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Original Article / Özgün Araştırma

The Effect of Neutrophil to Lymphocyte and Neutrophil to Platelet Ratios on Prognosis in Stroke Patients

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Abstract

Background: The aim of this study is to determine the correlation of neuroinflammatory response biomarkers neutrophil to lymphocyte ratio (NLR), neutrophil to platelet ratio (NPR) with risk factors, etiology, and prognosis in stroke patients.

Methods: Cases diagnosed with ischemic stroke were recruited in this study. Demographic data, comorbidities, laboratory findings, carotid doppler ultrasonography, NIHSS (National Institutes of Health Stroke Scale) and MRS (modified rankin scale) scores of the cases were documented. Afterwards, the cases were divided into 3 groups (posterior circulation infarct, anterior circulation infarct, and lacunar infarct).

Results: A total of 133 patients, 65 female and 68 males, aged between 24 and 94 were included in this study. At the end of hospitalization, NLR (p=0.001) and NPR (p=0.007) were significantly found high in patients with unfavorable functional outcome (MRS≥3) and those who died compared to NLR (p=0.001) and NPR (p=0.008) in the favorable functional outcome group. The NLR cut-off value for unfavorable functional outcome (95% confidence interval lower limit of area-under-curve of ROC≥0.7) was found to be 4.0.

Conclusion: High NLR and NPR values measured at first admission in patients with acute ischemic stroke are highly associated with unfavorable functional outcome and mortality, and NLR and NPR are important prognostic biomarkers in patients with acute ischemic stroke.

Keywords: Ischemic stroke, NLR, NPR, arterial thrombosis and embolism

İnmeli Olgularda Nötrofil/Lenfosit ve Nötrofil/Trombosit Oranlarının Prognoz Üzerine Etkisi

Öz

Amaç: İnme hastalarında nöroinflamatuar yanıt biyobelirteçlerinden nötrofil/lenfosit oranı (NLR), nötrofil/trombosit oranı (NPR) ile risk faktörleri, etiyoloji ve prognoz arasındaki korelasyonu belirlemektir.

Yöntemler: Bu çalışmaya iskemik inme tanısı ile izlenen hastalar dahil edildi. Hastaların demografik verileri, komorbiditeleri, laboratuvar bulguları, karotis doppler ultrasonografi, NIHSS (National Institutes of Health Stroke Scale) ve MRS (modifiye rankin skalası) skorları kaydedilerek arka sirkülasyon enfarktüsü, ön sirkülasyon enfarktüsü ve laküner enfarktüs olmak üzere gruplara ayrıldı.

Bulgular: Çalışmaya yaşları 24 ile 94 arasında değişen 65'i kadın, 68'i erkek toplam 133 hasta dahil edildi. Hospitalizasyon sonunda, olumsuz fonksiyonel sonuçlu (MRS≥3) ve ölen hastalarda NLR (p=0,001) ve NPR (p=0,007), olumlu fonksiyonel sonuç grubundaki NLR (p=0,001) ve NPR (p=0,008)'ye göre anlamlı olarak yüksek bulundu. Olumsuz fonksiyonel sonuç için NLR cut-off değeri (%95 güven aralığı alt sınırı ROC≥0,7) 4.0 saptandı.

Sonuç: Akut iskemik inmeli hastalarda ilk başvuruda ölçülen yüksek NLR ve NPR değerleri, olumsuz fonksiyonel sonuç ve mortalite ile yüksek oranda ilişkilidir ve NLR ve NPR, akut iskemik inmeli hastalarda önemli prognostik biyobelirteçlerdir.

Anahtar kelimeler: iskemik inme, NLR, NPR, arteriyel tromboz ve emboli.

INTRODUCTION

Cerebrovascular disease ranks first among adult deaths after ischemic heart disease[1].Inflammatory cytokines, leukocyte and platelet infiltration followed by impaired blood brain barrier play a role in the pathophysiology of acute ischemic stroke[2]. Neutrophils from leukocytes infiltrating ischemic regions are thought to play an important role in brain damage[3].

The body has two types of defense systems: innate and adaptive. Innate immunity provides the first defense against infiltration[4]. Mainly neutrophils, monocytes, macrophages, NK cells and complement systems play a role in this. Antigen-dependent lymphocytes play a role in adaptive immunity.NLR may reflect the balance between innate and adaptive immunity[5].

