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The Predictive Effect of Mean Platelet Volume (MPV) and Neutrophil-to-Lymphocyte Ratio (NLR) on the Functional Outcome of Acute Ischemic Stroke

ABEER A. TONY, M.D.*; EFFAT A.E. TONY, M.D.**; WAFAA S. MOHAMMED, M.D.*** and EMAD F. KHOLEF, M.D.***

The Departments of Neurology, Internal Medicine** and Clinical Pathology***, Faculty of Medicine, Aswan*,*** and Assiut** Universities, Egypt*

Abstract

Background: Inflammation has been reported to constitute a major component of ischemic stroke pathology. Nevertheless, to the best of our knowledge, no previous studies have investigated the NLR and MPV values in the cases of stroke stratified by subtype.

Aim of Study: The aim of our study is to predict the role MPV and NLR in short-term outcome in patients with ischemic stroke and their association to stroke severity, stroke risk factors and functional outcome.

Patients and Methods: This prospective cross sectional study directed on 125 patients with first time acute ischemic stroke. All members exposed to full history taking, detailed clinical examination and neurological checking. Brain imaging was performed after hospital admission. Blood tests were drawn for appraisal of the mean platelet volume (MPV) (in FL) and the neutrophil-lymphocyte ratio (NLR).

Results: Our results revealed that the mean value for NLR was higher in dead patients with ischemic stroke. By ROC curve, higher NLR at admission predicted the mortality than MPV. We found higher NLR levels in patients with more severe stroke. However, We did not observe a significant correlation between the MPV, the stroke severity, and outcome.

Conclusion: NLR was an independent risk factor and serves as a sensitive index for the prognosis of ACI patients. Further well-designed and large-scale prospective studies are necessary to evaluate platelet MPV and NLR for observing patients with cerebral infarction among different territories of Egypt and for stroke subtypes.

Key Words: *Acute ischemic stroke – National Institutes of Health Stroke Scale (NIHSS) – Modified Rankin Scale (mRS) – Mean platelet volume (MPV) – Neutrophil/lymphocyte ratio (NLR).*

Introduction

STROKE is the third leading cause of death after cardiovascular disorders and cancer while it ranks first among disorders leading to disability worldwide [1]. Inflammation has been reported to constitute a major component of ischemic stroke pathology [2,3]. Ischemic brain injury secondary to an arterial occlusion, which is characterized by acute local inflammation and changes in levels of inflammatory cytokines was demonstrated [4]. Recently, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and similar parameters (e.g., red blood cell distribution width [RDW] and mean platelet volume [MPV]), have been examined as a new expression of the inflammatory biomarkers in many diseases such as atherosclerosis, cerebral infarction and active inflammatory diseases [5-10].

MPV is a parameter detected during routine blood count and to which clinicians do not usually pay much attention. Platelet volume is known to be a marker determined from megakaryocytes during platelet production, which is associated with platelet function and activation [11]. Some studies have reported higher MPV values in patients with stroke and acute myocardial infarction than in control subjects [12-14]. The role of elevated MPV for predicting poor outcome of brain stroke was reported as independent to other clinical parameters such as lipid profile and other biochemical parameters [15].

NLR is the ratio of absolute neutrophil count to absolute lymphocyte count. NLR is a simple marker of subclinical inflammation and high NLR points to a predominance of inflammatory factors in the aetiopathogenesis of different conditions and possibly indicates subgroups of patients with similar disorder that will benefit from anti-inflammatory agents [16]. It has recently emerged as

Correspondence to: Dr. Abeer A. Tony, The Department of Neurology, Faculty of Medicine, Aswan University, Egypt

an independent useful prognostic marker to predict the mortality and prognosis of some cardiovascular and neurologic diseases [17-19]. Nevertheless, to the best of our knowledge, no previous studies have investigated the NLR and MPV values in the cases of stroke stratified by subtype. Thus, the aim of our study is to predict the role MPV and NLR in short-term outcome in patients with ischemic stroke and their association to stroke severity, stroke risk factors and functional outcome.

