

# Neutrophils/lymphocytes index compared to mean platelets volume/platelets count index, as long hospital stays and survival indicator of stroke. How much is little?

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## Abstract

**Introduction:** Stroke is one of the main causes of disability in elderly, and the main cause of neurological emergencies. Mean platelet volume (MPV) has a positive correlation with prothrombotic diseases, highlighting thrombotic events and venous thrombosis disease. **Aim:** We aim to determine the relation between neutrophil/lymphocyte (N/L) index and MPV/platelet count (PC) index with prognosis in cerebral vascular events in the Mexican population. **Methods:** We included 236 patients with 137 males (74-78 years) and 81 females (64-72 years); 58 hemorrhagic cases, 44 parenchymal, eight subarachnoid, and 6 subdural; 160 ischemic cases, including 149 ischemic, 2 lacunar, and 9 Transient Ischemic Attack (TIA). All patients had brain imaging, initial, and follow-up hematic cytometry to determine indexes and compare it between them. **Results:** Neutrophils/lymphocytes index lower than 3 ( $p = 0.015$ ) and MPV/PC index higher than 0.031 ( $p = 0.001$ ) increase significantly in stroke during the first 48 h. MPV > 10 fl increase mortality ( $p = 0.014$ ); considering all strokes; receiver operating characteristic curve showed AUC values of MPV/PC 0.822 (0.760-0.885) ( $p = 0.001$ ) and N/L 0.661 (0.579-0.742) ( $p = 0.001$ ) with a significant difference between AUC values ( $p = 0.001$ ). **Conclusions:** In our study, mortality rises in patients over 70 years old, especially in hemorrhagic events, females; and patients with higher N/L and MPV/PC indexes. The MPV/PC is better at predicting severity and long hospital stay in stroke compared to the N/L index. The high platelets levels are related to stroke as well as other studies before; however, this is related to the worst prognosis, increasing mortality and long hospital stay in our population.

**Keywords:** Mean platelet volume. Neutrophils lymphocytes ratio. Neutrophils/lymphocytes. Stroke. Mortality.

**Índice de neutrófilos/linfocitos en comparación con MPV/PC, así como estancias hospitalarias prolongadas e indicador de supervivencia de eventos cerebrovasculares. ¿Cuánto es poco?**

## Resumen

**Introducción:** Los eventos vasculares cerebrales (EVC) son una de las principales causas de discapacidad en los adultos, además de ser la principal emergencia neurológica. El VPM tiene una correlación positiva con enfermedades protrombóticas, destacando los eventos cerebrovasculares trombóticos y la enfermedad de trombosis venosa. **Objetivo:** Determinar la asociación del índice N/L (Neutrófilo/Linfocito) y el índice VPM/PT (Volumen Plaquetario Medio/Plaquetas totales) con el pronóstico

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de población mexicana con EVC. **Métodos:** El estudio actual incluyó a 236 pacientes, incluidos 137 hombres (74-78 años) y 81 mujeres (64-72 años); se desarrollaron 58 eventos hemorrágicos, incluidos 44 parenquimatosos, 8 subaracnoides y 6 subdurales; así como 160 eventos isquémicos, incluidos 149 isquémicos, 2 lacunares y 9 AIT (Ataque Isquémico Transitorio). A todos los pacientes se les realizaron tomografía de cráneo así como biometría hemática inicial y de seguimiento, determinando ambos índices y comparándolos entre ellos. **Resultados:** El índice de neutrófilos/linfocitos menor a 3 ( $p = 0.015$ ) y un índice de plaquetario medio/plaquetas totales mayor a 0.031 ( $p = 0.001$ ) aumentaron significativamente en pacientes con EVC durante las primeras 48 horas del evento. Mientras que valores mayores a 10 fL de VPM se asociaron a incremento de mortalidad ( $p = 0.014$ ); considerando todos los EVC. La curva ROC mostró área bajo la curva de la relación VPM/PT 0.822 (0.760-0.885) ( $p = 0.001$ ) y neutrófilos/linfocitos 0.661 (0.579-0.742) ( $p = 0.001$ ) con una diferencia significativa entre los valores de área bajo la curva ( $p = 0.001$ ). **Conclusiones:** La mortalidad es mayor en pacientes mayores de 72 años, en EVC hemorrágico, pacientes mujeres, así como aquellos con valores altos de índices neutrófilos/linfocitos y VPM/PT; el índice VPM/PT es mejor que el índice neutrófilos/linfocitos como marcador de gravedad en EVC, relacionado con mayores días de estancia intrahospitalaria. Estos índices podrían utilizarse para predecir la mortalidad y estancia prolongada en pacientes con EVC.

