



Neutrophil/Lymphocytes Ratio in Acute Ischemic Stroke

Akut İskemik İnmede Nötrofil/lenfost Oranı

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ABSTRACT

Objectives: Neutrophil and lymphocyte numbers are known to play a role in the inflammatory response and in the atherosclerotic process. The elevated level of neutrophil/lymphocyte ratio (NLR) is associated with prognosis, disease severity and mortality in cardiovascular diseases and atherosclerosis. In this study, we aimed to investigate whether NLR changed in acute ischemic stroke (AIS) patients, whether there was a relationship between NLR and lesion size, type of involvement, age, sex, and whether NLR had effect on short term prognosis.

Methods: One hundred and seventy-four patients admitted with AIS diagnosis were included in the study. Patients' existing files were screened for anamnesis, physical and neurological examinations, chronic illness history, antiplatelet and anticoagulant use, complete blood count, cholesterol panel, routine biochemical examinations, cranial Computed Tomography and Magnetic Resonance Imaging findings. Patients were grouped according to Bamford classification and TOAST classification.

Results: Of the participants, 88 (50.9%) were female, 86 (49.1%) were male and the mean age was 73.8 ± 10.5 years. NLR was significantly higher in patients with AIS in terms of normal reference values. When patients were assessed within themselves, NLR increased as age increased. In the 50-59 and 60-69 age groups, NLR was higher in males. No gender difference was found over 70 years old patients. The NLR values of the total anterior circulation infarct group were significantly higher than the other groups ($p=0.011$; $p=0.038$; $p=0.001$). The NLR values of the patients with exitus were meaningfully higher than the surviving patients ($p=0.006$).

Conclusion: The NLR value is elevated in patients with AIS and correlates with increased age, male gender and wide infarct area. Higher NLR seems to predict short-term mortality and may be used as a prognostic tool.

Keywords: Acute ischemic stroke; neutrophil lymphocytes rate; neutrophil/lymphocyte ratio.

ÖZET

Amaç: Nötrofil ve lenfosit sayılarının inflamatuvar yanıtta ve aterosklerotik süreçte rol oynadığı bilinmektedir. Nötrofil/lenfosit oranı (NLO) seviyesinin yüksekliği kardiyovasküler hastalıklarda ve aterosklerozda prognoz, hastalık şiddeti ve mortalite ile ilişkilidir. Bu çalışmada, NLO'nun akut iskemik inme (Aİİ) hastalarında yükselip yükselmediğinin, yaş ve cinsiyete göre değişiminin, lezyon boyutu ve tutulum tipi ile ilişkisinin ve kısa dönem prognoz üzerindeki etkisinin araştırılması amaçlandı.

Yöntem: Aİİ tanısı alan 174 hasta çalışmaya alındı. Hastaların mevcut dosyaları taranarak, anamnez bilgileri, fizik ve nörolojik muayeneleri, kronik hastalık öyküleri, antiagregan ve antikoagülan kullanıp kullanmadıkları, hemogram kolesterol paneli, rutin biyokimya tetkikleri, kraniyal BT ve MRG bulguları incelendi. Hastalar Bamford ve TOAST sınıflandırmasına göre olarak gruplandırıldı.

Bulgular: Çalışmaya alınanların 88'i (%50.9) kadın, 86'sı (%49.1) erkek ve yaş ortalamaları 73.8 ± 10.5 yıl idi. Aİİ hastalarında NLO referans değerlere göre anlamlı düzeyde yüksek saptandı. Hastalar kendi içinde değerlendirildiğinde yaş arttıkça NLO artıyordu. Erkeklerde 50-59 ve 60-69 yaş gruplarında NLO daha yüksek bulundu. Yetmiş yaş ve üzerinde cinsiyet farkı bulunmadı. TACI grubunun NLO değerleri diğer gruplara göre anlamlı oranda yüksek saptandı. Eksitus olan hastaların NLO değerleri diğer hastalardan anlamlı oranda yüksek bulundu.

Sonuç: Aİİ olgularında NLO değeri yükselmektedir ve yaş artışı, erkek cinsiyet ve geniş infarkt alanı olması bu yükselme ile korelasyon göstermektedir. NLO'nun kısa dönem mortalite ile olan ilişkisi, prognoz için prediktif bir değer taşıdığını ortaya koymaktadır.

Anahtar sözcükler: Akut iskemik inme; nötrofil lenfosit oranı; NLR.

