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Review article:

Mean platelet volume and neutrophil-lymphocyte ratio as predictors of mortality in patients with sepsis and septic shock

Volumen medio plaquetario e índice neutrófilo-linfocito como predictores de mortalidad en pacientes con sepsis y choque séptico

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Abstract

Sepsis is a disease with high mortality, particularly in developing countries whose severity and prognosis are estimated by scales such as the Acute Physiology and Chronic Health disease Classification System II (APACHE II) and the Sequential Organ Failure Assessment (SOFA). Currently, there are multiple parameters and cell markers that have been found useful to improve these scales utility. Thus, the mean platelet volume (MPV) and the neutrophil to lymphocyte ratio (NLR) have taken special attention, since their easy access and cost make them a potential diagnostic and prognostic tools in critically ill patients with sepsis. Due to the variability on these markers cut-offs in previous studies, it is difficult to determine the appropriate value to indicate their efficacy as mortality predictors. However, the evidence suggests that a VMP value ≥ 9 fL would be representative to predict mortality. On the other hand, no cut-off point has been established for NLR but its usefulness as a diagnostic index of infection has been demonstrated. In this study, a literature search was carried out in the MEDLINE, LILACS and WEB of SCIENCES databases, using the keywords sepsis, APACHE, SOFA, Mean Platelet Volume, Neutrophil-lymphocyte ratio.

Keywords: Sepsis, APACHE, SOFA Scale, Mean Platelet Volume

Resumen

La sepsis es una enfermedad con alta mortalidad, más aún en países subdesarrollados, su gravedad y pronóstico se estiman por escalas conocidas como el Acute Physiology and Chronic Health disease Classification System II (APACHE II) y el Sequential Organ Failure Assessment (SOFA). En la actualidad, existen múltiples parámetros e índices celulares que se postulan como candidatos para convertirse en factores eficaces que potencien la utilidad de las escalas antes mencionadas.

Es así que el volumen medio plaquetario (VMP) y el índice neutrófilo-linfocito (INL) han tomado protagonismo, ya que su fácil acceso y costo los convierten en un potencial recurso diagnóstico y pronóstico para pacientes en estado crítico con sepsis. Existe evidencia variable en cada uno de ellos, pero resulta difícil determinar un punto de corte establecido que marque eficacia, sin embargo, la evidencia sugiere que para el VMP un valor mayor o igual a 9 fL sería representativo para predecir mortalidad, mientras que para el INL aún no se puede sugerir un punto de corte, pero sí se establece su utilidad acertada como índice diagnóstico de infección. Se realizó una búsqueda de información en las bases de datos MEDLINE, LILACS y WEB of SCIENCES, con las palabras clave en inglés (Sepsis, APACHE, SOFA, Mean Platelet Volume, Neutrophil-lymphocyte index) y en español (Sepsis, APACHE, SOFA, Volumen Medio plaquetario, Índice Neutrófilo-Linfocito).

Palabras clave: Sepsis, APACHE, Escala SOFA, Volumen Plaquetario Medio

Introduction:

Sepsis is defined as a deregulated response to infection[1] that encompasses high mortality in intensive care units (ICU). It is estimated that sepsis mortality rate is close to 30% in developed countries, reaching up to 80% in developing countries [2-3].

In the United States, the incidence shows 3 cases per 1,000 inhabitants (751,000 affected per year) and in Spain it reaches 104 cases per 100,000 inhabitants per year, with a mortality rate of 20.5%. Likewise, septic shock occurs in 31 cases per 100,000 inhabitants each year, with a mortality rate of 45.7% [4]. Ecuador does not present reliable statistics, but it is estimated that mortality rates due to this illness are similar to those reported in the region.

Sepsis is an important health problem due to its incidence, morbidity and mortality rates, which requires the adoption of specific measures for an early diagnosis and treatment. For instance, using early antibiotic treatment has shown to reduce progress to advanced stages such as septic shock and dysfunction (BMD) and thereby decreasing both mortality and sequelae after discharge from the ICU [4].