Patients and Methods

This cross-sectional prospective study conducted in the stroke unit of our neuropsychiatric Department, Faculty of Medicine, Aswan University from January 2017 to December 2017. It comprised 125 patients with first-ever acute ischemic stroke. Patients were eligible for inclusion if they were admitted to our unit with AIS defined according to the clinical evaluation of presence of focal neurological deficit of sudden onset that persisted beyond 24hs and confirmed by brain imaging (either CT scan and/or MRI brain). We excluded patients with intracranial hemorrhage, brain neoplasm, trauma, history of previous stroke, history of acute and chronic inflammatory diseases, malignancy, autoimmune diseases, renal or hepatic disease, history of use of anticoagulants or anticonvulsants and peripheral vascular diseases as well as those with a history of myocardial infarction <3 months.

The patients or their relatives gave written informed consent. A detailed medical and neurological history was taken and clinical and laboratory examinations were performed for all patients. The study was approved by ethics committee of our college.

Clinical data collection and blood sampling:

All patients will be submitted for Complete neurological examination where the following clinical and demographical data were taken; age, sex, stroke etiology, presence of stroke risk factors (as smoking history, hyperlipidemia, diabetes mellitus, history of hypertension, history of transient ischemic attacks, history of myocardial infarction or any cardiac problems). Stroke severity was assessed by National Institutes of Health Stroke Scale (NIHSS) measured at the time of admission. Functional outcome was assessed by Modified Rankin Scale (mRS) at admission and 90 days after admission. The favorable functional outcome of stroke patients was defined as mRS score of 0-2 (independent) and mRS score of 3-5 was disabled outcome while mRS score of 6 being dead. Brain imaging (either CT scan and/or MRI) was performed after admission. Electrocardiography (ECG), Echocardiography (ECHO), were done for all patients. Blood samples from all patients were drawn for assessment of complete blood picture (CBC), Random blood glucose levels, renal function tests (RFT), liver function tests (LFT), and Lipid profile using standard laboratory methods. 2mls of venous blood was aseptically collected into an EDTA vacutainer tube. Complete blood counts were done on the samples within six hours after phlebotomy. The samples were analyzed by Beckman Coulter LH 750 (Beckman Coulter, Miami, USA) hematology analyzers that provided MPV (in FL). The NLR was calculated by dividing the mean neutrophil counts by the mean lymphocyte counts.

Statistical analysis:

Data was collected and analyzed those using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD or median (range) while nominal data was expressed in form of frequency (percentage). Chi-square test was used to compare the nominal data of different groups in the study while student *t*-test was used to compare mean of different two groups and ANOVA test for more than two groups. Multivariate regression analysis was used to determine the independent risk factors for prediction of mortality in the studied patients. Diagnostic accuracy of MPC was determined by using ROC curve. P value was significant if <0.05.

Results

The study population included 125 patients with stroke, 68% were males and 32% were females. The mean age of included patients was 62.64± 10.99 years. Demographic, clinical characteristics and laboratory results of the study population were summarized in Table (1).

In univariate analysis, there was no significant differences between survivors and died as regarding RBCs, Hb, platelets count and mean platelets volume with p>0.05. However, the leucocytic count and neutrophil/lymphocyte (N/L) ratio values were found to increase significantly in dead patients (p= 0.02 and 0.03 respectively) Table (2).

ROC analysis was performed to determine the cut-off value of WBCs, Platelets, MPV and NLR in prediction of death within the studied patients. Table (3). Comparison of the area under curve revealed that NLR had the widest area under the

curve (p=0.00) Fig. (1). A N/L ratio of 4.99 or higher predicted the mortality with a sensitivity of 82.9% and a specificity of 78.9% as shown in Fig. (2).

The final logistic regression model showed that the only predictor for severity of cerebrovascular stroke based on national institute of health stroke scale was N/L ratio (OR=1.99; 95% CI=1.78-5.67; p=0.01) Table (4).

Based on NIHSS, 55 (44%) patients had minor stroke while moderate and severe stroke presented in 35 (28%) patients for each. It was noticed that MPV had insignificant differences between different grades of the score (p=0.94). However, N/L ratio was significantly higher in those patients with severe stroke (p=0.03) (Table 5).