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According to the World Health Organization, stroke is defined as a clinical syndrome that occurs without any visible cause other than vascular causes, with the rapid development of signs and symptoms of brain function loss as a result of impaired brain blood flow and these findings lasting longer than 24 h.^[1]

Neutrophil/lymphocyte ratio (NLR) is an indicator which is calculated by using neutrophil and lymphocyte values in the whole blood test and is used frequently today. NLR is generally considered to be an indicator of sub-clinical inflammation. In many areas, studies are being conducted on the effect on prognosis.

In studies on NLR; hypertension, diabetes mellitus, metabolic syndrome, left ventricular dysfunction, acute coronary syndrome, heart valve disease, thyroid dysfunction, renal and hepatic dysfunction, malignancy, local or systemic infection, inflammatory diseases - as an indicator of inflammation - NLR has been shown to be elevated.^[2,3]

In this study, it was aimed to investigate whether NLR was elevated in patients with acute ischemic stroke (AIS), the change according to age and gender, the relationship between lesion size and type of involvement, and its effect on short-term prognosis. In addition, NLR's relationship with the presence of diabetes, hypertension, hyperlipidemia; the correlation between gamma glutamyl transferase (GGT), mean platelet volume (MPV) values was investigated.

Methods

Patients

In this study, records of 174 patients who were hospitalized and diagnosed with the first or recurrent AIS between 2013 and 2016 at a tertiary research and training hospital were analyzed retrospectively. Patients over 50 years of age who had no history of trauma, surgical operation, hematological malignancy, infection, intoxication, liver, and renal disease were included in the study with our ischemic stroke clinic. Patients were divided in six groups; according to gender and age: 50-59, 60-69, 70 and over. As the reference value for NLR, the average values in the Turkish study of Aydin et al.^[4] were taken.

Patients Data

The current files of the patients are scanned, anamnesis information, physical and neurological examinations,

chronic disease histories, whether they use antiplatelet and anticoagulants during application, complete blood count (leukocyte, erythrocyte, hematocrit, MPV, neutrophil, lymphocyte), cholesterol panel (high-density lipoprotein, low-density lipoprotein, and triglycerides), routine biochemistry tests, electrocardiogram, transthoracic echocardiography, Carotid and Vertebral Doppler, cranial computed tomography and magnetic resonance imaging findings were examined. Patients were grouped as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarcts (LACI), posterior circulation infarct (POCI) according to Bamford classification and as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, stroke of undetermined etiology according to TOAST classification.

Laboratory

In all patients, within the first 24 h after admission to the hospital, complete blood count examinations were performed with ABBOTT CELL DYN 3700 blood counting device by taking blood from the antecubital vein into tubes containing K3EDTA. This analyzer uses laser and impedance method together. The blood samples were studied at room temperature within 1 h.

Distribution of the NLR of the patients by age and gender; the relationship between the normal population in the same age group was evaluated. In addition, the relationship between patients' risk factors such as diabetes, hypertension, hyperlipidemia, GGT, MPV values, discharge patterns from the hospital (healthy with deficit, death, referral to intensive care unit) and stroke localization and NLR values were compared.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics 22 (IBM SPSS, Turkey) programs were used. The suitability of the parameters to normal distribution was evaluated with the Shapiro Wilks test. While evaluating the study data; in addition to descriptive statistical methods (mean, standard deviation, frequency), Kruskal Wallis test was used to compare the parameters that did not show normal distribution in the comparison of quantitative data and Mann Whitney U test was used to determine the group that caused the difference.

Student t-test was used to compare patient and control groups. Spearman's rho correlation analysis was used to

examine the relationships between parameters that do not conform to normal distribution. $P < 0.05$ was considered statistically significant.

Results

The study was performed on 174 cases, whose ages ranged between 50 and 100. The average age of the cases was calculated as 73.88 ± 10.52 years.

Of the cases included in the study; 50.9% were women and 49.1% were men. According to age and gender distribution; 2.3% of women are between the ages of 50-59, 9.7% are between the ages of 60-69, 38.9% are over the age of 70, while; 8.6% of men were between the ages of 50-59, 12.6% between the ages of 60-69, 28% were over the age of 70. Diabetes was detected in 54.3%, as well as hypertension in 77.1% and hyperlipidemia in 36% of the cases. According to the Bamford Classification, 30.3% of the cases were grouped as PACI, 34.9% as POCI, 28.5% as LACI and 6.3% as TACI. According to the TOAST classification, 53.1% were evaluated as small vessel occlusion, 9.1% as large vessel atherosclerosis, 12.6% as cardioembolic and 15.1% as other. Considering the outcome of the patients; 89.1% of cases survived, 6.3% died, 4.6% were taken to the intensive care unit (Table 1).

