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Neurotrophil/lymphocyte ratio and its relationship with functional recovery in stroke patients

İnmeli hastalarda nötrofil/lenfosit oranı ve fonksiyonel iyileşme ile ilişkisi

Gönül VURAL[1], Şadiye GÜMÜŞYAYLA[1], Gülsüm AKDENİZ[2]

ABSTRACT

Aim: *Neutrophil/lymphocyte ratio (NLR) is considered to be a parameter that reflects the negative consequences of both neutrophil elevation as a marker of acute inflammatory response and lymphocyte depression as a marker of physiological stress. The present study aims to investigate the changes of NLR in stroke sub-groups and their relation to the functional recovery.*

Methods: *A total number of 418 subjects participated in the present research including 294 patients diagnosed with ischemic stroke, 35 patients who experienced a transient ischemic attack (TIA), 19 patients with hemorrhagic stroke and 70 control subjects. NLRs of all subjects were calculated and their Rankin scores at discharge were recorded.*

Results: *NLR was found to be significantly elevated in stroke patients compared to the control subjects (p<0.01). When the subgroups were compared to the control subjects, the findings indicated significantly higher NLR in all subgroups (p<0.01). Comparisons between stroke subgroups showed that the NLR in the subgroup with hemorrhagic stroke was significantly higher than that estimated for all ischemic stroke subgroups. NLR was also significantly higher in patients with atherosclerotic and embolic ischemic stroke, compared to patients with lacunar stroke or TIA (p<0.01). Correlation analysis demonstrated a statistically significant positive correlation between Rankin scores and NLR (p<0.001, r=0.237).*

Conclusion: *The findings suggest that NLR elevated in all types of stroke and its correlation with clinical disability scores underline the significance of the measures and future strategies with an aim to decrease or even to prevent inflammation to reduce brain damage.*

Keywords: *Neutrophil/lymphocyte ratio, inflammation, stroke*

ÖZ

Amaç: *Nötrofil/lenfosit oranı, hem akut inflamatuvar yanıtı gösteren nötrofil yüksekliği hem de fizyolojik stresi yansıtan lenfosit düşüklüğünün olumsuz etkilerini gösteren bir parametre olarak kabul edilmektedir. Nötrofil yüksekliği direkt olarak iskemiye bağlı olabileceği gibi, inme gelişmesinden sorumlu inflamasyonun bir yansıması da olabilir. Hemorajik inmeli hastalarda ise kanamaya bağlı inflamatuar yanıtta bir artış söz konusudur ki bu beyin hasarının artmasına neden olur. Bu çalışma, inme alt gruplarında nötrofil/lenfosit oranının nasıl değiştiğini ve fonksiyonel iyileşmeyle ilişkisini araştırmak için planlandı.*

Yöntem: *Çalışmamıza iskemik inmeli 294 hasta, geçici iskemik ataklı 35 hasta, 19 hemorajik inme vakası ve 70 kontrol birey olmak üzere olmak üzere toplam 418 kişi alındı. Her bir vakanın nötrofil/lenfosit oranı hesaplandı; hastaların taburculuk Rankin skoru kaydedildi.*

Bulgular: *Nötrofil/lenfosit oranı inmeli hastalarda kontrollere kıyasla anlamlı olarak daha yüksek bulundu (p<0,01). Alt grupların kontrol grubuyla analizinde aterosklerotik, kardiyoembolik, laküner, geçici iskemik atak ve hemorajik inme grubunun nötrofil/lenfosit oranları kontrollere göre anlamlı olarak daha yüksekti (p<0,01). İnme subtipleri karşılaştırıldığında hemorajik inmeli grupta nötrofil/lenfosit oranı tüm iskemik inme alt gruplarından anlamlı olarak daha yüksekti (p<0,01). Nötrofil/lenfosit oranı aterosklerotik ve embolik iskemik inmeli hastalarda hem laküner inmeli hastalardan hem de geçici iskemik ataklı hastalardan anlamlı olarak daha yüksekti (p<0,01). Korelasyon analizleri Rankin skorlarıyla nötrofil/lenfosit oranı arasında istatistiksel olarak anlamlı pozitif korelasyonun varlığını ortaya koydu (p<0,001, r=0,237).*