According to modified Rankin score (mRS), 17 (13.6%), 15 (12%), 33 (26.4%), 25 (20%) and 35 (28%) of our studied patients were slightly disabled, moderately disabled, moderately to severely disabled, severely disabled and died respectively. Although MPV had no significant changes between different grades of the score, N/L was significantly increasing as the score increased (p=0.00) (Table 6).

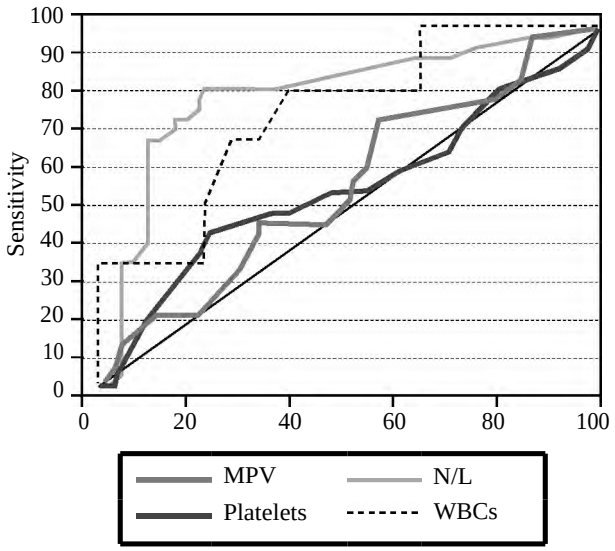

Fig. (1): ROC analysis for diagnostic indices of WBCs, Platelets, MPV and N/L for prediction of death in the study groups.

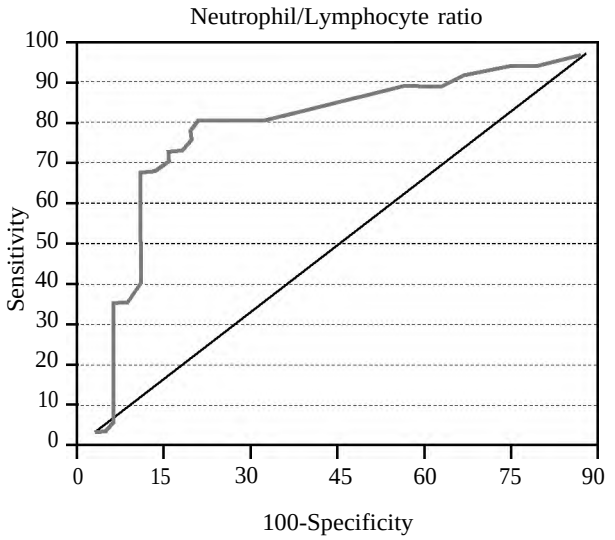

Fig. (2): ROC analysis for diagnostic indices of N/L for prediction of death in the study groups.

Table (1): Characteristics of the studied patients with acute ischemic stroke: Serum Parameters and Mortality in the Study group.

Parameters	Number=125
Age (years) Mean ± SD	62.64± 10.99
Sex (No %):	
Male	85 (68%)
Female	40 (32%)
Duration of stroke (hours) Mean ± SD	4.34± 1 .04
Modified Rankin scale (mRS) Mean ± SD	5 . 09± 1 .23
NIHSS Mean ± SD	19.05±2.98
Number of deaths (No,%)	35 (28%)
Vascular risk factors (No,%):	
Hypertension	71 (64%)
Dyslipidemia	35 (28%)
Diabetes Mellitus	32 (28.8%)
Smoking	52 (46.8%)
Ischemic heart disease	15 (11.11%)
Non valvular atrial fibrillation	8 (6.4%)
Abnormal Carotid duplex (No,%)	75 (60%)
Abnormal Vertibrobasilar duplex (No,%)	18 (14.4%)
Laboratory Investigations	Mean ± SD
Red blood cells ($x10^3$/ml)	4.99±0.65
Hemoglobin level (g/dl)	14.33± 1.03
Leukocytes ($x10^3$/ml)	10.05±2.51
Platelets count ($x10^3$/ml)	260.11 ±63.45
Mean platelet volume (fl)	9.77± 1.18
Neutrophil/lymphocyte (N/L) ratio	4.56±0.52
Cholesterol (mg/dl)	235.24±40.01
Triglyceride (mg/dl)	171.06±44.85
HDL (mg/dl)	47.43± 13 .56
LDL (mg/dl)	1 04.76±23 .9 8
Random blood glucose (RBG) (mg/dl)	167.66±44.87
Erythrocyte sedimentation rate (ESR)	55.09± 12.43

Data was expressed in form of mean ± SD.