A statistically significant difference was found between the NLR levels of the groups ($p = 0.001$). As a result of the bilateral comparisons made to determine which group the significance originated from, NLR levels of 50-59 age group of women were found to be significantly lower than 60-69 ages old male group ($p = 0.004$), over 70 years old female ($p = 0.016$), and male group ($p = 0.003$).

NLR levels of 50-59 years old male patients were significantly lower than male patients aged 60-69 years ($p = 0.015$), female patients over 70 years old ($p = 0.014$) and male patients over 70 years old ($P = 0.002$). NLR levels of women in the 60-69 age group were significantly lower than those in the 60-69 age group ($p = 0.036$), female cases over 70 ($p = 0.028$) and male cases over 70 ($p = 0.009$).

The results we found were as follows; NLR value increased with age. In patients between the ages of 50-59 and 60-69, NLR was significantly higher in males than females. It was determined that there was no significant difference between men and women aged 70 and over. There was no statistically significant difference between NLR levels of cases in other groups ($p > 0.05$) (Table 2).

Table 1. Demographic Features of Patients

	n	%
Gender		
Female	88	50.9
Male	86	49.1
Group		
Female: 50–59	4	2.3
Male: 50–59	15	8.6
Female: 60–69	17	9.7
Male: 60–69	22	12.6
Female: 70 and above	68	38.9
Male: 70 and above	49	28.0
Diabetes Mellitus		
+	95	54.3
–	80	45.7
Hypertension		
+	135	77.1
–	40	22.9
Hyperlipidemia		
+	63	36
–	112	64
Bamford Classification		
PACI	53	30.3
POCI	61	34.9
LACI	50	28.5
TACI	11	6.3
TOAST		
Small vessel occlusion	93	53.1
Large vessel atherosclerosis	16	9.1
Cardioembolic	22	12.6
Other	44	15.1
Discharge		
Survived	156	89.1
Exitus	11	6.3
Intensive care unit	8	4.6

Reference values were taken in study by Aydın et al.^[4] TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; LACI: Lacunar infarcts; POCI: Posterior circulation infarct.

There was no statistically significant difference between NLR averages of patients and reference values in women aged 50-59 ($p > 0.05$). In cases between 50 and 59 years old male and 60-69 years old female cases; there was no statistically significant difference between NLR averages of patient and reference values ($p > 0.05$). In all cases between 60 and 69 years old men and 70 years old and above; NLR mean of the patient group was found to be statistically significantly higher than the reference values ($p = 0.018$) (Table 3).

Table 2. NLO Values by Age and Gender in AIS Cases

Group	NLO		P
	Mean±SD	Median	
Female: 50–59	1.38±0.12	1.42	0.001*
Male: 50–59	2.19±1.48	1.67	
Female: 60–69	2.28±1.34	1.94	
Male: 60–69	3.19±1.78	3.07	
Female: 70 and above	4.07±3.88	2.87	
Male: 70 and above	3.87±2.95	2.86	

Kruskal Wallis Test; *p<0.05; AIS: Acute Ischemic Stroke.

Table 3. Comparison of Patient and Reference NLO values

	n	NLO		P
		Mean±SD		
Female: 50–59				
Patient	4	1.38±0.12		0.447
Reference		1.84±1.21		
Male: 50–59				
Patient	15	2.19±1.48		0.929
Reference		2.16±1.31		
Female: 60–69				
Patient	17	2.28±1.34		0.577
Reference		2.09±1.4		
Male: 60–69				
Patient	22	3.19±1.78		0.018*
Reference		2.41±1.54		
Female: 70 and above				
Patient	68	4.07±3.88		0.000*
Reference		2.49±1.77		
Male: 70 and above				
Patient	49	3.87±2.95		0.049*
Reference		2.96±3.26		

Student t-test; *p<0.05.

According to the Bamford Classification, a statistically significant difference was found between the NLR levels of the groups (p=0.018). As a result of the bilateral comparisons made to determine which group the significance originated from, the NLR levels of the TACI group were significantly higher than the PACI (p=0.011), POCI (p=0.038) and LACI (p=0.001) groups. NLR levels of cases with exitus were found significantly higher than cases that did not result in death (p=0.006). There was no significant difference between other forms of discharge in terms of NLR levels (p>0.05) (Table 4).

