Evaluation of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratio Values in Patients with Ischemic Stroke in Terms of Disease Severity Based on NIHSS

İskemik İnme Hastalarında Nötrofil/Lenfosit ile Platelet/Lenfosit Oranının NIHSS'e Göre Hastalık Prognoz Tahminindeki Yeri

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ABSTRACT

Aim: Stroke is the most common neurological cause of morbidity and mortality worldwide. Therefore, controlling the risk factors in an early phase is critically important. In this study, we aimed to investigate the advantages of neutrophile lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) values against each other in predicting the prognosis of ischemic stroke.

Material and Method: 143 ischemic stroke patients were included in to study. Blood sample analysis was done to calculate NLR and PLR. Patients' NIHSS at first admission was also calculated. Multiple statistical analyses were used to analyze the statistical significance of NLR and PLR's predictive power in poor prognosis.

Results: We found that NLR was lower in those with a stroke scale score of 5 and below; the difference was statistically significant (p=0.015). The results of the ROC curve analysis showed that the NLR value was statistically significant in predicting patients categorized as NIHSS 6 and above (p<0.001).

Conclusion: This study is one of the first in the literature to evaluate the advantages of NLR and PLR values against one another in predicting stroke prognosis. Results show that the NLR value has a higher statistical significance in predicting prognosis than the PLR value. It is believed that prospective randomized studies can draw more meaningful conclusions on a larger set of patients.

Key words: *stroke scale; neutrophil/lymphocyte ratio; ischemic stroke; platelet/lymphocyte ratio; prognosis; cerebrovascular disorders*

ÖZET

Amaç: İnme, dünyadaki morbidite ve mortalitenin en yaygın nörolojik nedenidir. Bu nedenle risk faktörlerini erken bir aşamada kontrol etmek kritik derecede önemlidir. Bu çalışmada, nötrofil lenfosit oranı (NLO) ve platelet lenfosit oranı (PLO) değerlerinin iskemik inme prognozunu öngörmede birbirlerine olan avantajlarını araştırmayı amaçladık.

Materyal ve Metot: Çalışmaya 143 iskemik inme hastası dahil edildi. NLO ve PLO değerini hesaplamak için kan örneği analizi yapıldı. Hastaların ilk başvurudaki NIHSS değeri hesaplandı. NLO'nin istatistiksel önemini ve kötü prognozda PLR'nin öngörü gücünü analiz etmek için çoklu istatistiksel analiz kullanıldı.

Bulgular: İnme ölçeği puanı 5 ve altında olanlarda NLO'nun daha düşük olduğu tespit edildi, aradaki fark istatistiksel olarak anlamlı bulundu (p=0,015). ROC eğri analizi sonuçları, NIHSS 6 ve üstü olarak kategorize edilen hastaları tahmin etmede NLR değerinin istatistiksel olarak anlamlı olduğu saptandı. (p<0,001).

Sonuç: Bu çalışma, inme prognozunu öngörmede NLO ve PLO değerlerinin birbirine göre avantajlarını değerlendiren literatürdeki ilk çalışmalardan biridir. Sonuçlar, NLO değerinin, PLO değerine kıyasla prognozu tahmin etmede daha yüksek bir istatistiksel öneme sahip olduğunu göstermektedir. Daha geniş hasta grubunda ileriye dönük randomize çalışmalarla daha anlamlı sonuçların çıkarılabileceğine inanılmaktadır.

Anahtar kelimeler: *inme ölçeği; nötrofil/lenfosit oranı; iskemik inme; trombosit/lenfosit oranı; prognoz; serebrovasküler bozukluklar*

Introduction

A stroke is a neurological deficit after focal vascular damage to the central nervous system. Stroke is the most common neurological cause of morbidity and mortality in the world[1]. Therefore, it is critically important to understand all the factors involved in the development of stroke and to control the risk factors in an early phase[1]. Prognostic evaluation is important in choosing treatment but remains a serious challenge for clinicians. Therefore, it is important to find low-cost

and inclusive factors to evaluate stroke prognosis[2]. The inflammatory response has been shown to contribute to all pathophysiological processes in acute ischemic stroke[1]. Neutrophils and lymphocytes play an important role in regulating the immune response to cerebrovascular disease. An increase in white blood cells and neutrophils in patients with acute ischemic stroke in early stages has been associated with larger infarct volumes and an increased risk of stroke[1]. On the other hand, a decrease in lymphocyte count has been associated with poor functionalities in the three months after acute ischemic stroke.

