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Original Article / Özgün Araştırma

Neutrophil-lymphocyte Ratio may be an Early Predictor of the Prognosis in Ischemic Stroke Cases

Nötrofil-lenfosit Oranı İskemik İnme Hastalarında Prognozun Erken Bir Göstergesi Olabilir

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Abstract

Objective: Prognostic predictors in the very early period of acute stroke are still needed. Neutrophil-lymphocyte ratio (NLR) was reported as a useful prognostic indicator for vascular diseases. However, its' time-related changes are not sufficiently studied. In the present study, we aimed to investigate if the NLR at the first day of hospitalization is associated with some clinical and laboratory findings in patients with ischemic stroke and if they change in the following days.

Materials and Methods: The hospital data of 80 consecutive acute ischemic stroke patients were retrospectively documented and evaluated. NLR values that were calculated twice; on the day of admission and at least five days later, were compared to check if there are any significant changes. Since the study was conducted as a retrospective registry analysis, consent was not obtained from the patients.

Results: NLR ratios were similar in the two follow-up blood samples (p=0.873). In the evaluation according to stroke severity; the NLR cut-off point on the day of admission was 2.86 (sensitivity 88.9%, specificity 72.6%). This cut-off value showed a higher sensitivity and specificity in the cases who did not have an infection during hospital stay (sensitivity 100%, specificity 83%). Age, leukocyte and thrombocyte counts, risk of hospital infection and duration of hospital stay were significantly lower in the cases with NLR <2.9 than those with NLR ≥2.9.

Conclusion: NLR calculated on the first day of admission can be useful and adequate for assessing the severity of stroke, predicting the length of hospital stay and the risk of infection during hospitalization.

Keywords: Neutrophil-lymphocyte ratio, ischemic stroke, prognosis

Öz

Amaç: Akut inme sonrası çok erken dönemde prognozun değerlendirilmesine yardımcı olacak parametrelere halen ihtiyaç vardır. Nötrofil-lenfosit oranının (NLO) vasküler olaylarda prognostik bir gösterge olarak kullanılabileceği bildirilmiştir ancak zamanla ilişkili değişiklikleri yeterince araştırılmamıştır. Bu çalışmada iskemik inme hastalarında hastaneye ilk yatış günündeki NLO'nun inmenin klinik ağırlığı, hastanede kalış süresi, enfeksiyon gelişme riski gibi bazı klinik bulgular ve laboratuvar bulgularla ilişkili olup olmadığının ve günler içinde NLO'da değişiklik bulunup bulunmadığının araştırılması amaçlanmıştır.

Gereç ve Yöntem: Ardı ardına başvuran 80 iskemik inme hastasının sosyodemografik özellikleri, klinik verileri, laboratuvar sonuçları ve hastanedeki takip bilgileri retrospektif olarak değerlendirilerek önceden hazırlanan forma kaydedilmiş ve ilk başvuru gününde ve bundan en az beş gün sonra alınan kontrol kanlarından hesaplanan NLO arasında ilişki olup olmadığı istatistiksel olarak araştırılmıştır. Çalışma retrospektif sistem taraması olarak yapıldığından hastalardan onam alınmadı.

Bulgular: Farklı günlerde bakılan NLO oranları arasında farklılık izlenmemiştir (p=0,873). İnme şiddetine göre yapılan değerlendirmede; başvuru günündeki NLO kesme noktası 2,86 idi (sensitivite %88,9, spesifite %72,6). Hastane yatışı sırasında enfeksiyon gelişen ve gelişmeyen hastalar ayrı ayrı gruplanarak yapılan istatistik değerlendirmede enfeksiyon bulgusu izlenmeyen hastalarda NLO için belirlenmiş olan kesim noktası olan 2,86'nın sensitivite ve spesifitesinin daha yüksek olduğunu göstermiştir (sensitivite %100, spesifite %83). NLO 2,9'dan düşük hastaların yaş ortalaması, lökosit, trombosit değerleri, enfeksiyon gelişme riskleri ve hastanede yatış süreleri NLO ≥2,9 olanlardan istatistiksel açıdan anlamlı olarak daha düşük bulunmuştur.

