Neutrophil to lymphocyte ratio, stroke severity and short term clinical outcomes in acute ischemic stroke

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Abstract

Background: Neutrophil to lymphocyte ratio is an easily evaluated systemic inflammation indicator. However, there are limited reports on neutrophil to lymphocyte ratio and functional outcome in ischemic stroke. In this study, we aimed to evaluate the association of neutrophil to lymphocyte ratio and stroke severity, short term functional outcomes and mortality in patients with acute ischemic stroke. *Methods:* The clinical data of patients who were > 18 age-old and hospitalized with acute ischemic stroke in Baskent University Hospital, Ankara, Turkey between January 2018 and May 2019 were studied retrospectively. Neutrophil to lymphocyte ratio were measured. The neutrophil to lymphocyte ratio and National Institute of Health Stroke Scale (NIHSS) score at admission, mortality during hospitalization and Modified Rankin Scale (mRS) score at discharge of the patients with acute ischemic stroke were correlated. *Results:* Among the acute ischemic stroke patients due to the exclusion criteria, the data of 134 patients were evaluated. Median age of the patients were 76± 12.5 years and 82 patients (61.2%) were male. The median NIHSS scores of the patients at admission was 5±4.5. Mortality during the hospitalization was seen in 8 patients (6%). The median neutrophil to lymphocyte ratio value of the patients at admission were found to be 2.6±3.4. Neutrophil to lymphocyte ratio and NIHSS scores of the patients at admission, duration of the hospitalization, mRS scores at discharge and mortality during hospitalization were found to be positively correlated.
Conclusion: Neutrophil to lymphocyte ratio is a simple and easily measured marker and can be used as a potential indicator for prognosis in acute ischemic stroke. However further prospective multicenter investigations are required to confirm the role of neutrophil to lymphocyte ratio for predicting the prognosis in acute ischemic stroke patients.

Keywords: Neutrophil to lymphocyte ratio, acute ischemic stroke, mortality, clinical outcomes, prognosis

INTRODUCTION

Cerebrovascular diseases are important causes of mortality and morbidity in general population and ischemic stroke represents approximately 80-85% of the cases.[1,2] Thus it is important to find indicators that are reliable and easily applicable in the evaluation of acute ischemic stroke patients according to risk factors and predict the prognosis.[2,3]

Immunological response following stroke consists of a complex process including dysfunction of endothelium by activation of many inflammatory cells, distortion in blood brain barrier and release of reactive and oxidant molecules.[4] This inflammatory process initiates in several hours and contributes to formation of progressive brain damage in patients.[1,4,5] Therefore many inflammatory indicators and cellular components such as leucocyte count, micro-ribonucleic acid (RNA), proinflammatory cytokines and their association with infarct volumes, prognosis and mortality has been investigated in acute ischemic stroke.[2,4,5]

Increased leucocyte levels in complete blood counts were shown to be associated with increased mortality and poor functional outcomes in acute ischemic stroke patients.[5,6] Leucocyte subtypes, which have variable inflammatory and immunological functions, causes differential effects on pathophysiology of atherosclerosis and clinical results of cerebrovascular and cardiovascular diseases.[5,7] In previous studies

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it was reported that, increased leucocyte and neutrophil counts have correlation with increased stroke severity and infarct volume in patients and were observed to be associated with recurrent stroke development, while lymphocyte numbers were associated with early recovery and positive functional outcomes.[1,5]

Neutrophil to lymphocyte ratio is an easily evaluated inflammation indicator among universally and commonly used complete blood count parameters in patients.[3] Recently, neutrophil to lymphocyte ratio has been evaluated as an indicator of systemic inflammation in prediction of mortality in cardiovascular and peripheral artery diseases.[1-3] It is considered to be a better indicator compared to total leucocyte count in cardiovascular diseases.[1] In addition neutrophil to lymphocyte ratio is associated with poor prognosis in patients with cancer.[1] There is limited evidence on relation of neutrophil to lymphocyte ratio and functional results in ischemic stroke patients.