Sonuç: *Nötrofil/lenfosit oranı sistemik inflamatuvar statusu gösteren bir parametredir. İnmenin her tipinde artmış olması ve klinik özürlülük skorlarıyla korelasyonu, beyin hasarlarının azaltılmasında enflamasyonu azaltmaya ya da önlemeye yönelik önlemlerin ve geliştirilecek stratejilerin önemini ortaya koymaktadır.*

Anahtar kelimeler: *Nötrofil/lenfosit oranı, enflamasyon, inme*

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[1]Department of Neurology, Yildirim Beyazit University, Ankara, Turkey
[2]Department of Biophysics, Yildirim Beyazit University, Ankara, Turkey
Corresponding author: Gönül Vural, Department of Neurology, Yildirim Beyazit University, Ankara, Turkey
e-mail: gonulvrl@gmail.com

ORCID ID's:

G.V. 0000-0002-1245-7273, Ş.G. 0000-0002-2279-2016, G.A. 0000-0002-9411-3318

INTRODUCTION

Stroke is the most common cause of mortality and disability in elderly patients[1]. Nowadays, medical therapy of acute ischemic stroke is limited to thrombolytic therapy, which can only be administered to a limited number of patients due to the risk of relatively high intracranial bleeding complications[2,3]. Therefore, supportive care remains the mainstay treatment for the majority of patients after acute stroke. The condition is already the case for hemorrhagic stroke patients[4]. At this point, the presence of markers that can be used in predicting prognosis is important for physicians who provide care for patients with stroke.

Inflammation plays a key role in the pathophysiology of both ischemic and hemorrhagic cerebrovascular disease. The inflammatory process, which involves endothelial activation, disruption of the blood-brain barrier, leukocyte infiltration and the accumulation of oxidant and inflammatory mediators, rapidly develops within hours and results in secondary brain injury[5-8]. Several markers have been investigated as predictors of prognosis in stroke patients, and it has been suggested that the neutrophil/lymphocyte (N/L) ratio may be used as an inflammatory parameter to this end. The N/L ratio is considered to be a marker that allows simultaneous evaluation of the negative effects of both neutrophil elevation as an indicator of acute inflammation and lymphocyte depression as a signal of physiological stress[4,7-11]. The present study investigates the association between N/L ratio and functional outcome at discharge in patients with hemorrhagic or ischemic cerebrovascular stroke which are major causes of mortality and morbidity, particularly in the elderly.

MATERIAL and METHODS

The medical records of the patients who were admitted to our clinics with diagnoses of acute stroke were reviewed retrospectively. The patients who were referred to an emergency unit within the first 24 hours following symptom onset, and from whom routine venous blood samples were obtained were included in the study. The demographical data and medical history of the patients were reviewed. Patients with liver, renal or cardiac failure at the time of admission, those with concomitant acute coronary syndrome, those with a malignancy or a systemic infection, cases presenting with a picture of ketotic or nonketotic hyperglycemic coma, and those using steroids or immunosuppressive medications were excluded from the study. Patients who died during follow-up or who were transferred to another center with a requirement of intensive care were also excluded from the study. The N/L ratio of each patient and the control subjects included in the study was calculated by dividing the neutrophil count by the lymphocyte count. The type and subtype of the stroke were also recorded, and the functional outcome at discharge was described based on a modified Rankin Scale (mRS). This study was approved by the Ethics Committee of Yıldırım Beyazıt University Faculty of Medicine.