Several validated scales are used to predict the severity and mortality of sepsis like APACHE, SOFA and the Logistic System of Organ Dysfunction (LODS) [5]. At the moment, biomarkers such as procalcitonin, C- reactive protein, interleukin 6, among others, are being used as sepsis indicators, however, given their high cost, are difficult to acquire in most medical centers. In this context, the MPV and the NLR have taken an important role as predictors of severity and mortality associated to sepsis, since they are derived from routine blood tests (hematic biometry) and more economic to perform, contributing to an early identification of the problem and subsequent treatment [6-7].

Role of platelets in sepsis

Platelets play a fundamental role in the mechanism of blood coagulation. These cell fragments lack of nucleus and deoxyribonucleic acid (DNA) but contain messenger ribonucleic acid (mRNA) derived from the megakaryocyte. This precursor cell is located mainly at the medullary level and possess a production capacity ranging from one thousand to three thousand platelets, these cells circulate in the blood for approximately ten days [8].

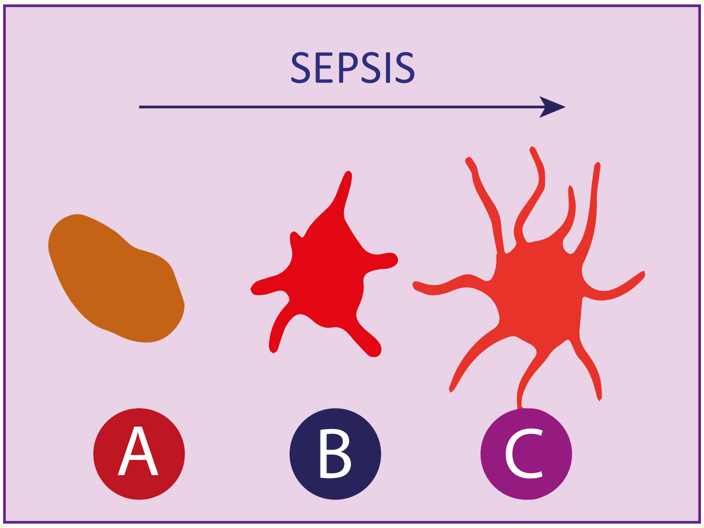
Four types of platelet granules are known: alpha granules, dense granules, lysosomes and T granules, the latter still under study. Large platelets contain an excess of α- granules enhancing their prothrombotic activity, by means of releasing factors such as P-selectin, chemotactic factor, platelet factor, among others which in situations of metabolic stress are prone to form more clots.

In addition, large platelets have an increased enzymatic and metabolic activity compared to small platelets, resulting in the increase in thromboxane A2 and B2 and decreased thrombomodulin and glycoprotein IIb IIIa receptor expression. These particular variations in large platelets and their environment give them the ability to become reticulated, a characteristic that makes them poorly responsive to antiplatelet treatment [8-9].

The endothelium damage related to inflammatory and infectious diseases, including sepsis, is directly linked to failure in the primary hemostasis process, resulting in defective repair, where inflammatory mediators and activated platelets can trigger thrombotic phenomena [10].

The total platelet mass is conformed by the plateletcrit and the mean platelet volume. It has been found an inverse relationship between the platelet size and the number of platelets. A decrease in plateletcrit stimulates thrombopoietin and subsequently the megakaryocyte modifies its nuclear structure, making it lobulated with a large amount of DNA, leading to form larger platelets with a higher mean platelet volume, which is characteristic of destructive thrombocytopenia. On the contrary, the mean platelet volume will be lower in thrombocytopenias that occur in marrow aplasia or hypoplasia (figure 1) [11-12].

Figure 1. *Morphological changes of platelets during sepsis.*



A small inactivated discoid platelet is seen in A; *a change towards a spherical shape can be seen, with pseudopods and an increase in their volume, in B and C.*

Source: *The author*

Microthrombotic events are key in the pathophysiology of sepsis. Platelets represent therapeutic targets due to their inflammation and coagulation mechanisms that promote endothelial damage by the expression and release of cytokines, chemokines and surface molecules that are stored in platelet granules and triggers the recruitment of leukocytes to the injured tissue.