The platelet-to-lymphocyte ratio (PLR) was an important marker of atherosclerosis's inflammation and severity of atherosclerosis[3]. In a study, the blood PLR value was significantly increased in patients with transient ischemic attack and stroke compared to the control group[4].

In this study, we aimed to investigate the advantages of neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) values against each other in predicting the prognosis of ischemic stroke.

Methods

Population Selection

We retrospectively evaluated the records of 257 consecutive ischemic stroke patients hospitalized in Kars Harakani state hospital from 2014 to 2016. Patients with hematological disease, history of cancer, severe renal and hepatic insufficiency, and a history of infection starting within 72 hours from the onset of stroke symptoms were excluded from the assessment. Patients with a brain stem, cerebellar, and acute hemorrhagic stroke wherein the effect of NLR and PLR values on the prognosis could not be examined and which could seriously affect the prognosis were also excluded. Also, patients receiving antibiotics, immunosuppressive therapy, and non-steroidal anti-inflammatory drugs were excluded from the study. Three patients were not evaluated due to lack of data, and seven were due to pneumonia during the stroke. Thus, a total of 143 patients were included in the study.

Studying Protocol

Electronic records of patients hospitalized for ischemic stroke were scanned from the hospital's electronic database system. Patients who developed stroke symptoms in the last 72 hours were selected. Patients' demographic and clinical characteristics were evaluated according to the National Institutes of Health Stroke Scale (NIHSS). NIHSS five and below were described as minor stroke and NIHSS six and above as severe stroke.

Chronic diseases of the patients were listed as hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, and hyperlipidemia.

Analysis of Blood Samples

Complete blood count tests were performed using the patients' first peripheral venous blood samples within the admission date. When calculating NLR and PLR, the arithmetic mean was calculated based on the individual numerical values of lymphocyte, neutrophil, and platelet values.

Statistical Analysis

Patients' data were entered into the SPSS 20.0 program, and statistical analysis was done with r 3.3.2v (open source) program. In statistical analyses, the significance level was set at $p < 0.05$. Categorical variables were summarized as numbers and percentages. Spearman Rho correlation coefficient was used to examine the associations between numerical variables. The normality of numerical variables was checked with Kolmogorov–Smirnov test. NIHSS cut-off values were taken as five and below for mild stroke and six and above for severe stroke. Mann-Whitney U method was used to check whether there was a significant difference between NLR and PLR considering the demographic characteristics of the patients and to investigate the significant variability of blood NLR and PLR values according to the cut-off value of the patients' stroke scale (NIHSS) scores at first admission. ROC curve analysis was performed to assess the significance of predicting morbidity between NLR and PLR in terms of sensitivity and specificity based on the cut-off value.

Results

Basic Characteristics

Sixty-six patients (47.83%) were male, and 77 (52.17%) were female. 23 patients (16.7%) had diabetes, 75 (54.35%) hypertension, 39 (28.68%) atrial fibrillation, 16 (11.68%) coronary artery disease, and 13 (21.67%) hyperlipidemia. Stroke scale score was five and below in 48.91% of the patients, six and above in 51.09%.

NLR value was 2.7 (2.03–4.38) in males, and 2.71 (1.8–4.68) in females, with no significant difference between them (p=0.771). PLR value was 133.665 (106.94–199.1) in males and 135.64 (104.28–186.85) in females, with no statistically significant difference (p=0.998).

NLR value was 2.750 (1.84–4.83) in patients with diabetes and 2.705 (1.96–4.33) in patients without diabetes; the difference between medians was not found statistically significant (p=0.831). The PLR value was 132.76 (95.23–176.72) in patients with diabetes, and 136.23 (106.94–197.72) in patients without diabetes, with no significant difference between medians (p=0.484).

There was no difference between NLR and PLR (p>0.05) depending on whether or not patients had hypertension, atrial fibrillation, coronary artery disease, and hyperlipidemia (Table 1).

Correlation Between Stroke Severity and NLR-PLR Value:

We investigated for any significant difference between patients' blood NLR and PLR values by their stroke scale scores at first admission. We found that the neutrophil/lymphocyte ratio was lower in those with a stroke scale score of five and below (2.26 (1.74–4.19)) as compared to those with a score of six and above (3.18 (2.11–5.25)); the difference was found to be statistically significant (p=0.015). On the other hand, the platelet/lymphocyte ratio was lower in those with a stroke scale score of five and below (130.18 (104.91–186.2)) as compared to those with a score of six and above (138.595 (100.75–193.1)), with no statistically significant difference between them (p=0.490).