Table 4. NLO Levels According to Bamford and TOAST Classification and Discharge

	NLO		P
	Mean±SD	Median	
Bamford			
PACI	3.11±1.91	2.86	0.018*
POCI	3.72±3.09	2.71	
LACI	2.81±2.47	2.15	
TACI	7.0±6.64	4	
TOAST			
Small vessel occlusion	3.52±3.17	2.8	0.197
Large vessel atherosclerosis	2.23±1.12	1.8	
Cardioembolic	3.71±3.14	2.59	
Other	3.84±3.32	2.81	
Discharge			
Survived	3.22±2.46	2.47	0.022*
Exitus	6.83±6.62	3.90	
Intensive care unit	4.44±4.46	2.90	

Kruskal Wallis Test; *p<0.05; TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; LACI: Lacunar infarcts; POCI: Posterior circulation infarct.

Discussion

In the pathogenesis of cerebral infarction, there is an inflammatory reaction that ends with liquefaction necrosis. Cytokines and adhesion molecules increase leukocyte migration in the infarct area.^[5-8] It has been suggested that the inflammatory reaction outside the infarct site damages the penumbra.^[9]

The first response to ischemic brain injury is neutrophil migration to the damaged area.^[10] Intraparenchymal perivascular migration develops within 6–24 h. In ischemic and reperfused areas, neutrophils secrete proteolytic enzymes such as acid phosphatase and free oxygen radicals.^[11,12]

Although there are contradictory data, T cell lymphocytes are thought to play a vital role in repairing inflamed tissues.^[7,13] Cytokine and growth factors released from T-cells modulate microglial activation. New clinical studies show that high NLR levels and high leukocyte count are associated with prognosis, disease severity, and mortality in cardiovascular diseases and atherosclerosis.^[14-17]

In the study conducted by Celikbilek et al., High NLR was found in AIS patients compared to the control group and transient ischemic attack (TIA) group.^[18] In our study, NLR values were found to be significantly higher compared to

reference values in male cases aged 60-69 years and 70 years old, and female cases over 70 years old, who had AIS. Balestrino et al. It has been shown that leukocyte and neutrophil counts were higher in AIS patients and associated with poor prognosis.^[19,20] Christensen et al. found similar results.^[20]

In the study of Gökhan et al., it was found that neutrophil and lymphocyte counts were also significantly higher in patients with acute ischemic and hemorrhagic stroke compared to TIA patients.^[21] Rodríguez-Yáñez and Castillo and Buck et al. showed that the lowest leukocyte count was in the lacunar patient group in patients with acute stroke.^[22,10] Similarly, in our study, when the patients were divided according to the Bamford classification; In the TACI group, the NLR ratio was significantly higher than the other groups. This finding supports the thesis that NLR correlates with the severity of the cerebrovascular disease.

In the study conducted by Tokgoz et al. NLR was found to be an independent predictor for short-term mortality in AIS.^[23] Similarly, in our study, NLR was found to be significantly higher in patients with exitus compared to other patient groups. Elkind et al. determined higher leukocyte counts in the subtypes of cardioembolic and atherosclerotic stroke.^[24] Güven et al. showed that the leukocyte and neutrophil values were highest in the large- artery atherosclerosis and cardioembolic stroke subgroups; and the lowest in the lacunar group.^[14]

In Gökhan et al.'s study, NLR was found to be significantly higher in large artery atherosclerosis than in other groups. In cardioembolic stroke group, NLR was significantly lower than other stroke subtypes.^[21] In our study, when patients were grouped according to TOAST classification which showed no significant difference between the groups. NLR value of AIS patients was significantly higher than the control group. A significant relationship was found between the infarct size and NLR. NLR was significantly higher in the TACI group compared to the other groups. Patients who died had higher NLR levels. It was found that high NLR correlated with an increase in short-term mortality in AIS.

Conclusion

As a result, NLR value increases in AIS cases. Increase of age, male gender and wide infarct area correlate with this increase. Its relationship with short-term mortality reveals that NLR has a predictive value for prognosis.

Disclosures

Ethics Committee Approval: Fatih Sultan Mehmet Training and Research Hospital, file number 1517, date: 31.01.2017.