**Palabras clave:** VPM. INL. Neutrófilos/linfocitos. EVC. Mortalidad.

## Introduction

Stroke occurs when blood perfusion is reduced, leading to neuron death; ischemic events present around 85% and hemorrhagic in 15%. Ischemic events are classified into embolic, thrombotic, or lacunar<sup>1</sup>. Although hypertensive decontrol is the main etiology, some others as clotting disorders, carotid dissection, or drugs must be investigated<sup>2</sup>.

Chronic inflammation led to higher platelet levels and lower lymphocytes levels, increasing the risk of stroke events<sup>3</sup>. Platelets reflect inflammation, and the mean platelet volume (MPV) express platelet activation, this marker is elevated in stroke and is associated with poor outcome; on the other hand, the level of platelet count (PC) is inversely proportional to MPV in stroke, this might be related to the increasing consumption in the process of thrombus formation<sup>4</sup>.

The MPV/PC index is a better indicator of inflammation and platelet activation compared to MPV or PC alone<sup>5</sup>. This inflammation is even found in some tumors, including hepatocellular carcinoma, pancreatic cancer, and lung cancer, increasing the MPV/PC index<sup>6</sup>.

High levels of MPV and neutrophils lymphocytes ratio (NLR) are found in carotid artery stenosis and cardiac arrest<sup>7</sup>. However, NLR and MPV are higher when carotid artery stenosis is between 70 and 99%<sup>7</sup>.

Platelet size plays an important role as a cardiovascular risk factor, while NLR and platelet/lymphocyte index express systemic inflammation<sup>8</sup>. Low platelets levels are related to thrombosis events, increasing cardiac events and mortality<sup>9</sup>. Furthermore large platelets are more reactive than small platelet<sup>10</sup>.

Previously some other indexes were studied, specially the MPV, NLR, and erythrocyte sedimentation rate

(ESR) which are related with C-reactive protein (CRP) in stroke events; males keep better relation between CRP/NLR and ESR indexes, while females have a good relation between CRP/MPV and NLR/ESR indexes<sup>11</sup>.

The MPV expresses platelet production and inflammation, increasing the prothrombotic events<sup>12</sup>. However, there is a direct relation between platelet size in cardiovascular events, increasing the cardiovascular risk in patients with large platelets<sup>8</sup>.

The MPV and MPV/PC are higher in stroke events, even in patients who suffered cardiac arrest or post-AMI stroke<sup>13</sup>. Opposite to acute inflammation, lower levels of MPV express chronic inflammation and rheumatic diseases<sup>14</sup>. The increase in MPV and NLR/PLT predicts severity of stroke and TIA at admission and after 3 months<sup>15</sup>.

Despite the fact that MPV increases in stroke events, this may be increased in other diseases such as hypertension, diabetes, and atrial fibrillation, increasing the risk of stroke<sup>16</sup>. The MPV predicts outcomes in stroke events, and even during the following 90 days after thrombolysis events<sup>17</sup>. The MPV is higher in acute non-lacunar than lacunar ischemic strokes, and this is directly related to the MPV and lesion size<sup>18</sup>.

The high platelet levels are increased in all cardiovascular events, especially in myocardial infarction and ischemic stroke, this fact increases mortality in all stroke events<sup>19</sup>. The MPV, as an expression of platelets activation, is useful for prognosis of cardiovascular and stroke<sup>20</sup>. On the other hand, platelets activation expresses inflammation which produces brain damage and leads to spread microvascular dysfunction, edema enlargement, and eventually worsen functional outcomes<sup>21</sup>; this is reflected with higher MPV levels, which are found in all stroke types<sup>22</sup>.