ROC Analysis

The results of the ROC curve analysis showed that, according to the AUC (area under the curve) value of the NL variable, the NLR value was statistically significant in predicting patients categorized as NIHSS six and above (p<0.001) (Fig. 1). The ROC curve, sensitivity, and specificity values for the NLR value are below. Youden's index is calculated as J=sensitivity + specificity - 1 and takes a value in the range of (-1, +1). When Youden's index J is less than zero, the test has no diagnostic value. The correlation criterion can be determined based on where the Youden index value is maximal. Accordingly, the correlation criterion was set at ≤2.7. The sensitivity value obtained for this value is 62.86%, and the specificity value is 62.69%.

Table 1. Comparison of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratios by gender, Diabetes, Hypertension, Atrial Fibrillation, Coronary Artery Disease, Hyperlipidemia, and Stroke Scale Status

	Neutrophile/Lymphocyte	p	Platelet/Lymphocyte	P
Gender				
Men (n=66)	2.70 (2.03–4.38)	0.771	133.665 (106.94–199.1)	0.998
Women (n=72)	2.71 (1.8–4.68)		135.64 (104.28–186.85)	
Diabetes Mellitus				
Yes (n=23)	2.750 (1.84–4.83)	0.831	132.76 (95.23–176.72)	0.484
No (n=115)	2.705 (1.96–4.33)		136.23 (106.94–197.72)	
Hypertension				
Yes (n=75)	2.86 (1.85–4.83)	0.368	138.480 (110.26–199.1)	0.182
No (n=63)	2.495 (2–4.08)		128.825 (100.75–184.61)	
Atrial Fibrilation				
Yes (n=39)	2.88 (2.09–5.02)	0.447	122.915 (97.64–198.69)	0.404
No (n=97)	2.7 (1.85–4.33)		136.23 (110.89–188.11)	
Coronary Artery Disease				
Yes (n=16)	2.705 (1.635–4.55)	0.502	122.665 (79.01–156.65)	0.153
No (n=121)	2.725 (1.955–4.505)		137.28 (106.94–197.72)	
Hyperlipidemia				
Yes (n=13)	1.96 (1.71–4.38)	0.414	127.71 (115.42–197.72)	0.936
No (n=47)	2.88 (2.01–5.02)		134.48 (110.89–187.67)	
NIHSS*				
5 and below (n=65)	2.26 (1.74–4.19)	0.015*	130.18 (104.91–186.2)	0.490
6 and over (n=70)	3.18 (2.11–5.25)		138.595 (100.75–193.1)	

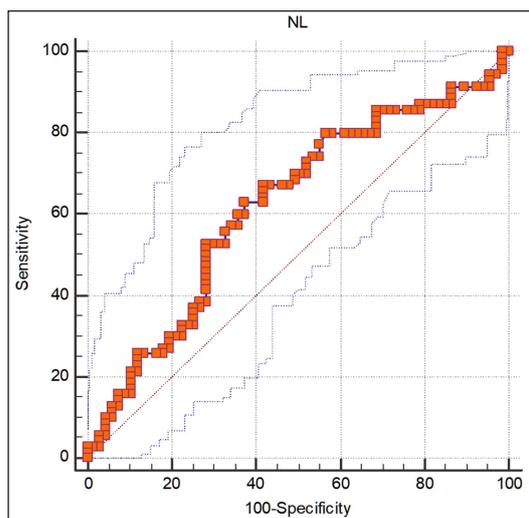*: p<0.05 Mann-Whitney U test *Stroke Scale
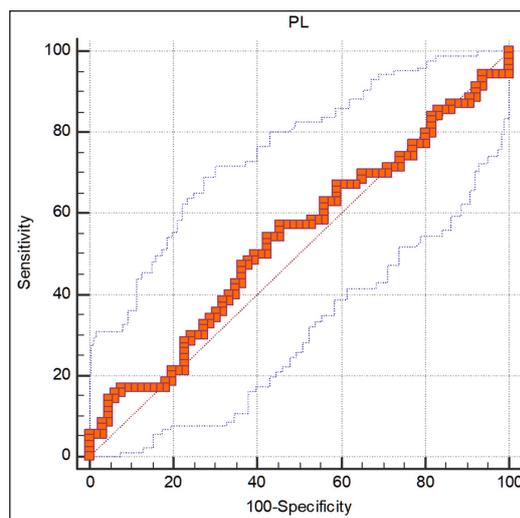
Figure 1. *NLR predictive value.*

Figure 2. *PLR predictive value.*

The results of the ROC curve analysis showed that according to the AUC (area under the curve) value of the PL variable, the PLR value was not found to be statistically significant in predicting patients categorized as NIHSS six and above (p=0.4914) (Fig. 2).