Neutrophils can rapidly recruit into cerebral vessels several hours after ischemic stroke[3]. It has been reported that lymphocytes can invade the area of inflammation even a few days after the event in acute ischemic stroke[6]. In addition, stroke may increase neuron dysfunction by causing an increase in neutrophils and a decrease in some lymphocytes with cerebral protective properties[7]. Inflammatory cytokines released from platelets are both the initiator and promoter of the atherosclerotic process[8]. Due to the ease of measurement and low cost, the interest in the ratio of blood cells in the diagnosis and follow-up of stroke has increased. In previous studies, some publications reported that high NLR at first admission was associated with stroke severity, mortality, and infarct size, while others reported that NLR had no effect on mortality. In a study conducted with patients with acute ischemic stroke, NPR was found to be high in patients with hemorrhagic transformation[9].Therefore, we conducted a more comprehensive study compared to previous studies and aim of this study is to determine the correlation between neutrophil to lymphocyte and neutrophil to platelet ratios with stroke subtype, risk factors, mortality and prognosis.

METHODS

This study was a prospective, hospital-based study which consisted of patients who were

hospitalized with the diagnosis of ischemic stroke. The Ethics Committee for Medical Research of Adana Numune Training and research hospital (new name Health Sciences University Adana Faculty of Medicine City Hospital) approved the study (No:ANEAH.EK.2016/74 and 2016-04-26).

A total of 133 patients aged 24-94 years who were followed up in the neurology clinic due to the diagnosis of ischemic stroke were included in this study. Patients who were diagnosed with ischemic stroke neuroradiologically (neurological examination, brain CT and brain diffusion MRI), had not undergone major surgery in the last 3 months, had a current clinical status not depending on trauma, tumor, infectious disease or hematological disorder, and were not diagnosed with intracranial, subdural, epidural, and subarachnoid hemorrhage were included in the study. Those who did not meet these criteria were not included in the study. The patients were classified as posterior circulation infarct, anterior circulation infarct, and lacunar infarct in the diagnosis based on the classification made by Blanford et al., in 1991 according to their clinical findings. The cases' demographic data, comorbidities, laboratory findings, carotid doppler ultrasonography, NIHSS and MRS scores were documented[10,11]. At the end of the hospitalization period, MRS≥ 3 was associated with unfavorable functional outcome; whereas, MRS <3 was associated with favorable functional outcome.

The checked parameters were demographic data, comorbid diabetes mellitus (DM), hypertension (HT), serum lipid and cholesterol levels, atrial fibrillation (AF), heart failure, coronary artery disease (CAD), heart valve disease and previous stroke history, effects of drugs used (antihypertensive, Acetyl salicylic acid, clopidogrel, antilipidemic, insulin), intravenous (IV) and intra-arterial (IA) thrombolytic (tissue plasminogen activator,

TPA) and thrombectomy treatments applied during hospitalization, NLR and NPR at the first admission, admission glucose, fibrinogen, creatinine values, admission and exit (discharge or exitus) neurological NIHSS and exit MRS at discharge.

Statistical Analysis

The results of the study are presented as mean ± SD and, where appropriate, median and IQR. Chi-square test and Shapiro Wilk analyzes were performed for categorical variables, and Student-T and Mann-Whitney U analyzes for continuous variables. Pearson Correlation Coefficient or Spearman Rank Correlation Coefficient was used to evaluate correlations between measurements. A receiver operator characteristic (ROC) curve analysis was performed to determine the appropriate cut-off points in estimating the distinction between well and poor prognosis for the NLR variable. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

One hundred thirty three patients who met the inclusion criteria and were hospitalized in the neurology clinic and intensive care unit were included. 65 (48.9%) female and 68 (51.1%) male patients were included, their mean age was 67.9±13.9 and 93% of them were over 45 years old.

Seventeen (12.8%) of the patients died during follow-up. The stroke type was anterior circulation in 56 (42.1%) of patients, posterior circulation in 50 (37.6%) and lacunar stroke in 27 (20.3%). According to the diagnosis, the groups showed similar rates in terms of age, gender, alcohol and smoking use, insulin-statin-antiaggregant-antihypertensive-NOAC (new oral anticoagulation)-warfarin use, carotid and vertebral artery stenosis rate, ejection fraction, cholesterol, and creatinine levels (Table 1).