Thus this study aimed to evaluate and discuss the association of neutrophil to lymphocyte ratio and stroke severity, early functional outcomes and mortality in patients who are hospitalized and followed with diagnosis of acute ischemic stroke.

METHODS

In this study patients who were >18 age-old and hospitalized with acute ischemic stroke diagnosis in Baskent University Hospital between January 2018 and May 2019, were evaluated retrospectively. Ischemic stroke diagnosis was confirmed with brain computed tomography or magnetic resonance imaging. Patients who had history of infection up to one week before admission or during hospitalization, were receiving immunosuppressive treatment or steroid, had malignancy or hematological disease, had history of surgery or major trauma in the last one month were excluded. The demographic data and etiology of stroke were collected. Age, gender, vascular risk factors such as consumption of cigarette and alcohol, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, presence of ischemic heart diseases were recorded. The subtypes of ischemic stroke were determined according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.[8] Data of the complete blood count from the samples of peripheral venous blood in EDTA tubes collected from the patients at admission were examined. Hemoglobin, leucocyte,

thrombocyte, neutrophil and lymphocyte counts were recorded. Neutrophil to lymphocyte ratio was calculated as the ratio of neutrophil value to lymphocyte value of complete blood counts at admission. In addition, biochemical tests such as fasting glucose, creatinine, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, and C - reactive protein (CRP) and sedimentation values of patients were listed. NIHSS scores were used to evaluate stroke severity of the patients at administration.[9] Functional status of the patients at discharge were assessed by mRS scores. Duration of the hospitalization and the mortality rates during the hospitalization were also recorded. The correlations between neutrophil to lymphocyte ratio and duration of hospitalization, NIHSS scores at admission, mRS scores at discharge and mortality during hospitalization were statistically evaluated.

This retrospective study was approved by the Baskent University Faculty of Medicine Ethical Review Committee (KA20/256). Statistical analyses were applied using SPSS 23 for Windows (SPSS Inc. Chicago, IL). Distribution of data was determined by using the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages, numerical variables which have normal distribution were presented as mean±standard deviation, and which are not normally distributed were presented as median±standard deviation. Correlation between two variables, one of them as neutrophil to lymphocyte ratio, was assessed by Pearson, Spearman or Point-Biserial correlation analysis as appropriate. $p < 0.05$ was considered statistically significant.

RESULTS

In our study, due to exclusion criteria, we managed to evaluate a total number of 134 patients. Median age of the patients were 76± 12.5 years and 82 patients (61.2%) were male. When the patients' vascular risk factors were assessed, 105 patients (78.4%) had hypertension, 37 patients (27.6%) had hyperlipidemia, 56 patients (41.8%) had diabetes mellitus, 29 patients (21.6%) had atrial fibrillation, 33 patients (24.6%) had ischemic heart disease, 34 patients (25.4%) had history of smoking and 23 patients (17.2%) had history of previous cerebrovascular disease.

According to TOAST classification, stroke due to large artery atherosclerosis was detected in 19 patients (14.2%), cardioembolic stroke was

found in 53 patients (39.5%), lacunar stroke was observed in 28 patients (20.9%) and cryptogenic stroke was found in 34 patients (25.4%). Recurrent ischemic stroke after discharge was observed in 7 patients (5.2%). Demographic and clinical characteristics of the patients were shown in Table 1.

The total blood count parameters of patients were detected as mean of the hemoglobin was 13.6±2 g/dL and median of the leucocyte was 7.7±5 $10^3/\mu L$, neutrophil was 4.7±2.6 $10^3/\mu L$ and lymphocyte was 1.8±1.2 $10^3/\mu L$. The median neutrophil to lymphocyte ratio value of the patients at admission were 2.6±3.4 (minimum: 0.89, maximum: 27.30). The laboratory tests of the patients are listed in Table 2.

