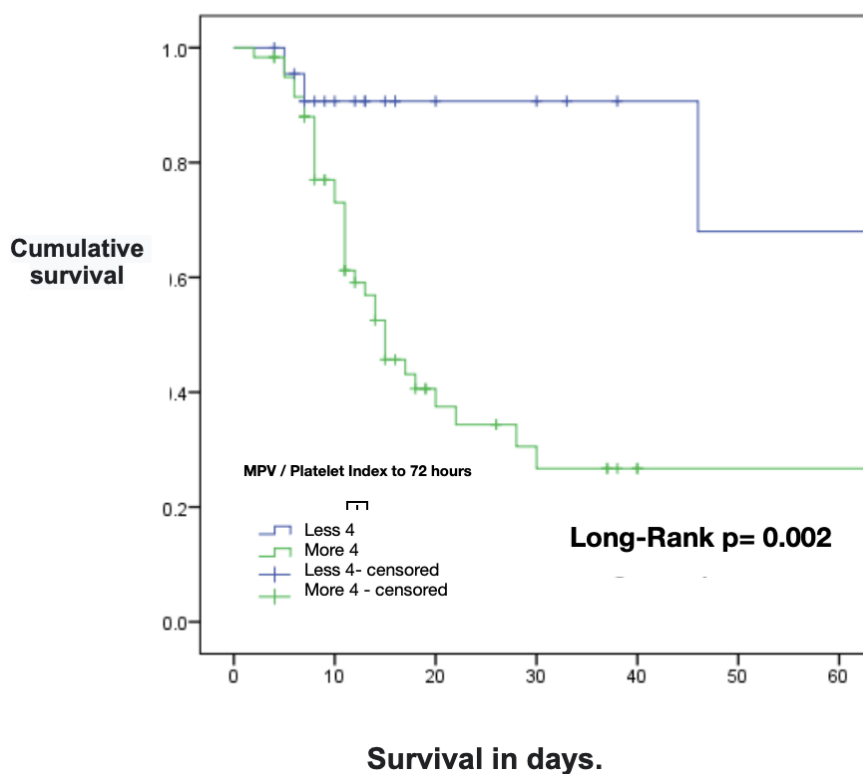


Table 2. Correlation between Δ VPM, admission MPV/platelet index, MPV/ platelet 72hrs and variables.

Variable	DVPM		Admission MPV/Platelet index		72 hours MPV/Platelet index	
	r	Valor P	r	Valor p	r	Valor p
Age	-0.140	0.902	-0.340	0.761	-0.067	0.550
APACHE II	-0.930	0.402	-0.009	0.935	0.080	0.489
SOFA	-0.770	0.500	0.080	0.482	0.320	0.004
Leukocytes (x 10 ³ / mm ³)	-0.120	0.285	-0.021	0.854	0.048	0.669
Hemoglobin (g/dL)	0.350	0.752	-0.047	0.675	-0.016	0.888
Platelets admission x10 ³ / mm ³	-0.079	0.479	-0.988	0.000	-0.711	0.000
Platelets 72 hrs (x10 ³ / mm ³)	-0.180	0.103	-0.724	0.000	-0.985	0.000
MPV admission (fL)	-0.147	0.185	0.338	0.002	0.235	0.032
MPV 72 hrs (fL)	0.007	0.949	0.432	0.000	0.590	0.000
Δ MPV (fL)	N/A	N/A	0.053	0.633	0.161	0.147
MPV/Platelets admission	0.053	0.633	N/A	N/A	0.719	0.000

MPV/Platelets 72 hrs.	0.161	0.147	0.719	0.000	N/A	N/A
APACHE II Acute Physiology and Chronic Health Evaluation II; SOFA Sequential Organ Failure assessment; MPV Mean Platelet Volumen.						