Table I: Clinical and Demographic Characteristics

		N	%
Age	≥45	124	93.23
	<45	9	6.77
Gender	M	68	51.1
	F	65	48.9
Discharge	Posterior infarct	50	37.6
	Anterior infarct	56	42.1
	Lacunar infarct	27	20.3
Comorbidity	HT	25	18.8
	DM	6	4.5
	Cardiovascular disease (MI,CAD, CHF,AF, etc.)	6	4.5
	Previous CVD	3	2.25
	At least two diseases (DM,HT,CAD; hyperlipidemia etc.)	134	25.56
	≥3diseases (DM,HT,CAD+)	47	35.3
	No feature	12	9.02
Habits	Smoking (active smoker)	31	23.3
	Smoking (ex-smoker)	14	10.5
	Never smoke	88	66.1
	Alcohol (actively consuming)	7	5.26
	Alcohol (consuming in the past)	3	2.25
	Never consume	123	92.48
Medications they were taking	Insulin	21	15.8
	Statin	8	6.01
	Antiagregant	39	29.3
	Antihypertensive	69	51.88
	NOAC	5	3.76
	Warfarin	9	6.76

F:Female, M:Male, HT: hypertension, DM: Diabetes mellitus, MI: myocardial infarction, CAD: coronary artery disease CHF: congestive heart failure, AF: atrial fibrillation, SVH: cerebrovascular disease, NOAC: New oral anticoagulant,

Fibrinogen (p=0.0036) and INR (p=0.0020) were significantly higher in patients with anterior infarction. There was more hemorrhagic transformation in the anterior infarction group than in the other groups, but there was no difference in NLR and NPR between those with and without hemorrhagic transformation. While the NIHSS and MRS scores at admission were grater in the anterior infarct group, the exit NIHSS score was significantly lower (Table 2) but did not differ between groups with carotid stenosis <50% and ≥50% (p=0.272).

Table II: Demographic and clinical and laboratory findings based on diagnosis

	Anterior infarct (n= 50)	Posterior infarct (n=56)	lacunar infarct n=27	P value
Age	65.9 ±13.9(40-87)	71.2±14.04(24-94	65.8±13.3(35-91)	P=0.201
F N (%)	31 (55.4)	19 (38)	15(55.6)	
M N (%)	25 (44.6)	31 (62)	12 (44.4)	P=0.023
≥50 carotid stenosis	18 (32.1)	8 (16)	2 (7.4)	P=0.058
Vertebral artery stenosis	7 (12.5)	7 (14)	4 (14.8)	P=0.134
EF	54.5±9.4(30-73)	54±9.6(25-65)	53.6±7.7(35-70)	P=0.474
HDL	35.6±12.7(8-84)	37±10.26(23-66)	41.28±13.75(24-86)	P=0.158
LDL	115.5±40.7(40-235)	120.3±34.7(44-218)	127.9±40.9(64-242)	P=0.452
TG	155.78±86.2(49-527)	151.7±79.5(25-461)	172.5±79.2(62-397)	P=0.288
Creatinine	1.03±0.68(0-5)	0.99±0.55(0-4)	1.09±0.99(0-6)	P=0.731
INR	1.19±0.22(1-2)	1.08±0.09(1-1)	1.12±0.2(1-2)	P=0.020
Glucose	172.5±118.9(79-614)	182.04±92.2(80-507)	173.8±81.1(76-384)	P=0.125
Average blood Pressure	107.1±19.3(73-148)	106.2±22.7(76-200)	102.5±19.3(73-151)	P=0.695
Fibrinogen	346.3±175.8(0-669)	278.5±178.8(0-669)	238.6±190.3(0-486)	P=0.036
The use of insulin (N)	8	6	7	P=0.043
The use of statin (N)	5	1	2	P=0.098
The use of antiagregant (N)	15	16	8	P=0.097
The use of antihypertensives (N)	27	26	16	P=0.084
The use of NOAC (N)	1	4	0	P=0.040
The use of warfarin (N)	5	2	2	P=0.139
Hemorrhagic transformation	7	0	1	P=0.098
NLR	6.51±4.9(1-22)	4.6±3.75(0-18)	4.12±3.7(2-20)	P=0.02
NPR	0.04±0.016(0-0)	0.03±0.015(0-0)	0.04±0.029(0-0)	P=0.267
Admission NIHSS	12.06±4.60(4-20)	9.48±4.17(2-20)	8±4.46(4-22)	P=0.000
Exit NIHSS	3.06±2.83(0-8)	4.19±2.99(0-9)	4.28±2.62(1-9)	P=0.013
MRS	3.48±1.98(0-6)	3.15±1.65(0-6)	2.32±1.37(1-6)	P=0.015