Table (2): Correlation between different serum parameters and mortality in the study group.

Parameters	Died (n=35)	Survivors (n=90)	*p*-value
Red blood cells (x10^3/ml)	5.07±0.32	4.78±0.61	0.39
Hemoglobin level (g/dl)	14.82±0.31	14.17± 1.85	0.21
Leukocytes (x10^3/ml)	12.75±3.23	8.74±2.02	0.02
Platelets count (x10^3/ml)	263.08±70.55	259.76±48.55	0.34
Mean platelet volume (fl)	9.63± 1.02	9.80±0.79	0.56
Neutrophil/lymphocyte (N/L) ratio	5.95±0.39	3.99±0.51	0.03

Data was expressed in form of mean ± SD. *p*-value was significant if <0.05. *Student *t*-test was used.

Table (3): Statistical diagnostic measures for the determined cut-off values of serum parameters in the detection of mortality.

	AUC	Cut-off value	SEN	SPE	PPR	NPR	*p*-value
WBCs	0.76	>9.8	82.9%	62.2%	46%	90.3%	0.09
Platelets count	0.56	>267	42.9%	77.8%	42.9%	77.8%	0.34
MPV	0.55	>9	74.3%	44.4%	34.2%	81.6%	0.29
N/L	0.81	>4.99	82.9%	78.9%	60%	92%	0.00 1

p-value was significant if <0.05. N/L : Neutrophil/ lymphocyte ratio'. PPR: Positive predictive rate.
WBCs: White blood cells. SEN: Sensitivity. NPR: Negative predictive rate.
MPV : Mean platelets volume. SPE : Specificity. AR, AUC: Area under the curve.

Table (4): Multivariate logistic regression analysis for determining the role of MPV & N/L ratio in predicting stroke severity by NIHSS.

Variables	Odds Ratio	95% Confidence interval	*p*-value
Age (year)	1.2	2.1–3.68	0.46
Mean platelets volume (MPV)	2.33	0.93–2.56	0.45
Neutrophil/lymphocyte ratio (N/L)	1.99	1.78–5.67	0.01

p-value was significant if <0.05. NIHSS: National institute of health stroke scale.

Table (5): Relation between MPV & N/L and severity of stroke (on the basis of NIHSS).

Parameters	NIHSS			
	Score 1-4: Minor stroke (n=55,44%)	Score 5-14: Moderate stroke (n=35,28%)	Score 15-20: Severe stroke (n=35, 28%)	*p*-value
MPV (fl)	9.99±0.75	9.21 ± 1.11	10.01 ±0.67	0.94
N/L ratio	4.34±0.22	5.01 ±0.18	6.22±0.33	0.03

Data was expressed in form of mean ± SD and *p*-value was significant if <0.05.
NIHSS: National institute of health stroke scale. MPV : Mean platelets volume.
n: Number. N/L : Neutrophil leukocyte ratio

Table (6): Relation between MPV & N/L ratio and functional outcome of patients with stroke (on the basis of Modified Ranking's score mRS).

Parameters	Modified Rankin's Score (mRS)					
	Score 2: Slight disability (n=17, 13.6%)	Score 3: Moderate disability (n=15, 12%)	Score 4: Moderately severe disability (n=33, 26.4%)	Score 5: Severe disability (n=25, 20%)	Score 6: Death (n=35, 28%)	*p*-value
MPV (fl)	9.03±0.9	8.93± 1.11	9.62±079	9.13± 1.1	9.63± 1.02	0.45
N/L ratio	3.99±0.12	3.92±0.51	4.1±0.93	4.05±0.44	5.95±0.39	0.001

Data was expressed in for of mean SD and *p*-value was significant if <0.05.
n: Number. MPV: Mean platelets volume. N/L: Neutrophil leukocyte ratio.