Statistical analysis

The data were analyzed using the SPPS 20 statistical package program (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Variables were presented as mean±standard deviation values and percentages, and the data were analyzed after controlling for normality and variance homogeneity prerequisites (Shapiro Wilk and Levene's Test). An independent samples 2-group t test (Student's t test) was used to compare two groups, while comparisons of two or more groups were made with a One-Way Variance Analysis. The relationship between two continuous variables was evaluated with a Spearman correlation coefficient. P values of <0.05 and <0.01 were considered statistically significant.

RESULTS

The study involved 418 patients in total, including patients having diagnoses of ischemic stroke (n= 294) transient ischemic attack (TIA) (n=35), hemorrhagic stroke (n=19), and control subjects (n=70). The ischemic stroke subtypes were determined based on

Table 1. Clinical and demographic characteristics of groups.

	n	gender M/F	age mean±SD	HT n (%)	DM n (%)
ischemic stroke					
atherosclerotic	167	99/68	68.6±13.1	87 (%52)	47 (%28)
cardioembolic	92	43/49	71.4±12.1	53 (%58)	34 (%37)
lacunar	35	24/11	63.3±12.1	17 (%49)	10 (%29)
transient ischemic attack	35	18/17	67.2±15.4	20 (%57)	12 (%34)
hemorrhagic stroke	19	12/7	68.2±12.6	15 (%79)	2 (%11)
control group	70	25/45	69.7±8.7	9 (%13)	11 (%16)

the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification. Accordingly, cases of large artery atherosclerosis (n=167), 92 cardioembolic stroke (n=92) and lacunar stroke (n= 35) were identified. Table 1 shows the demographical characteristics of the patients.

The mean age of the patients who suffered a lacunar stroke was significantly lower than the mean age of both groups of patients who suffered atherosclerotic or cardioembolic strokes, as well as the control group ($p<0.05$, $p<0.01$, and $p<0.01$, respectively). The mean age was not significantly different between the other groups ($p=0.80$). The neutrophil count, lymphocyte count and N/L ratio were significantly higher in the ischemic stroke patients when compared to the controls ($p<0.01$, $p<0.05$, and $p<0.01$, respectively) (Table 2).

A comparison of the subgroups with the control group demonstrated that the N/L ratios in atherosclerotic, cardioembolic, lacunar stroke, TIA and hemorrhagic stroke subgroups were significantly higher than the control group ($p<0.01$) (Table 3). When the stroke subgroups were compared, the N/L ratio in the hemorrhagic stroke group was found to be significantly higher than in all other groups, and the N/L ratios in the atherosclerotic and embolic ischemic stroke patients were found to be significantly higher than in both the lacunar stroke and TIA patient groups (Table 4).

The mean Rankin score was 3.04±1.8, and correlation analyses demonstrated statistically significant positive correlations between Rankin scores and N/L ratios ($p<0.001$; $r=0.237$) (Table 5).

Table 2. Neutrophil and lymphocyte counts, neutrophil / lymphocyte ratios of patients with ischemic stroke and control group.

	patients with ischemic stroke n=294	control group n=70	p value
neutrophil ($10^3/mm^3$)	6.1±2.6	4.2±1.5	p<0.01**£
lymphocyte ($10^3/mm^3$)	2.1±1.1	2.4±0.9	p<0.05*£
neutrophil / lymphocyte ratio	3.8±4.2	1.9±1.0	p<0.01**£

**p<0.05, **p<0.01, £ Student's t test*

Table 3. Neutrophil/lymphocyte ratios of patients and control group according to stroke subgroups

	neutrophil/lymphocyte ratio mean±SD	p value
ISCHEMIC STROKE (n=294) Control (n=70)	3.8±4.2/1.9±1.0	p<0.01**£
Atherosclerotic (n=167) Control (n=70)	3.6±3.6 /1.9±1.0	p<0.01**£
Cardioembolic (n=92) Control (n=70)	4.7±5.6/1.9±1.0	p<0.01**£
Lacunar (n=35) Control (n=70)	2.8±1.8/1.9±1.0	p<0.01**£
TRANSIENT ISCHEMIC ATTACK (n=35) Control (n=70)	2.7±1.9/1.9±1.0	p<0.01**£
HEMORRHAGIC STROKE (n=19) Control (n=70)	6.2±4.6/1.9±1.0	p<0.01**£