F:female, M:male, EF: ejection fraction, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: triglyceride, NOAC: New oral anticoagulant Parameters were expressed as mean±SD, median (min.-max.), numbers and percentage

NLR and NPR were found to beelevated in patients with unfavorable functional outcome (MRS≥3) at the end of the hospitalization period than patients with favorable functional outcome (MRS<3) (Table 3).

Table III: NLR and NPR findings of patients with unfavorable functional outcome (MRS≥3) and favorable functional outcome (MRS<3)

Variable	Exit MRS≥3 (n=88) (Unfavorable functional outcome)	Exit MRS<3 (n=45) (Favorable functional outcome)	p
NLR	4.5 (0.4-22.1)	2.7 (0.7-19.6)	0.001*
NPR	0.03 (0.01-0.08)	0.02 (0.01-0.13)	0.007*

p<0.05 statistical significance Parameters were expressed as median (min.-max.)

While the highest mortality rate was observed in the anterior circulation infarct group (14.3%), the lowest mortality rate was found in the lacunar group (3.7%). NLR and NPR were found to be elevated in patients who died (MRS=6) compared to those who were discharged (Table 4).

Table IV: Comparison of NLR and NPR results of deceased patients with values of the discharged ones

Variable	Exit MRS 6(Ex) (n=17)	ExitMRS <6 (n=116)	*p*
NLR	9.7(2.3-22.1)	3.9(0.4-19.6)	**<0.001***
NPR	0.04(0.02-0.06)	0.03(0.01-0.13)	**0.008***

p<0.05 statistical significance

DISCUSSION

Numerous studies have drawn attention to the role of neuroinflammation in ischemic stroke[12–14]. NLR, neutrophil, leukocyte and platelet counts are significantly associated with survival in acute ischemic stroke[15]. NLR and PNR have recently been reported as potential new biomarkers of the initial inflammatory process and are predictors of prognosis in patients with ischemic stroke[16–20]. This study was designed to investigate whether NLR is an independent risk factor for unfavorable functional outcome and mortality in acute ischemic stroke, as in previous studies, and to determine that NPR may be a cost-effective method that can be used in acute ischemic stroke prognosis. Our study confirmed that NLR and NPR measured at the first admission are independent risk factors for unfavorable functional outcome and mortality in acute ischemic stroke.

Platelets can directly cause arterial thrombosis and embolism in ischemic stroke and also be the main processor of activators stored in platelet granules that mediate other peripheral blood cells[21]. Previously, at 3-month follow-up of acute ischemic stroke, PNR was identified as an independent factor with greater accuracy than PLR and platelet/White blood cell ratio (TWR)[1]. We investigated the NPR, which plays an active role in acute ischemic stroke, and as a new finding, we found that high NPR is associated with unfavorable functional outcome and mortality.

While Some studies have reported NLR cut-off values such as 3.3[22]; 3.51[23] and 2.995[24]for unfavorable functional outcome in acute ischemic stroke, Çelikbilek et al., stated NLR cut-off as 4.1 for prediction of mortality in patients with atherothromboticstroke[25]. In our study, the NLR cut-off value was found to be 4.0 with 71.2% sensitivity and 38% specificity for unfavorable functional outcome.

Although it has been stated that NLR is higher in patients with symptomatic carotid stenosis than in asymptomatic patients, it is a predictive indicator of carotid stenosis[26,27].In our study, it was observed that there was no difference in NLR values between those with 50% or more carotid stenosis and those with stenosis below 50%, which may be due to the fact that both groups consisted of symptomatic subjects. In a study comparing 279 patients, it was reported that high NPR was an independent predictive factor for hemorrhagic transformation, and the rate of hemorrhagic transformation was high in large artery atherosclerosis and anterior

circulation infarctions[9]. Likewise, we found a higher rate of hemorrhagic transformation in anterior circulation infarcts than in the other groups, but NPR did not differ significantly between groups for hemorrhagic transformation. This might have been caused by the small sample size with the hemorrhagic transformation in the present study. As previously stated by various authors, NLR did not show significance between groups for hemorrhagic transformation in our study either[28]. Although mortality and hemorrhagic transformation rates were higher in the anterior circulation infarction group in the present study, the lower exit NIHSS scores of those who did not die may be due to a better prognosis depending on early revascularization and good perfusion.