Discussion

Studies on NLR and MPV have grown recently following the discovery of their immense values in prediction and prognosis of many medical conditions. These parameters are potent markers of inflammation which underlies the basic pathologies of various diseases. The easy of availability of these parameters without additional costs to the patients may gradually replace the older markers of inflammation **[16]**.

Our result revealed that the mean value for NLR and total lecuocytic count are higher in the patients with ischemic stroke who died in comparison to those who survived (p=0.03). Celikbilek etal reported that NLR is a novel index for cerebral infarction regardless of classical cardiovascular risk factors. Also, it predicts poor prognosis in ischemic cerebrovascular disease **[20]**. Also, In a study in Turkey with patients who presented to the emergency service with cerebrovascular accident (stroke and transient ischemic attack), the NLR was significantly higher in patients who died (p,0.001) and in those with ischemic or hemorrhagic stroke than in those with transient ischemic attack (p,0.001) **[21]**.

In our study, an NLR of 4.99 or higher at admission was predicted the mortality with a sensitivity of 82.9% and a specificity of 78.9%. The predictive value of NLR in the detection of mortality compared to WBCs, Platelets, MPV was described in this study by a wider area in the ROC curve (AUC 0.81) than that of WBCs (AUC 0.76), Platelets (AUC 0.56) and MPV (AUC 0.55). In accordance with the presented results, several authors reported that the NLR is an independent mortality predictor in the short and long term **[19, 22, 23]**. NLR levels were found higher in patients with moderate/severe stroke than in patients with minor stroke (OR 1.99, p=0.01). This result support the hypothesis that NLR is a good predictive factor of stroke and stroke prognosis **[24]**.

In this study, We did not observe a significant correlation between the MPV, the stroke severity, and outcome. Previous studies show inconsistent results; some studies have found a relation between high MPV level and high risk of stroke **[25-27]**. However, there are also studies in which such association was not found **[28,29]**.

There are limited data about the effect of pharmacological therapy on platelet count and size. A randomized controlled trail measured a lower MPV level after 4 weeks of antiplatelet drugs treatment **[30]**. Since the patients included in our study had at least one background disease (hypertension, diabetes mellitus, atrial fibrillation, etc.), some of them may have been under antiplatelet drugs treatment at the time of admission, a fact that could have affected their MPV level. Another explanation to the inconsistency in the results is the very poor standardization of the methodologies used for MPV measurement which vary from device to device **[31]**. In addition, MPV can be influenced by the time interval between sampling and analysis **[32]**. MPV results become increasingly unreliable after 4h **[33]**. Complete blood count analysis in our laboratory has almost proceeded within 4h from sampling start.

The interpretation of this study has some limitations. First, We did not measure the level of inflammatory markers, such as TNF-a, IL-6, and CRP. Therefore, we did not compare the prognostic value of the NLR and those inflammatory factors. Second, we did not detect the location of cerebral infarction, this fact could affect the results since the severity of stroke was determined by the NIHSS, which has a good correlation with the middle cerebral artery infracts but underestimates severity of posterior circulation strokes **[34]**. Despite these limitations, our study has important clinical implications of that the presence of a high NLR at admission in acute cerebral infarction has predictive value for stroke and stroke prognosis. This simple, inexpensive, and widely available biomarker that can be attainable by using an automatic haematology analyser can offer an additional noninvasive tool for risk stratification to assess the severity and prognosis of cerebral infarction.

Conflict of interest:

There is no conflict of interest in this work.

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التأثير التنبئى لحجم لصفيحات المتوسط مع مؤشر العدلات إلى اللمفيات بالدم على النتيجة الوظيفية للسكتة الدماغية الحادة

مقدمة البحث: يشكل الألتهاب عنصراً رئيسياً فى أسباب السكتة الدماغية. ولن تقم اية دراسات بحثية سابقة بتحديد قيم حجم الصفيحات المتوسط مع مؤشر العدلات إلى اللمفيات بالدم فى حالات السكتات الدماغية الطبقية حسب نوعها.