Sonuç: Hastaneye ilk başvuru gününde hesaplanan NLO değerleri inmenin ağırlığının değerlendirilmesinde, hastanede yatış süresini ve yatış sırasında enfeksiyon gelişme riski yüksek olan hastaları öngörmede yararlı ve yeterli olabilir.

Anahtar Kelimeler: Nötrofil-lenfosit oranı, iskemik inme, prognoz

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Introduction

Stroke is one of the leading causes of mortality and morbidity all over the world. The vast majority of strokes are ischemic. In the pathophysiology of acute ischemic stroke, the inflammatory process with disruption of the blood-brain barrier, endothelial activation, release of proinflammatory and oxidant mediators, and leukocyte and platelet infiltration have important roles (1,2,3).

Stroke severity in the acute period is an important indicator for prognosis. Many systemic and neurological complications may develop in the early period of hospital stay after acute stroke and may deteriorate the clinical picture. These can both prolong the length of stay and worsen the prognosis by causing secondary damage. Many prognostic factors have been reported, but there is still a need for parameters to help evaluate prognosis at a very early stage.

The neutrophil-lymphocyte ratio (NLR) is an easily accessible, low-cost indicator of subclinical inflammation. It has been known for a long time that high NLR is a poor prognostic marker in patients with acute coronary syndrome (4,5,6,7,8). In some studies, conducted in recent years, it has been shown that NLR may also have prognostic value in acute ischemic cerebrovascular events (9,10,11,12,13).

In this study, it was investigated whether the NLR detected on the first day of hospitalization in patients with ischemic stroke was associated with clinical parameters such as severity of stroke, length of hospital stay, risk of infection, laboratory and imaging findings. In addition, the NLRs obtained from the complete blood counts (CBC) measured at least 5 days after the hospitalization day were calculated and it was evaluated whether they differed from the values obtained on the first hospitalization day.

Materials and Methods

In the study, the data of the patients who were admitted to the Gaziantep University Neurology Department consecutively between December 2015 and September 2016 within the first 5 days after AIS were evaluated retrospectively.

Inclusion Criteria:

1. Diagnosis of AIS with brain imaging [brain computed tomography (CT) or diffusion magnetic resonance imaging (MRI)] and/or clinical findings.
2. Patients admitted within the first 5 days after the acute onset date.
3. No significant deficiencies in the medical records.
4. Aged >18 years old.

Exclusion Criteria:

1. Having a systemic disease that may cause a change in the parameters planned to be examined in whole blood count.
2. Using immunosuppressive therapy.
3. Being pregnant or in the postpartum period at time of admission.
4. Inability to access medical records.
5. Intravenous recombinant tissue plasminogen activator (IV rTPA) or endovascular intervention has been performed.

Sociodemographic and cardiovascular characteristics of all patients included in the study, known risk factors for stroke, drugs used before admission and during hospitalization, clinical information, CBCs on the day of hospitalization (within the first 5 days after stroke onset), electrocardiography (ECG), echocardiography (ECHO), Doppler ultrasonography (USG) findings and cranial MRI results were recorded on a pre-prepared form. The results of the second CBC repeated at least 5 days after the first CBC were also recorded on the same form. The National Institutes of Health Stroke scale (NIHSS) was used to evaluate the stroke severity of the patients at admission. The presence of signs of infection was determined according to the evaluation of clinical and laboratory findings and follow-up notes.

The NLRs in the blood sample collected at admission and in the control blood sample collected at least 5 days later in patients meeting inclusion criteria were calculated. The NLR was found by dividing the numerical value of the neutrophil count in the CBC by the numerical value of the lymphocyte count.