The limitations of our study are the selection of participants only from a single institution with strict exclusion criteria, the relatively small sample size, the use of a single WBC measurement to estimate mortality, and the lack of long-term results. Multiple measurements and changes in these measurements over time may provide a more accurate mechanism for prediction.

CONCLUSION

This study revealed that high NLR and NPR values measured at first admission in acute ischemic stroke are highly correlated with unfavorable functional outcome and mortality, therefore NLR and NPR are important prognostic biomarkers. In addition, hemorrhagic transformation and mortality rates were higher in the anterior circulation infarction group. Finally, given that the role of inflammation is still complex, more studies should be conducted to better record more inflammatory indices in the future, not only in ischemic stroke but in many neurological diseases.

REFERENCES

1. Jin P, Li X, Chen J, et al. Platelet-to-neutrophil ratio is a prognostic marker for 90-days outcome in acute ischemic stroke. Journal of Clinical Neuroscience. 2019; 63: 110-115. doi: 10.1016/j.jocn.2019.01.028

2. Tokgoz S, Kayrak M, Akpinar Z, Seyithanoğlu A, Güney F, Yürüten B. Neutrophil Lymphocyte Ratio as a Predictor of Stroke. Journal of Stroke and Cerebrovascular Diseases. 2013;22(7):1169-1174. doi: 10.1016/j. jstrokecerebrovasdis.2013.01.011

3. Herz J, Sabellek P, Lane TE, Gunzer M, Hermann DM, Doeppner TR. Role of Neutrophils in Exacerbation of Brain Injury After Focal Cerebral Ischemia in Hyperlipidemic Mice. Stroke. 2015; 46(10): 2916-2925. doi: 10.1161/STROKEAHA.115.010620

4. Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. Journal of Clinical Investigation. 2020; 130(6):2 777-2788. doi: 10.1172/JCI135530

5. van der Willik KD, Fani L, Rizopoulos D, et al. Balance between innate versus adaptive immune system and the risk of dementia: a population-based cohort study. J Neuroinflammation. 2019; 16(1): 68. doi: 10.1186/s12974-019-1454-z

6. Kim JY, Kawabori M, Yenari MA. Innate Inflammatory Responses in Stroke: Mechanisms and Potential Therapeutic Targets. CMC. 2014; 21(18): 2076-2097. doi: 10.2174/0929867321666131228205146

7. Petrone AB, Eisenman RD, Steele KN, Mosmiller LT, Urhie O, Zdilla MJ. Temporal dynamics of peripheral neutrophil and lymphocytes following acute ischemic stroke. Neurol Sci. 2019;40(9):1877-1885. doi: 10.1007/s10072-019-03919-y

8. Bakogiannis C, Sachse M, Stamatelopoulos K, Stellos K. Platelet-derived chemokines in inflammation and atherosclerosis. Cytokine. 2019; 122: 154157. doi: 10.1016/j.cyto.2017.09.013

9. He W, Ruan Y, Yuan C, et al. High Neutrophil-to-Platelet Ratio Is Associated With Hemorrhagic

Transformation in Patients With Acute Ischemic Stroke. Front Neurol. 2019; 10: 1310. doi: 10.3389/fneur.2019.01310

10. Tale AC. Using the National Institutes of Health Stroke Scale. Stroke. 2017; 48: 513-519.

11. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017; 48(7): 2007-2012. doi: 10.1161/STROKEAHA.117.017866

12. Schuhmann MK, Stoll G, Bieber M, et al. CD84 Links T Cell and Platelet Activity in Cerebral Thrombo-Inflammation in Acute Stroke. Circ Res. 2020; 127(8): 1023-1035. doi: 10.1161/CIRCRESAHA.120.316655

13. Stoll G, Nieswandt B. Thrombo-inflammation in acute ischaemic stroke — implications for treatment. Nat Rev Neurol. 2019; 15(8): 473-481. doi: 10.1038/s41582-019-0221-1