The median NIHSS scores of the patients at admission was 5±4.5 (minimum: 2, maximum: 34). The median duration of hospitalization was 4±5.9days (minimum: 2 days, maximum: 40 days). As for the mRS scores at discharge, 36 patients (26.9%) had "0", 44 patients (32.8%) had "1", 21 patients (15.7%) had "2", 9 patients (6.7%) had "3", 13 patients (9.7%) had "4" and 3 patients (2.2%) had "5". Mortality during the hospitalization was seen in 8 patients (6%).

Neutrophil to lymphocyte ratio and NIHSS scores of the patients at admission was positively correlated (p<0.05) and duration of the hospitalization was significantly longer in individuals with higher neutrophil to lymphocyte ratio (p<0.05). When the association between functional outcomes of the patients and neutrophil to lymphocyte ratio was evaluated, it was positively correlated with discharge mRS scores (p<0.05). Neutrophil to lymphocyte ratio was detected significantly higher in individuals with mortality (p<0.05). No statistically significant association was found between recurrent ischemic stroke and neutrophil to lymphocyte ratio (p>0.05).

DISCUSSION

In this study the association of neutrophil to lymphocyte ratio with stroke severity, early functional outcomes and mortality was investigated and it was found that neutrophil to lymphocyte ratio shows a positive correlation with increased NIHSS scores, poor functional outcomes at discharge and increased hospital mortality in patients with acute ischemic stroke.

Table 1: Demographical and clinical characteristics of the patients with acute ischemic stroke

	(n=134)
Age in years, median ±SD	76± 12.5
Male, n(%)	82 (61.2%)
Hypertension, n(%)	105 (78.4%)
Hyperlipidemia, n(%)	37 (27.6%)
Diabetes mellitus, n(%)	56 (41.8%)
Atrial fibrillation, n(%)	29 (21.6%)
Coronary artery disease, n(%)	33 (24.6%)
Smoking, n(%)	34 (25.4%)
Stroke history, n(%)	23 (17.2%)
Stroke subtypes, n(%) Large artery atherosclerosis Cardioembolic stroke Lacunar stroke Cryptogenic stroke	 19 (14.2%) 53 (39.5%) 28 (20.9%) 34 (25.4%)
Mortality, n (%)	8 (6%)
Recurrent stroke, n (%)	7 (5.2%)
NIHSS, median ±SD	5±4.5
Duration of hospitalization in days, median ±SD	4±5.9

NIHSS: National Institute of Health Stroke Scale, SD: standard deviation

Table 2: Laboratory findings of the patients with acute ischemic stroke

Hemoglobin, g/dL(mean ±SD)	13.6±2
Leucocyte, 10^3/μL(median ±SD)	7.7±5
Neutrophil, 10^3/μL (median ±SD)	4.7±2.6
Lymphocyte, 10^3/μL(median ±SD)	1.8±1.2
NLR(median ±SD)	2.6±3.4
Creatinine, mg/dL(median ±SD)	0.9±1.4
Fasting glucose, mg/dL(median ±SD)	105.5±126.7
LDL, mg/dL (mean±SD)	117.7±39
Triglyceride, mg/dL(median ±SD)	124±82.5
HDL, mg/dL(median ±SD)	41±36.9
CRP, mg/L(median ±SD)	5±14.6
Sedimentation, mm/hour(median ±SD)	15±14.8

NLR: Neutrophil to lymphocyte ratio, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, CRP: C-reactive protein, SD: standard deviation.