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References

1. The Atlas of Heart Disease and Stroke. Available from: http://www.who.int/cardiovascular_diseases/resources/atlas. [Last accessed on 2015 Dec 25].
2. Núñez J, Núñez E, Bodí V, Sanchis J, Miñana G, Mainar L, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol* 2008;101:747–52.
3. Sabatine MS, Morrow DA, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM, et al. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: A TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine cost of therapy with an invasive or conservative strategy-thrombolysis in myocardial infarction 18 trial) sub study. *J Am Coll Cardiol* 2002;40:1761–8.
4. Aydın İ, Ağılı M, Aydın FN, Kurt Y, Cayci T, Trker T, et al. The reference ranges of neutrophil-lymphocyte ratio in different age groups. *Gulhane Med J* 2015;57:414–8.
5. Barone FC, Feuerstein GZ. Inflammatory mediators and stroke: New opportunities for novel therapeutics. *J Cereb Blood Flow Metab* 1999;19:819–34.
6. Yan J, Greer JM, Etherington K, Cadigan GP, Cavanagh H, Henderson RD, et al. Immune activation in the peripheral blood of patients with acute ischemic stroke. *J Neuroimmunol* 2009;206:112–7.
7. Yilmaz G, Granger DN. Leukocyte recruitment and ischemic brain injury. *Neuromolecular Med* 2010;12:193–204.
8. Yilmaz G, Arumugam TV, Stokes KY, Granger DN. Role of T lymphocytes and interferon-gamma in ischemic stroke. *Circulation* 2006;113:2105–12.
9. Huang J, Upadhyay UM, Tamargo RJ. Inflammation in stroke and focal cerebral ischemia. *Surg Neurol* 2006;66:232–45.
10. Buck BH, Liebeskind DS, Saver JL, Bang OY, Yun SW, Starkman S, et al. Early neutrophilia is associated with volume of ischemic tissue in acute stroke. *Stroke* 2008;39:355–60.
11. Clark RK, Lee EV, White RF, Jonak ZL, Feuerstein GZ, Barone FC. Reperfusion following focal stroke hastens inflammation and resolution of ischemic injured tissue. *Brain Res Bull* 1994;35:387–92.
12. Garcia JH, Liu KF, Yoshida Y, Lian J, Chen S, del Zoppo GJ. Influx of leukocytes and platelets in an evolving brain infarct (Wistar rat). *Am J Pathol* 1994;144:188–99.
13. Schwartz M, Moalem G. Beneficial immune activity after CNS injury: Prospects for vaccination. *J Neuroimmunol* 2001;113:185–

- 92.
14. Güven H, Çilliler AE, Sarıkaya SA. Etiological and prognostic significance of early leukocyte and neutrophil height in acute ischemic stroke. *J Neurol Sci (Turk)* 2010;27:311–8.
 15. Ait-Oufella H, Salomon BL, Potteaux S, Robertson AK, Gourdy P, Zoll J, et al. Natural regulatory T cells control the development of atherosclerosis in mice. *Nat Med* 2006;12:178–80.
 16. Gupta S, Agrawal A, Agrawal S, Su H, Gollapudi S. A paradox of immunodeficiency and inflammation in human aging: Lessons learned from apoptosis. *Immun Ageing* 2006;3:5.
 17. Nasr N, Ruidavets JB, Arnal JF, Sie P, Larrue V. Association of neutrophil count with microembolization in patients with symptomatic carotid artery stenosis. *Atherosclerosis* 2009;207:519–23.
 18. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *J Clin Lab Anal* 2014;28:27–31.
 19. Balestrino M, Partinico D, Finocchi C, Gandolfo C. White blood cell count and erythrocyte sedimentation rate correlate with outcome in patients with acute ischemic stroke. *J Stroke Cerebrovasc Dis* 1998;7:139–44.
 20. Christensen H, Boysen G. C-reactive protein and white blood cell count increases in the first 24 hours after acute stroke. *Cerebrovasc Dis* 2004;18:214–9.
 21. Gökhan S, Ozhasenekler A, Mansur Durgun H, Akil E, Ustündag M, Orak M, et al. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. *Eur Rev Med Pharmacol Sci* 2013;17:653–7.
 22. Rodríguez-Yáñez M, Castillo J. Role of inflammatory markers in brain ischemia. *Curr Opin Neurol* 2008;21:353–7.
 23. Tokgoz S, Kayrak M, Akpınar Z, Seyithanoğlu A, Güney F, Yürüten B, et al. Neutrophil lymphocyte ratio as a predictor of stroke. *J Stroke Cerebrovasc Dis* 2013;22:1169–74.
 24. Elkind MS, Sciacca RR, Boden-Albala B, Rundek T, Paik MC, Sacco RL, et al. Relative elevation in baseline leukocyte count predicts first cerebral infarction. *Neurology* 2005;64:2121–5.