The stimulation of thrombopoietin over the megakaryocyte changes its structure by emitting elongated pseudopodia into a structure called proplatelet that promotes the formation of young platelets, that are characterized by a larger size and greater prothrombotic activity compared to old platelets. [13-14-15].

According to sepsis pathophysiology, young platelets are known to maintain an excessive activity in response to the stimulus generated by proinflammatory interleukins, consequently, increasing in size and modifying its morphology to a spherical shape [16]. In addition, they actively participate in innate and adaptive immunity by expressing Toll-like transmembrane receptors, which recognize pathogen-associated molecular patterns (PAMPs) and surface receptors for immunoglobulin G, respectively. Nishimura et al. [17] demonstrated that young platelets promote negative outcomes in sepsis due to their functional differences.

Mean Platelet Volume Measurement Measuring the MPV is complex from a technical point of view, therefore this parameter is not widely used on a daily basis. One of the most used techniques for its measurement is the Beckman-Coulter system that uses impedanciometry to determine the MPV through an adjusted platelet curve and laser scattering at two angles with a platelet histogram calculated by the highest scattering angle. The results obtained from these two modalities of MVP measurement have been correlated, obtaining around a 40% difference between them. It is worth mentioning that there is no standardized calibration for these techniques. The type of anticoagulant affects the final MVP measurement. In fact, it was observed a progressive increase in platelet size when EDTA was used, in contrast to the samples processed employing citrate as anticoagulant [12].

Locally, tubes containing 7.5 mg of tripotassium EDTA salts are used widely to analyze platelets and their parameters, since this anticoagulant protects them by reducing their activation and minimizing damage caused by the contact of blood with the glass tube [18].

Mean platelet volume in sepsis Several works have studied the behavior of the MVP in different scenarios. Velez P, et al. conducted a prospective, observational, longitudinal study with 125 patients with sepsis and 125 patients without sepsis admitted to the ICU. The MVP was evaluated at admission and on day 3 of hospitalization. The results showed that based on a cut-off point of 9.85 fL, the MVP obtained an area under the curve (AUC) of 0.58, S: 30.48%, E: 88.76%, PPV 76.20%, NPV 52%, odds ratio (OR: 3.30). It was concluded that this parameter value is higher in patients with sepsis [19].

Other studies carried out by the same group associated an increase in mortality in critically ill patients with an MPV > 8.7 fL (AUC: 0.87) [20-21].

Comparably, a cut-off point ≥ 8.45 fL at the onset of sepsis showed a high probability of not surviving [22]. Similar results were obtained by researchers from the Klinikum St. Georg (Leipzig, Germany) [23] evaluating 151 patients with documented sepsis where this parameter was positively evaluated as a predictor of mortality at the onset of symptoms, during hospitalization and the report of positive blood cultures. Sánchez-Calzada et al, [24] through a prospective study including 202 patients, concluded that the MPV < 7.7 fL is a parameter that can rule out infectious etiology. Tajarernmuang et al. [25] performed a meta-analysis of 11 observational studies where 3,274 patients in critical condition were included. The results obtained concluded that an increased value of MPV at day 3 is a good biomarker of mortality. Another meta-analysis carried out by 7 included 10 studies that evaluated MPV in critically ill patients with sepsis, concluding that increased MPV values are associated with higher mortality rates, especially if the evaluation is performed 72 hours after clinical evolution. Yalavarthi et al, in 2018[26], observed the behavior of platelet indexes (MPV, platelet count and distribution width) in patients with immune thrombocytopenia, thrombocytopenia of non-immunological causes (sepsis) and other causes, concluding that, given the presence of thrombocytopenia due to accelerated platelet destruction, the MPV had a significant increase.

Estrada R, et al [27], performed a retrospective class study including 98 patients from the emergency service. They concluded that a MPV value > 9.2 fL is a strong predictor of mortality in patients with sepsis and septic shock at day 28, and showed an area under the curve of 0.64, positive predictive value (PPV) 56.2%, negative predictive value (NPV) 74.2%, sensitivity (SE) 51.4%, specificity (SP) 77.7%. Importance of lymphocytes and neutrophils within the immune response mechanisms in sepsis The innate immune response triggers a set of immediate cellular reactions to control and eradicate an infectious agent.