## Methods

This is a cross-sectional study that was done during the period from April 2020 to January 2022. Patients with ages over 18 years old were included into the analysis, including all types of strokes, demonstrated with imaging study (brain tomography or brain magnetic resonance) during the first 48 h of the event, with hematic cytometry at hospital admission, and interned into any hospital service. Hemorrhagic events were considered as stroke; however, just ischemic events were considered in the final analysis. We collect laboratory parameters from all hematic cytometry of WBC, MPV, neutrophils, lymphocytes, platelets; demographic parameters, sex, age; and stroke events, type of stroke, hospital stay days, hospital stay until discharge, die, or alive. All these parameters were analyzed and we obtained a relation between number of neutrophils and lymphocytes (N/L), which were considered normal with values between 0.78 and 3.53, and was divided into three groups, low risk < 1.5, intermediate risk 1-5-3, and high risk > 3. The VPM was considered normal with values from 7 to 10 fl, a relation between VMP and platelets count was obtained, with a VPM/PC index was normal if the relation was lower than 0.031. Hematic cytometry was collected at admission and during hospitalization. Kaplan-Meier survival statistics and the log-rank test were used to compare stroke events according to sex, N/L, and MPV/PC index and type of stroke. A plot for comparison of receiver operating characteristic curve (ROC) curves among MPV/PC and N/L index was done. All the tests were two-sided and p-value < 0.05 was considered significant. All analyses were done using SPSS 20.0 (SPSS, Inc., Chicago, IL, USA).

## Results

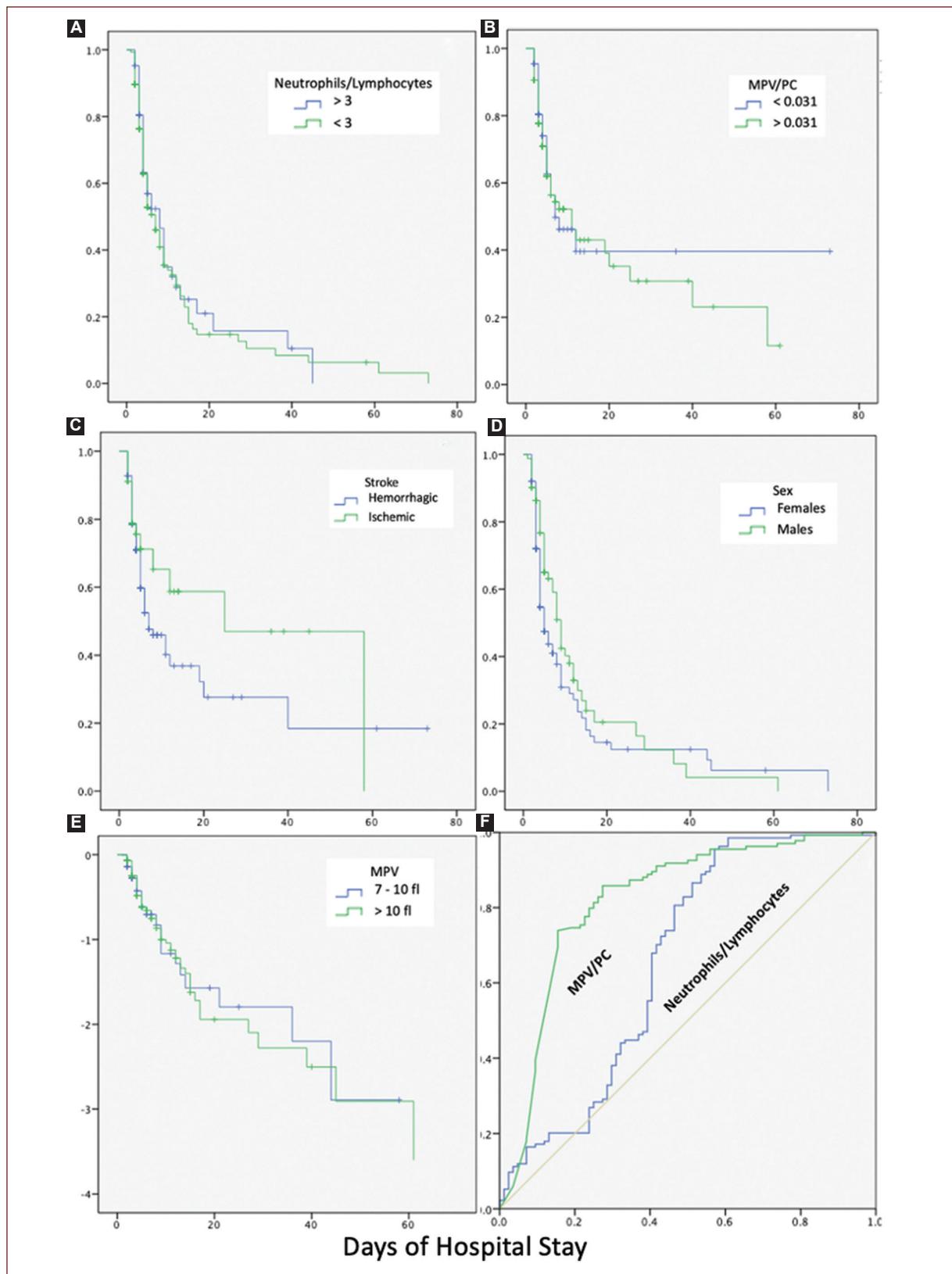
We collected 236 patients including 137 males (74-78 years) and 81 females (64-72 years); with 58 hemorrhagic cases, including 44 parenchymal, eight subarachnoid, and six subdural; and 160 ischemic cases, including 149 ischemic, 2 lacunar, and 9 TIA. Only 18 patients were discharged to other health-care centers, excluding these patients from final analysis. A neutrophils/lymphocytes index lower than 3 (p 0.015) had a 68.4% of sensitivity and 83.2% of specificity, with a PPV of 72% and NPV of 89%; and a MPV/PC index higher than 0.031 (p = 0.001) with a 71.2% of sensitivity and 84.9% of specificity, with a PPV of 62% and NPV of 94%; both indexes increased significantly in stroke patients during the first 48 h from the event, increasing