In order to investigate whether NLR changes at different times of AIS, the first and control NLRs in CBCs were statistically compared. It was statistically evaluated whether there was a relationship between the NLR values detected on the first day of hospitalization and clinical and laboratory findings.

In this study, statistical evaluations were completed and interpreted in a few steps:

i) Considering that the severity of stroke might have important effects on the results, it was planned to repeat some statistical analyses by grouping the patients according to the NIHSS scores determined according to the neurological examination findings at admission. Since patients who received thrombolytic and/or interventional treatment were excluded from the study, the NIHSS score ≤4 limit was not used in measuring the severity of stroke for statistical evaluations based on the severity of clinical symptoms. Instead, it was planned to determine a score that would allow statistical studies according to the NIHSS score distribution of the study group.

ii) Whether there was a significant cut-off point according to the severity of the stroke among the NLR values found was tested by receiver operating characteristic (ROC) analysis. Whether the presence of infection would change the cut-off point was also re-evaluated by regrouping the patients with and without infection separately.

iii) Once a significant cut-off point for NLR was obtained, patients with values below the found cut-off point were grouped as Low NLR group, and those with values above the cut-off point were grouped as High NLR group. Statistical evaluations in terms of age, gender, smoking, medications, C-reactive protein (CRP), sedimentation, CBC, glucose, ECG, ECHO, Doppler USG findings, NIHSS scores and length of hospitalization were repeated.

Approval for the study was obtained from Gaziantep University Clinical Research Ethics Committee with the decision number 07.06.2015/201 on 07.05.15.

Statistical Analysis

The conformity of the numerical data to normal distribution was determined by the Shapiro-Wilk test. Student's t-test was used for the comparison of normally distributed variables in 2 independent groups, and Mann-Whitney U test was used for non-normally distributed variables. Paired Sample t-test was used to test the variation at different times in order to evaluate the dependent variables with normal distribution. The relationship between categorical variables was tested by using chi-square

analysis. Pearson correlation analysis was used to determine the relationships between numerical variables. Multiple linear regression analysis was used to determine the variables affecting the numerical dependent variables. In order to diagnose with the help of a numerical variable, the cut-off point determination processes were performed with ROC analysis. SPSS 22.0 package program was used in the analysis. P<0.05 was considered significant.

Results

A total of 80 patients were included in the study according to inclusion and exclusion criteria. The ages of 44 (55%) female and 36 (45%) male patients included in the study were between 23 and 88 (63.6±15.2 years). The demographic data of the patients are summarized in Table 1.

Sixteen patients (20%) had no known disease history. In addition to 10 patients who had known atrial fibrillation (AF) at the time of admission, AF was detected in 5 more patients during hospital stay. Fourty-five patients (56.3%) had more than one previously known disease (Table 1).

Sixty-two patients (77.5%) had their first ischemic stroke, 18 (22.5%) had recurrent ischemic stroke. Thirty patients had a stroke while using antiaggregant therapy and 5 patients suffered stroke while receiving anticoagulant therapy.

The location of acute infarction was hemispheric (25 lacunar syndrome) in 69 patients (86.3%), and brain stem in 8 patients (10%). No abnormality was detected in brain CT and/or brain diffusion MRI in 3 of the patients. According to their the medical records, these patients presented with clinical symptoms consistent with ischemic stroke, such as very acute onset and findings that would be explained by an artery area.