***p<0.01, £ Student's t test*

Table 4. Comparison of neutrophil/lymphocyte ratios of stroke subgroups.

	n	neutrophil/ lymphocyte ratio mean±SD	p value
Atherosclerotic Ischemic Stroke [c,d,e]	167	3.6±3.6	
Cardioembolic Ischemic Stroke [c,d,e]	92	4.7±5.6	
Lacunar Ischemic Stroke [a,b,e]	35	2.8±1.8	p<0.01**σ
Transient Ischemic Attack [a,b,e]	35	2.7±1.9	
Hemorrhagic Stroke [a,b,c,d]	19	6.2±4.6	

*** p<0.01, σ: One-way analysis of variance*
[a] different from the thrombotic group
[b] different from the embolic group
[c] different from the lacunar group
[d] different from the transient ischemic attack group
[e] different from the hemorrhagic group

Table 5. Relationship between Rankin score and neutrophil/ lymphocyte ratio.

		neutrophil/lymphocyte ratio
RANKIN SCORE	r	.237* ψ
	p	p<0.001*
	n	348

*ψ Spearman Correlation Coefficient, *p<0.001*

DISCUSSION

Our findings indicate that N/L ratio, as evidence of increased inflammation, is elevated in every type of stroke, and this elevation is strongly correlated with functional loss.

Inflammation of the brain tissue increases in response to vascular damage, and leukocytes, which are markers of systemic inflammation, are seen to aggravate ischemic cerebral tissue damage. Neutrophil infiltration into the brain tissue starts within the first 6-12 hours of ischemic damage[12]. Neutrophils accumulate in the cerebral vessels within hours, and impair microvascular perfusion by obstructing microvascular structures, contributing eventually to an enlargement of the infarction field[13,14].

In ischemic brain tissue, lymphocytes start to increase later, after 3-6 days. With respect to lymphocytes, different subtypes are known to have different roles in the response given to cerebral ischemia, and while some subtypes may contribute to the development of inflammation, others may play a role in the repair of inflamed brain tissue by releasing anti-inflammatory cytokines[12].

This complex inflammatory response, which involves several different cell types in the region of cerebral damage, results in the development of brain damage and functional impairment[15]. In fact, higher lymphocyte and neutrophil counts have been shown to be correlated with larger infarction volumes and increased stroke severity[16], and similarly, in patients with acute strokes, high neutrophil counts have been found to be associated with a poor prognostic outcome after three months, while a low lymphocyte count has been associated with insufficient neurological recovery during the first week following a stroke[17].

Immune reaction is also a major characteristic of intracranial hemorrhage that affects its course. Neutrophils are the first leukocytes to actively migrate from the peripheral blood to the brain, occurring within the first hours following a hemorrhagic stroke and resulting in secondary damage. Capillary permeability increases and the field of the perilesional edema enlarges upon release of inflammatory and cytotoxic mediators to the medium[18,19]. Endothelial and basal lamina damage, induced by the inflammatory cascade and blood leakage from the fragile capillaries in the granulation tissue contribute to the extension of hematomas[20]. In contrast, Morotti et al.[21] linked increased neutrophil counts to a reduced risk of hematoma expansion, and attributed this finding to the procoagulant effects of activated neutrophils during the hyperacute phase.

In addition to individual peripheral blood parameters, the N/L ratio has also been considered as a predictor of prognosis and mortality in stroke patients. In this regard, a number of studies have been carried out to investigate prognostic role of the N/L ratio in

cerebrovascular diseases.