14. Parikh NS, Merkler AE, Iadecola C. Inflammation, Autoimmunity, Infection, and Stroke: Epidemiology and Lessons From Therapeutic Intervention. Stroke. 2020; 51(3): 711-718. doi: 10.1161/STROKEAHA.119.024157

15. Adiguzel A, Arsava EM, Topcuoglu MA. Temporal course of peripheral inflammation markers and indexes following acute ischemic stroke: prediction of mortality, functional outcome, and stroke-associated pneumonia. Neurol Res. 2022; 44(3): 224-231. doi: 10.1080/01616412.2021.1975222

16. Zhao L, Dai Q, Chen X, et al. Neutrophil-to-Lymphocyte Ratio Predicts Length of Stay and Acute Hospital Cost in Patients with Acute Ischemic Stroke. Journal of Stroke and Cerebrovascular Diseases. 2016; 25(4): 739-744. doi: 10.1016/j.jstrokecerebrovasdis.2015.11.012

17. Zhu B, Pan Y, Jing J, et al. Neutrophil counts, neutrophil ratio, and new stroke in minor ischemic stroke or TIA. Neurology. 2018; 90(21): e1870-e1878. doi: 10.1212/WNL.0000000000005554

18. Kurt NG, Güloğlu C, Tamam Y, Üstündağ M, Murat O. The releationship between serum levels of gamma glutamyl transferase, mean thrombocyte volume, red blood cell distribution width, neutrophil to lymphocyte ratio with prognose and mortality in patients admitted emergency department with acute ischemic stroke. Dicle Tıp Dergisi. 2019; 46(2): 361-368.

19. Semerano A, Strambo D, Martino G, et al. Leukocyte Counts and Ratios Are Predictive of Stroke Outcome and Hemorrhagic Complications Independently of Infections. Front Neurol. 2020; 11: 201. doi:10.3389/fneur.2020.00201

20. Zhang X, Xue J, Yang W, et al. Inflammatory markers as independent predictors for stroke outcomes. Brain Behav. 2021; 11(1). doi: 10.1002/brb3.1922

21. Thomas M, Storey R. The role of platelets in inflammation. ThrombHaemost. 2015; 114(09): 449-458. doi: 10.1160/TH14-12-1067

22. Giede-Jeppe A, Madžar D, Sembill JA, et al. Increased Neutrophil-to-Lymphocyte Ratio is Associated with Unfavorable Functional Outcome in Acute Ischemic Stroke. Neurocrit Care. 2020; 33(1): 97-104. doi: 10.1007/s12028-019-00859-5

23. Chen C, Gu L, Chen L, et al. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Potential Predictors of Prognosis in Acute Ischemic Stroke. Front Neurol. 2021; 11: 525621. doi: 10.3389/fneur.2020.525621

24. Qun S, Tang Y, Sun J, et al. Neutrophil-To-Lymphocyte Ratio Predicts 3-Month Outcome of Acute Ischemic Stroke. Neurotox Res. 2017; 31(3): 444-452. doi: 10.1007/s12640-017-9707-z

25. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to Lymphocyte Ratio Predicts Poor Prognosis in Ischemic Cerebrovascular Disease: Neutrophil to Lymphocyte Ratio in Ischemic Stroke. J Clin Lab Anal. 2014; 28(1): 27-31. doi: 10.1002/jcla.21639

26. Massiot N, Lareyre F, Voury-Pons A, et al. High Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio are Associated with Symptomatic Internal Carotid Artery Stenosis. Journal of Stroke and Cerebrovascular Diseases. 2019; 28(1): 76-83. doi: 10.1016/j.jstrokecerebrovasdis.2018.09.001

27. Köklü E, Yüksel İÖ, Arslan Ş, et al. Is Elevated Neutrophil-to-Lymphocyte Ratio a Predictor of Stroke in Patients with Intermediate Carotid Artery Stenosis? Journal of Stroke and Cerebrovascular Diseases. 2016; 25(3): 578-584. doi: 10.1016/j.jstrokecerebrovasdis.2015.10.031

28. Quan K, Wang A, Zhang X, et al. Neutrophil to lymphocyte ratio and adverse clinical outcomes in patients with ischemic stroke. Ann Transl Med. 2021; 9(13): 1047-1047. doi: 10.21037/atm-21-710