Table 1. Demographic data of patients

	Number	%/mean ± SD*
Gender (F/M)	44/36	55/45
Age (years)	23-88 years	63.6±15.2*
Dominant hand (right/left)	73/7	91.3/8.8%*
Alcohol use	2	2.5%
Cigarette use	19	23.8%
Oral contraceptive use	2	2.5%
Length of stay (days)	3-60	14.61±10.7*
NIHSS score	1-24	6.24±5.3*
History of cerebrovascular accident (ischemic)	18	22.5%
Other known additional chronic diseases		
Hypertension	42	52.5%
Diabetes	24	30%
Coronary artery disease	20	25%
Atrial fibrillation	10	12.5%
Heart valve disease	6	7.5%
Congestive heart failure	5	6.3%
Multiple diseases	45	56.2%
Other	18	22.5%

Mean ± SD, NIHSS: The National Institutes of Health Stroke scale, F: Female, M: Male, SD: Standard deviation

The NLR on admission day was 3.5±2.9, and the control NLR calculated at least 5 days later was 3.4±3.3 (p=0.873) (Table 2).

The cut-off value for NLR in the study group was determined as 2.86 [sensitivity 88.9% (95% confidence interval (CI): 65.3-99.6), specificity 72.6% (95% CI: 59.8-83.1)], (area under the curve 0.830±0.0462). NLR was less than 2.9 in 46 (57.5%) patients (low NLR group), and it was 2.9 or higher in 34 patients (42.5%), (high NLR group).

The mean age, NIHSS scores, CRP, sedimentation, leukocyte and thrombocyte counts, and length of hospitalization of the patients in the high NLR group were significantly higher than those in the low NLR group (p=0.040, p=0.001, p=0.004, p=0.003, p=0.001, p=0.011 and p=0.001, respectively) (Table 3). There was a significant relationship between lesion location and NLR groups. NLR was found to be higher in patients with large lesions in hemispheric major arterial areas (p=0.001). There was no correlation between NLR and gender, smoking, previous medications, hematocrit, glucose level, presence of AF, left ventricular hypertrophy in ECHO, and Doppler findings.

When the patients were evaluated according to the presence of infection, signs of infection were observed in 24 of 80 patients, and no sign of infection was observed in 56 patients. A higher rate of infection was observed during hospitalization in the high NLR group than in the low NLR group (p=0.001). The sensitivity and specificity of the cut-off point (2.86) for NLR was found to be higher in patients without signs of infection [sensitivity 100% (95% CI: 29.2-100.0), specificity 83% (95% CI: 70.2%-91,9)]. When the group with signs of infection was evaluated alone, no cut-off point could be determined for NLR (Figures 1, 2).

The NIHSS scores were between 0 and 8 in the majority of the patient group. Considering the distribution characteristics of the study group according to the NIHSS scores, the patients were divided into two groups as patients with NIHSS score ≤8 and patients with NIHSS score ≥9 for statistical evaluations to be made according to the severity of clinical symptoms. The NIHSS score of 62 subjects was ≤8 (3.6±1.8), and the NIHSS score of 18 subjects was ≥9 (15.1±3.6). Mean age was significantly higher and length of hospital stay was significantly longer in the patients with NIHSS score ≥9 (70.8±1.8 and 22.1±13.4, respectively) compared to patients with NIHSS score ≤8 (61.5±15.5 and 12.4±8.8, respectively) (p=0.017 and p=0.001, respectively). No significant difference was observed in terms of other parameters (gender, smoking, drugs used, glucose, hematocrit, presence of AF, ECO and Doppler findings).

Regression analyses showed a positive correlation between length of hospital stay and high CRP and NIHSS scores (R^2=32.4%; beta=0.13, p=0.001 and beta=0.45, p=0.045, respectively). There was a positive correlation between NIHSS

Table 2. Comparison of neutrophil-lymphocyte ratios

	Number	Mean ± SD*	p
N/L (1st value)[1]	80	3.5004±2.92170	0.873
N/L (2nd value)[2]	80	3.4474±3.37959	

*Mean ± standard deviation; [1]NLR calculated from complete blood count taken at initial admission; [2]NLR calculated from complete blood count taken at least 5 days after the first blood sampling, NLR: Neutrophil-lymphocyte ratios

Table 3. Comparison of high and low NLR groups in terms of numerical variables (Cut-off point for NLR: 2.86)