Inflammation has a substantial role in the formation and progression of atherosclerosis.[3] Inflammatory response following acute ischemic stroke includes important pathophysiological processes that increases post ischemic damage in brain and the relation between the inflammation and poor prognosis following acute ischemic stroke has long been investigated.[2,10]

Chemokines and cytokines released from ischemic tissues during inflammation causes migration of leucocytes to ischemic region.[7,10] In previous studies, it was reported that leucocytes have effects on neurological functional outcomes and prognosis in individuals with acute ischemic stroke and these effects vary according to subtypes of leucocytes.[7,10] Neutrophils are the fundamental subtypes of leucocytes that respond early following stroke that result increased release of inflammatory mediators.[5,10,11] The accumulation in cerebral circulation within the hours causes disruption of microvascular perfusion and expansion of the infarct region.[1] It was demonstrated that neutrophils are associated with infarct volume, recurrent stroke risk and poor functional outcomes and a decrease is observed in the infarct volume of ischemic stroke as a result of a decrease in neutrophil count or prevention of the infiltration.[4,6,10] Lymphocytes show a trend of increase within 3-6 days following stroke in ischemic tissue.[1,11] While lymphocytes have an active role on ischemic brain damage pathogenesis, the data on the role of lymphocytes are controversial.[1,6,10] In some studies it was reported that lymphocytes have a recovering and repairing effect in inflammation, while in others it was suggested that lymphocytes are the source of proinflammatory cytokines and cytotoxic substances and have a negative impact on ischemic brain damage.[1,6]

In the study by Kim *et al*., total leucocyte and neutrophil values detected in acute ischemic stroke patients who had been admitted within 3 days following the initiation of symptoms are found to be associated with high NIHSS scores and increase in stroke severity, while low lymphocyte values are found to be associated with less early neurological recovery and long term poor functional outcomes.[7]

Neutrophil to lymphocyte ratio was found to be significantly high in individuals with acute ischemic stroke compared to healthy individuals.[12] In a study evaluating the neutrophil to lymphocyte ratio in individuals with acute ischemic stroke, transient ischemic attacks and control group, leucocyte number and neutrophil to lymphocyte ratio are reported to be significantly high in acute ischemic stroke patients compared to patients with transient ischemic attacks and control group.[3] In addition neutrophil to lymphocyte ratio was found statistically and significantly higher in patients with ischemic stroke patients compared to control group in another conducted study.[13]

Numerous data has shown that neutrophil number and neutrophil to lymphocyte ratio are better inflammatory indicators than leucocyte values in many diseases. Besides being inflammatory indicators, neutrophil numbers and neutrophil to lymphocyte ratio are suggested to be important indicators for predicting the poor clinical outcome in many diseases such as solid

organ tumors, atrial fibrillation, non-ST elevated myocardial infarction, ST elevated myocardial infarction, transient ischemic attacks and ischemic and hemorrhagic strokes.[2,3,10] In studies with acute ischemic stroke patients it was shown that matrix metallo-proteinase 9 levels, free oxygen radicals, chemokines and other inflammatory mediators increase due to increase in neutrophils and it may cause neuronal cell death, distortion in blood brain barrier and hemorrhagic transformation following ischemic stroke.[10]

Neutrophil to lymphocyte ratio was reported to be important in predicting functional outcomes and mortality in patients with ischemic stroke. Yu *et al*. demonstrated that high neutrophil to lymphocyte ratio in patients with acute ischemic stroke is associated with poor functional outcomes at discharge and higher mRS scores. However it is not found to be significantly associated with mortality during hospitalization.[5] In a study by Qun *et al*., it was found that high neutrophil to lymphocyte ratio at admission is associated with poor functional outcomes at 3 months and in a meta-analysis when mRS scores of patients are evaluated at third month after the stroke, neutrophil to lymphocyte ratio was found to be associated with statistically significant higher scores and poor functional outcomes.[6,10] Fang *et al*. reported that neutrophil count and neutrophil to lymphocyte ratio in patients with ischemic stroke from causes other than atrial fibrillation were significantly higher in patients with increased NIHSS scores and neutrophil to lymphocyte ratio was significantly associated with hospital mortality rates.[2] In another study, it was found that independent from infarct volume, neutrophil to lymphocyte ratio at hospital admission was able to predict the mortality at one month.[14] Similar to these studies[3,14], our study also demonstrated that neutrophil to lymphocyte ratio is associated with poor functional outcomes of patients at discharge and patients' mortality.