For this purpose, the action of immunological effectors such as dendritic cells and phagocytic polymorphonuclear cells (neutrophils and macrophages) is essential.

These cells function through the action of pattern recognition receptors (PRR) located at their cell membrane. Other immune cells such as macrophages, neutrophils and monocytes also have these receptors in their intracellular organelles.

Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD) receptors are the best-known types of PRR that are responsible of recognizing PAMPs and damage-associated molecular patterns (DAMPs). The latter are cytoplasmic, nuclear and mitochondrial structures of the bacterium that have inflammatory characteristics when they pass into the extracellular medium. Examples of these are adenosine triphosphate (ATP), mitochondrial deoxyribonucleic acid (mDNA), heat shock proteins (HSP), extracellular mitochondria, among others [28-29].

The lipopolysaccharide of the cell membrane of Gram-negative bacteria that is recognized by TLR-4 and the peptidoglycan of Gram-positive bacteria whose effector receptor is TLR-2, are considered the most relevant PAMPs. Once these structures are recognized, the signaling pathway is initiated by the action of the nuclear transcription factor kappa b (NF- kb), which carries the signal to the nucleus, where cell activation occurs and all the genes involved are expressed in the subsequent inflammatory response with the production of proinflammatory interleukins (IL) (IL-1, IL-6), tumor necrosis factor alpha (TNF-α), chemokines such as cell adhesion molecules type 1 (CAM 1), vascular cell adhesion molecules type I (VCAM-I) and vasodilators such as nitric oxide, among others [30-31].

Neutrophils are considered key cells within the innate immune system, as they recognize and destroy pathogens through processes such as adhesion, chemotaxis, phagocytosis, release of cytotoxic molecules, and netosis (32), followed by death by apoptosis. In severe sepsis, this regulation does not exist, consequently there is an excessive activation of neutrophils that lead them to a prolonged life, thus favoring endothelial dysfunction and cytotoxicity. Once they are activated by antigen-presenting cells, helper T lymphocytes are considered protagonists of the adaptive immune response, since they maintain a proinflammatory state. In severe sepsis, the accelerated

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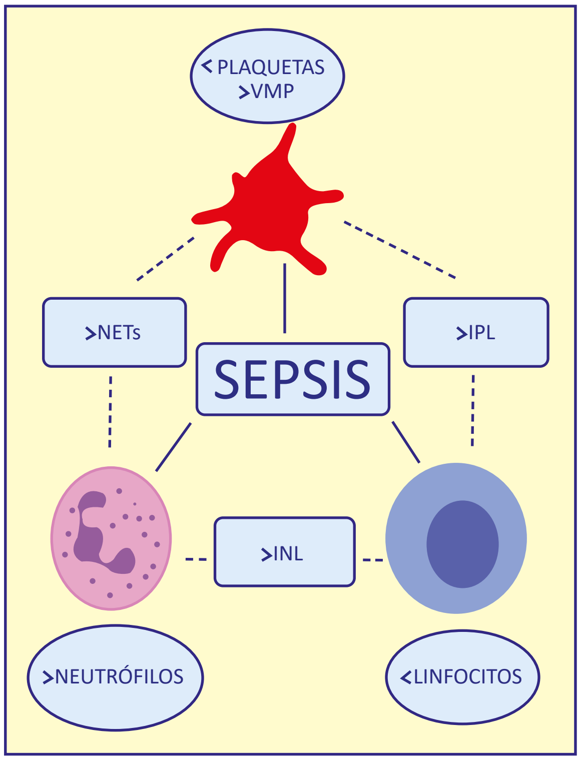
apoptosis of this cell line is characteristic, which leads to its depletion and loss of its regulatory functions. [33]

Similarly, local or systemic inflammation produces physiological and structural changes on the endothelial glycocalyx, mainly in the initial stages of sepsis, where the inadequate regulation may result in irreversible endothelial damage. In this context, neutrophils and monocytes maintain an ordered balance between inflammatory and anti-inflammatory factors. If this balance is disrupted, the action of cytokines and proinflammatory compounds is enhanced, resulting in the externalization and overexpression of molecules such as ICAM-1 and VCAM- 1 (covered by the glycocalyx), which cause the rolling, adherence and migration of leukocytes (diapedesis), leading to tissue damage and increased oxidative stress mediated by reactive oxygen species (ROS) and nitrogen. This entire chain of events will result in greater capillary leakage, edema, altered hemostasis and subsequent formation of microthrombi and loss of vascular tone [34].