	Low N/L ratio group (n=46) Mean ± standard deviation	High N/L ratio group (n=34) Mean ± standard deviation	P value
Age	60.7±14.6	67.7±15.2	0.040
NIHSS score	3.8±2.9	9.50±6.1	0.001
Length of stay	10.9±6.2	19.6±13.5	0.001
CRP	4.7±5.7	29.6±46.1	0.004
Sedimentation	24.3±14.2	40.5±23.9	0.003
Leukocyte count	7605.9 ±1956.4	10620.9±3637.6	0.001
Platelet count	270978.3±78569.9	338617.7±132656.3	0.011

NLR: Neutrophil-lymphocyte ratios, n: Number, CRP: C-reactive protein, NIHSS: The National Institutes of Health Stroke scale

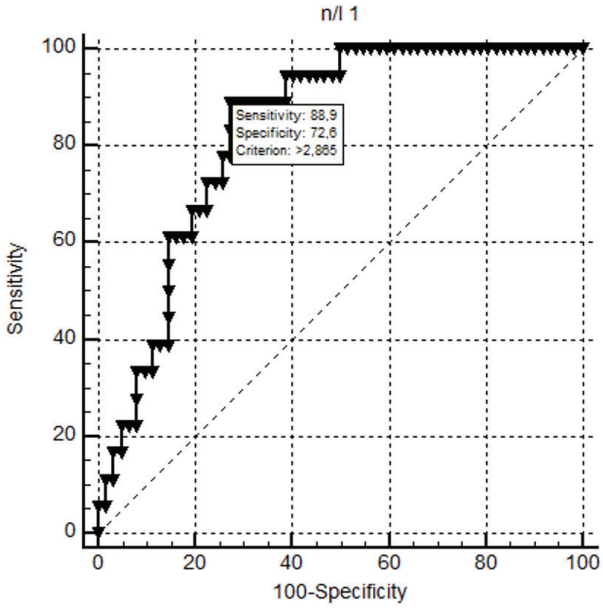

Figure 1. ROC analysis for NLR in all patients by NIHSS groups
NLR: Neutrophil-lymphocyte ratios, NIHSS: The National Institutes of Health Stroke scale, ROC: Receiver operating characteristic

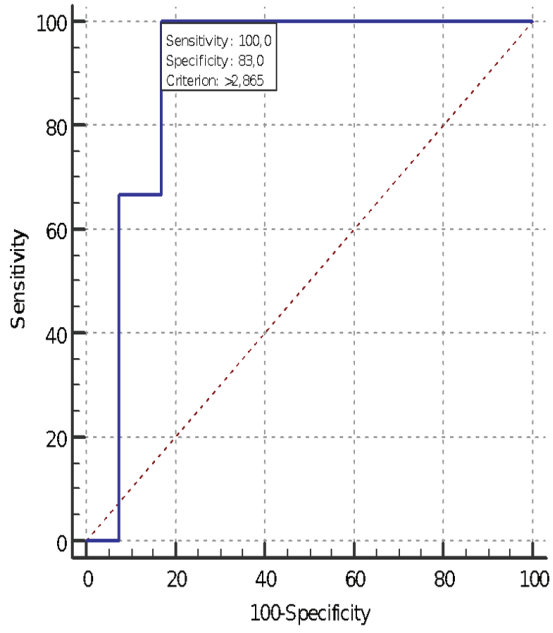

Figure 2. ROC analysis for NLR by NIHSS groups in patients without evidence of infection
NLR: Neutrophil-lymphocyte ratios, NIHSS: The National Institutes of Health Stroke scale, ROC: Receiver operating characteristic

scores and NLR and sedimentation (R^2= 11.2%; beta= 0.715, p=0.005 and beta=0.066, p=0.022, respectively).

Discussion

In our study, it was observed that patients with high NLR had a longer hospital stay, higher susceptibility to infections, and higher NIHSS scores. These results suggested that the NLR calculated on the first admission day in AIS might be a prognostic indicator for the early period.