Studies involving ischemic stroke patients have demonstrated that high N/L ratios can predict mortality, with cut-off values varying between 4 and 5[4,7,9,22,23]. In another study, involving patients suffering from an acute ischemic stroke, a high N/L ratio was found to be significantly correlated with poor functional outcome at discharge, a prolonged duration of hospital stay and increased hospital costs[24]. In a retrospective analysis of 177 patients with an intracerebral hemorrhage, an N/L ratio higher than the cut-off value of 4.5 was found to be an indicator of poor prognostic outcome, characterized by death or major disability (mRS≥3)[25]. In another study, including 224 patients with acute intracerebral hemorrhage, it was suggested that an N/L ratio higher than the cut-off value of 7.3 was a predictor of 30-day mortality[26]. A recent prospective study involving a large cohort of 855 patients with intracranial hemorrhage demonstrated that a high N/L ratio was accompanied by a larger hematoma volume, more frequent infectious complications, increased in-hospital mortality and poor functional outcome[10].

The relationship between increased inflammation and poor prognostic outcome in acute stroke patients has been demonstrated previously in several studies that are described above. However, most of these studies have focused rather on mortality, and their results revealed different cut-off values for the N/L ratio. Additionally, a limited number of studies have considered stroke subtypes. In the present study, we investigated the N/L ratio in stroke subtypes and its association with functional recovery, and our findings demonstrated that there is a very strong correlation between a high N/L ratio and a poor functional outcome at discharge. Moreover, the highest N/L ratio in this study was recorded in hemorrhagic stroke patients. In fact, the N/L ratio in the hemorrhagic stroke group was higher than those observed in the ischemic stroke subtype groups and in the TIA group. Among the stroke subtypes, the N/L ratio was similar between the atherosclerotic and cardioembolic groups, and significantly higher than that found both in the lacunar and TIA groups.

In a study in which the stroke subtypes were also identified, the N/L ratio was found to be significantly higher in atherosclerotic stroke patients when compared to both cardioembolic and lacunar stroke patients, and the authors attributed this finding to thrombus which has a greater importance than atherosclerotic inflammation in the pathophysiology of cardioembolic strokes[9]. Consistent with their finding, the N/L ratio was found to be higher in the cardioembolic group, similar to the ratio noted in atherosclerotic group in our study. We believe that, although there is ongoing inflammation in the vascular structures during the atherosclerotic process, the inflammation that develops in the brain following an ischemia is correlated with the severity of damage rather than etiology at this point, which may explain why the N/L ratio is lower in lacunar infarction and TIA patients. While no significant difference in terms of N/L ratio was found between ischemic and hemorrhagic stroke patients in the aforementioned study, the N/L ratio in our hemorrhagic stroke patients was found to be significantly higher than that in the patients with all ischemic stroke subtypes.

Our results demonstrate that inflammation is more pronounced in patients experiencing hemorrhagic cerebrovascular events, but is less common in the atherosclerotic and cardioembolic subtypes of ischemic strokes when compared to hemorrhagic strokes, but slightly higher than, the level of inflammation in patients with TIA and lacunar stroke. The N/L ratio, as a marker of inflammation, was also found to be correlated with functional loss, which is a finding that is consistent with our clinical observations. More catastrophic brain damage involving a higher degree of inflammation is accompanied by increased functional loss, and so a high N/L ratio, as a marker of inflammation, is associated with a poor functional outcome. Neurological recovery during the first week following a stroke will be accompanied by a lower rate of long-term morbidity.

In conclusion, our findings suggest that the N/L ratio, as a cheap, widely available and innate tool that combines the inflammatory index with adaptive im-

munity, can be used for the early diagnosis of a poor functional outcome risk during discharge in stroke patients. The fact that the N/L ratio is elevated in all stroke subtypes, and that it correlates with clinical disability scores, establishes its importance as a measure for the reduction of brain damage and decreasing or preventing inflammation, while also highlighting its role in developing new strategies aimed at improving clinical outcomes in stroke patients.

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