In summary, the main function of neutrophils and lymphocytes is to resolve the infection and repair the tissues through the regulated action of proinflammatory and anti-inflammatory cytokines, limiting the inflammatory process to the site of the injury. This balance alteration provokes a multi-organ damage and dysfunction which translates in higher mortality rates (Figure 2).

Figure 2. *Cytometric indexes derived from platelets, neutrophils, and lymphocytes with their production variants in sepsis.*



MPV (mean platelet volume), *NETs (netosis), NLR (neutrophil-lymphocyte ratio), LPR (lymphocyte platelet ratio).*

Source: *The author.*

Use of the neutrophil-lymphocyte ratio in sepsis

The NLR represents the relationship between the absolute count of neutrophils divided by the absolute count of lymphocytes, the use of this marker is based on neutrophilia and lymphopenia, which are characteristic responses in infectious states such as sepsis. A higher inflammatory state will be represented by a higher NLR [6]. Based on this premise, some studies have been carried out to evaluate this parameter as a predictor of severity and mortality in sepsis, obtaining variable results. [35] in 2014, obtained favorable results regarding to the performance of NLR as a prognostic factor for bacteremia with similar efficacy to procalcitonin. Akilli et al, in the same year, identified a NLR >11.6 as an independent factor for in-hospital mortality and at 6 months in patients admitted to the emergency room critically ill and requiring an ICU, concluding that values higher than the established cut-off point were related to a greater progression to sepsis and DMO [36].

In 2015, Reyes-Gálvez J. et al, performed a retrospective, observational, cross-sectional study, in patients with abdominal sepsis who underwent surgery. They set a NLR cut-off point of 18, with an AUC: 0.66 to predict severity and 0.70 for mortality, however, these results were not sensitive nor specific enough to establish its use, since the APACHE II scale showed better results [37].

Gonul G. et al, in 2015, correlated NLR with procalcitonin in a retrospective study that included 1,468 patients with suspected bacteremia and sepsis, concluding that a NLR value less than 5 was correlated positively with the elevation of procalcitonin for diagnosis of infection and sepsis [38].

In 2017, Vallejo et al, conducted an analytical, retrospective, observational study in patients with bacteremia diagnosed by positive blood cultures compared to patients with negative blood cultures, obtaining as results a NLR cut-off point of 13.2 with an AUC of 0 .71 with SE: 63% and SP: 71.6% [39].

In 2019 Velez et al. conducted an observational, prospective, analytical study in 149 ICU patients diagnosed with sepsis or septic shock, where they evaluated the NLR on the first and second day of hospitalization as a predictor of mortality. A negative association with mortality was obtained with an AUC of 0. 53, sensitivity of 47.1% and specificity of 48.4% [40].

Conclusions

According to the evidence it has not been established a standardized MPV cut-off point to analyze the increased mortality in septic patients. Factors such as variable study population, different measurement techniques, type of anticoagulant used, and measurement time after sampling made difficult to obtain a fixed value. However, values above 9 fL have shown a significant correlation with inflammatory and prothrombotic states associated with endothelial damage, such as sepsis.

As for the MPV, the NLR does not have an established cut-off point for diagnosis or prediction of mortality in sepsis. However, it is a useful parameter to assess an infection, and could be helpful for the diagnosis and prognosis of sepsis when associated with other parameters to enhance the results.

Today, there are many parameters that help in the diagnosis and prognosis of sepsis, some already in frequent use and others still under study. However, most of them are of limited accessibility.

New laboratory parameters with easy access, lower cost and proven effectiveness are needed. The markers that have been evaluated in this study have a promising future in the clinical field, since their daily use would allow earlier and more adequate sepsis management without requiring special and expensive tests. This would allow to redirect economic resources to cover different needs in the management of critically ill patients.

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