hospital stay days at medium of 15 days (13-18 days). The correlation between serum parameters and mortality in stroke according to sex group is presented in Kaplan-Meier graph (Fig. 1). Values > 10 fl of MPV were found to increase significantly in dead patients (p = 0.014); considering all strokes, a total of 37 patients died (63.7%) because of a hemorrhagic event, and 92 (57.5%) because ischemic event, this mainly related to complications of long hospital stay. However, both indexes had a good specificity to predict mortality and long stay days in ischemic events, being useless in hemorrhagic events; ROC analysis showed that areas under the curve (AUC) values were MPV/PC 0.822 (0.760-0.885) (p = 0.001) and N/L 0.661 (0.579-0.742) (p = 0.001) with a significant difference between AUC values (p = 0.001).

## Discussion

The relation between platelets and thrombotic events is well studied; however, platelets play an important role in inflammation, it has been reported that MPV is a good indicator of platelet size and activity, helping as an inflammatory marker in cardiovascular events and stroke<sup>23</sup>. However, the MPV values are useful as the severity index of stroke, while the N/L index helps to express systemic inflammation<sup>24</sup>. Thereby leukocytes help into the atheroma formation; while leukocytosis is involved into plaque destabilization, inducing acute thrombotic events as stroke events, so lower N/L index could be related with a good prognosis. We found that the N/L index was significantly lower, while the MPV/PC index was higher during the first 48 h of stroke; these indexes can help to distinguish between systemic inflammation and local thrombosis mainly during the first 48 h of the event; however, both indexes are an independent predictor of long hospital stay and morality in stroke patients, even ischemic events had a high mortality, the hemorrhagic events are still the more lethal events, so MPV/PC and N/L indexes are useless to predict mortality in those events.

The clinical data showed that patients with in-hospital strokes were more likely to have long hospital stay days and high mortality; this is directly related to high MPV levels, as well as, high MPV/PC index, and lower N/L index, which were found in our study population during stroke events. The main finding of our study relates to the association of N/L index and MPV/PC index as accessible and non-invasive indexes of prognosis in stroke patients.



**Figure 1.** **A:** Kaplan–Meier plots showing increase in mortality in patients with neutrophils/lymphocytes index lower than 3. **B:** increase in mortality in patients with MPV/PC index higher than 0.031. **C:** increase in mortality in patients with hemorrhagic stroke, compared to ischemic stroke. **D:** mortality according to sex. **E:** increase in mortality of patients with levels higher than 10 fl of MPV. **F:** ROC curve comparing MPV/PC and neutrophils/lymphocytes indexes predicting mortality.

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## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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