One of the limitations of the studies with NLR is the concern that changes due to infectious diseases may affect the results. Urinary and respiratory system infections may be encountered frequently during hospital follow-up of patients with ischemic stroke. The risk of developing infection increases in clinically severely affected patients and in case of longer hospital stay. In this case, the possibility that NLR varies according to hospitalization period in studies including patients with stroke, as in our study, is a problem that should be taken seriously. It can be said that one of the important findings of this study is that the NLR calculated from the blood sample taken in the very early stages of ischemic stroke and the NLR calculated from the blood sample taken in the following days are similar. This finding suggests that NLR in the early period can be highly determinative in predicting the later process.

The NIHSS is a widely used scale to determine the severity of stroke in acute strokes and to provide a numerical value. In our study, NLR showed a significant positive correlation with NHISS score. Similar to the results of our study, a positive correlation between the severity of stroke and NLR was reported previously

(13). In another study, it was stated that infarct volume, NLR, and NIHSS score were independent indicators of 30-day mortality (10). In addition, it was observed that infarct volume showed a positive correlation with NLR (10). In our study, infarct volume wasn't measured, however, the NLR was found to be higher in hemispheric major arterial area infarcts compared to hemispheric lacunar infarcts and brain stem infarcts.

Regression analyses showed that NIHSS score and CRP were independent risk factors for length of hospital stay in our study group. The reciprocal correlation of NLR and NIHSS score was also among the important findings of this study. These findings may suggest that high NLR is indicative of very early responses to stroke. However, these findings may also indicate that NLR is elevated in some patients before the occurance of stroke, during the process that predisposes to stroke and includes at least some inflammatory features. More knowledge is needed to explain and evaluate these relationships.

In our study, the cut-off point that could be used to predict clinical status and prognosis was determined as 2.86. This cut-off point was found to be similar for the entire patient group when patients with infection were excluded and only those without infection were included (2.86). Moreover, the calculated value appeared to have a higher sensitivity and specificity in patients without infection. In a meta-analysis, it was reported that NLR was predictive for 3-month mortality, independent of pneumonia, which is one of the most common infections after stroke (12). The results of this meta-analysis support our findings.

The presented study, showed that infection developed more frequently during hospital stay in patients with high NLR. Considering that the aforementioned NLRs belonged to the blood samples taken at the very early stage of the acute event, it could be said that NLR at admission is a parameter that can enable us predict which patients are prone to infection during hospital stay.

Study Limitations

The limitations of the study are the following: the study is retrospective, the second blood sample was not taken on the same day for each patient even if they were taken at least five days after the first blood sampling, some subgroups were not homogenized because the study included all consecutive patients, and the etiological classification of the patients included in the study was also retrospective. The lack of use of modified Rankin Scale in this study might create a limitation for the assessment of disability. In addition, choosing the NIHSS score thresholds different from the ones we determined or using a different assessment scale when grouping patients according to stroke severity might have changed the results and yielded different results.

Conclusion

As a result, the NLR obtained at admission to the emergency department, in the very early period of AIS was found to be similar to the NLR in the control blood sampling at least 5 days later. The NLR calculated at admission to the in AIS may be a prognostic indicator for the assessment of stroke severity, length of hospital stay, and risk of infection in stroke patients. However, more knowledge is needed in this area.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Gaziantep University Clinical Research Ethics Committee with the decision number 07.06.2015/201 on 07.05.15.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.Ç., A.M.N., Design: G.Ç., Y.E.F., A.M.N., Data Collection or Processing: G.Ç., Y.E.F., S.G., E.K.C., A.M.N., Analysis or Interpretation: G.Ç., Y.E.F., S.G., E.K.C., A.M.N., Literature Search: G.Ç., Y.E.F., A.M.N., Writing G.Ç., A.M.N.

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