هدف البحث: هو التنيؤ بدور حجم الصفيحات المتوسط مع مؤشر العدلات إلى اللمفيات بالدم على النتيجة الوظيفية للسكتة الدماغية الحادة فى المرضى الذين يعانون من السكتة الدماغية وأرتباطهم بشدة السكتة الدماغية، وعوامل خطورتها والنتائج الوظيفية للسكتة الدماغية الحادة.

طريقة البحث: لقد أجريت هذه الدراسة على ١٢٥مريض بالسكتة الدماغية الحادة للمرة الأولى فى الفترة من يناير٢٠١٧ إلى ديسمبر ٢٠١٧. وقد تم عمل الفحص السريرى والفحص العصبى مع إجراء أشعة الرنين المغناطيسى أو الأشعة المقطعية على المخ لجميع المرضى بعد دخول المستشفى. كما تم تقييم شدة السكتة الد ماغية بواسطة مقياسNIHSS وتم تقييم النتائج الوظيفية بواسطة مقياس رانكنالمعدل للحالة الوظيفية عند دخول المرضى المستشفى وبعد ٩٠ يوم من الدخول. و قد تم تقسيم مرضى السكتة الدماغية حسب مقياس رانكن إلى: مقياس رانكن من ٠–٢ (غير معاقاً)، مقياس رانكن من ٣–٥ (معاقاً) فى حين عندما يصل مقياس رانكن إلى ٦ (تعنى متوفياً) مع فحص الدم لتقييم متوسط حجم الصفائح الدموية ونسبة خلايا العدلات إلى الخلايا الليمفاوية بالدم.

نتائج البحث: شملت الدراسة ١٢٥مريض مصاب بالسكتة الد ماغية وكان نسبة الذكور ٦٨٪ أما الإناث يمثلن نسبة ٣٢٪، و متوسط أعمار جميع المرضى (٤ ٦٢.٦±١٠.٩٩عاماً) ولم تلاحظ أية فروق ذات دلالة إحصائية قيمة بين المرضى ومن وافتهم المنية فيما يتعلق بكرات الدم الحمراء، نسبة الهيموجلوبين، عدد الصفائح الدموية وحجم الصفائح الدموية. بالرغم من وجود زيادة كبيرة بدلالة إحصائية قيمة فى عدد الكريات البيض والقيمة النسبية للكريات العدلات إلى الخلايا الليمفاوية فى المرضى الذين وافتهم المنية. كما أظهرت الدراسة أن متوسط القيمة النسبية للكريات العدلات إلى الخلايا الليمفاوية فى المرضى الذين يعانون من السكتة الدماغية كان مرتفعاً بدلالة إحصائية ذات قيمة. وبإستخدام منحنى روك الإحصائى لوحظ أرتفاع مؤشر القيمة النسبية للكريات العدلات إلى الخلايا الليمفاوية (ذو حساسية من ٨٢.٩٪ وخصوصية من ٧٨.٩٪) عن حجم الصفيحات المتوسط فى تحديد شدة الأصابة المسببة للوفاة فى المرضى كما أظهرت الدراسة مستويات عالية للقيمة النسبية لكريات العدلات إلى الخلايا الليمفاوية فى المرضى الذين يعانون من السكتة الدماغية أكثر حدة بالرغم من أن الدراسة لم تظهر أى أرتباط بين حجم الصفيحات المتوسط مع شدة السكتة الدماغية، والنتيجة الوظيفية ما بعد الإصابة.

ونستنتج من هذه الدراسة: تعد القيمة النسبية لكريات العدلات إلى الخلايا الليمفاوية عاملاً مستقلاً ذو خطورة لتنبؤ بحدوث السكتة الدماغية الحادة لذا يلزم عمل النزيد من الدراسات المستقبلية وعلى نطاق واسع لتقييم حجم الصفيحات المتوسط والقيمة النسبية لكريات العدلات إلى الخلايا الليمفاوية لملاحظة المرضى الذين يعانون من أحتشاء دماغى بين المناطق المختلفة فى مصر والأنواع المختلفة للسكتة الدماغية.