In predicting the poor prognosis based on NIHSS score in an ischemic cerebrovascular accident, the optimal cut-off value according to the ROC curve was 2.7 for NLR and 136.23 for PLR.

Discussion

This study is one of the first in the literature to evaluate the advantages of NLR and PLR values against one another in predicting stroke prognosis. Results show that the NLR value has a higher statistical significance in predicting prognosis than the PLR value.

The main limitation of our study is that it is retrospective and has a limited number of patients.

Neutrophil and lymphocyte cells play an important role in the development of atherosclerosis. Neutrophils increase atherosclerosis through inflammatory reaction, protein hydrolysis, and oxygen stress reaction. Lymphopenia is also responsible for the development of atherosclerosis. Another possible mechanism is that the NLR value can reflect the autonomic nervous system[5]. Neutrophils have adrenergic receptors and are stimulated by sympathetic fibers. Lymphocytes have cholinergic receptors, and the lymphocyte function is regulated by parasympathetic nerves[5]. The role of lymphocytes in ischemic stroke is controversial. They are reported not only to have healing and repair effects but also to worsen the ischemic accident as they are a proinflammatory source of cytokines[1].

Recent studies have shown that the blood NLR value is statistically significantly associated with mortality in patients with acute ischemic stroke. A high NLR value at first admission to the hospital is associated with mortality from acute ischemic stroke in the first 60 days[6].

It is also suggested that basal neutrophil values are associated with the severity of tissue damage in ischemic stroke, the risk of stroke recurrence, and poor neurological consequences[4]. A study found markedly increased levels of blood neutrophils in patients with lacunar stroke, demonstrating a significant relationship between the level of neutrophils and the size of the stroke area independently from etiology[4]. In another study, blood NLR, eosinophils, and RDW values were identified as independent factors indicating the prognosis for ischemic stroke[3]. Given these studies, it makes sense that the NLR value also stands out in determining the prognosis in our study. In addition to chronic inflammation in the relationship between increased NLR and ischemic stroke, conditions related to increased neutrophil activity, such as the formation of neutrophil extracellular traps, may also be associated with thrombosis[7].

In another study, NLR was found to be higher in patients with poor prognosis according to Modified Rankin Scale (MRS)[8]. Similarly, in our study, the NLR value was significantly higher in patients with poor

prognoses (NIHSS >6) at first hospitalization. This picture can also be considered as a criterion for measuring morbidity. Similarly, it is suggested in a study that a high level of NLR presented the highest risk of unfavorable functional outcomes like ours[11].

PLR is of high prognostic value in terms of showing inflammatory destruction in cardiovascular diseases. It plays an important role in plaques' development, destabilization, and rupture. The decrease in the total and relative number of lymphocytes circulating in the blood is due to the increased production of cortisol caused by physiological stress. Therefore, high levels of platelet and low levels of lymphocytes can be associated with poor prognosis in ischemic accidents[9]. Moreover, a study found a markedly negative correlation between mortality and blood lymphocyte levels after ischemic stroke, indicating there may be a correlation between lymphopenia and the severity of stroke[4]. Sixteen studies were included in a systematic review and nine in the meta-analysis. On analysis of eight studies, there was no statistically significant relationship between PLR and poor functional outcomes in patients with stroke[12].

In our study, the PLR was found to be higher in patients with NIHSS six and above than in patients with NIHSS five and below, but the difference was insignificant.

Routine hematological measurements are superior to other blood markers because they are easily accessible, low-cost, objective, and therefore easily preferable in clinical practice[2].

In conclusion, it was found that the NLR value may be superior to the PLR value in determining the prognosis of ischemic stroke patients and planning treatment strategies. It is believed that prospective randomized studies can draw more meaningful conclusions on a larger set of patients.

Declarations of Interest

None

Funding

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