Neutrophil to lymphocyte ratio is also found to be associated with stroke severity and infarct volume. Zhao *et al*. showed in his study that neutrophil to lymphocyte ratio in patients with acute ischemic stroke was associated with duration of hospitalization.[11] Previous studies also found the neutrophil to lymphocyte ratio to be correlated with higher NIHSS scores at admission.[1,4,12-14] A study by Tokgoz *et al*. also found a positive correlation between infarct volume and neutrophil to lymphocyte ratio.[14]

In our study no significant association was found between recurrent ischemic stroke and neutrophil to lymphocyte ratio. On the other hand, Xue *et al*. found that recurrent ischemic stroke rate was higher in their patients with higher neutrophil to lymphocyte ratio.[1]

There are some limitations of our study. First, this study was conducted in only one center and the study was retrospective. In addition, neutrophil to lymphocyte ratio changes dynamically. However, in our study, only the neutrophil to lymphocyte ratios at admission were evaluated, the alterations in the ratios in serial tests during hospitalization were not investigated.

In conclusion, neutrophil to lymphocyte ratio can be a simple and easily available indicator to predict stroke severity, short term functional outcomes and mortality in acute ischemic stroke. However further investigations with higher number of patients and monitoring of the dynamic alterations are required to identify and understand the prognostic usefulness of neutrophil to lymphocyte ratio in ischemic stroke.

DISCLOSURE

REFERENCES

1. Xue J, Huang W, Chen X, *et al*. Neutrophil-to-lymphocyte ratio is a prognostic marker in acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2017; 26(3): 650-7.
2. Fang YN, Tong MS, Sung PH, *et al*. Higher neutrophil counts and neutrophil-to-lymphocyte ratio predict prognostic outcomes in patients after non-atrial fibrillation-caused ischemic stroke. *Biomed J*. 2017; 40(3): 154-162
3. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *J Clin Lab Anal* 2014; 28(1): 27-31.
4. Tokgoz S, Kayrak M, Akpinar Z, Seyithanoglu A, Guney F, Yuruten B. Neutrophil lymphocyte ratio as a predictor of stroke. *J StrokeCerebrovasc Dis* 2013; 22(7): 1169-74.
5. Yu S, Arima H, Bertmar C, Clarke S, Herkes G, Krause M. Neutrophil to lymphocyte ratio and early clinical outcomes in patients with acute ischemic stroke. *J Neurol Sci* 2018; 387: 115-8.
6. Zhang J, Ren Q, Song Y, *et al*. Prognostic role of neutrophil–lymphocyte ratio in patients with acute ischemic stroke. *Medicine* 2017; 96:45:e8624.
7. Kim J, Song TJ, Park JH, *et al*. Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction. *Atherosclerosis* 2012; 222(2): 464-7.
8. Adams HP Jr, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke.

Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24(1): 35-41.

9. Brott T, Adams HP Jr, Olinger CP, *et al*. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; 20(7): 864-70.

10. 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): 444-52.

11. 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. *J Stroke Cerebrovasc Dis* 2016; 25(4): 739-44.

12. Kurt NG, Guloglu C, Tamam Y, Ustundag M, Orak M. 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 Med J* 2019; 46(2): 361-8.

13. Aytac, E, Akpınar CK, Gurkas E. Neutrophil to lymphocyte ratio: A simple and readily available independent marker of mortality in acute ischemic stroke. *Firat Med J* 2017; 22(4): 192-6.

14. Tokgoz S, Keskin S, Kayrak M, Seyithanoglu A, Ogmegul, A. Is neutrophil/lymphocyte ratio predict to short-term mortality in acute cerebral infarct independently from infarct volume? J Stroke *Cerebrovasc Dis* 2014; 23(8): 2163-8.