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The Predictive Effect of the Neutrophil-to-Lymphocyte Ratio (NLR) on the Mortality of Acute Ischemic Stroke and its Subtypes: a Retrospective Cross-Sectional Study

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Abstract

Aim: In this study, we aimed to evaluate the association between the neutrophil-to-lymphocyte ratio (NLR) and short-term mortality in cases of acute ischemic stroke (AIS) and its subtypes in emergency departments (EDs).

Materials and Methods: This retrospective cross-sectional investigation included 164 patients presenting to the ED with AIS. The demographic characteristics of the patients, hemogram test results at presentation, co-morbidities, AIS subtype, arrival time at the ED (time between symptoms initiation to ED presentation, in hours), National Institutes of Health Stroke Scale (NIHSS) scores, modified Rankin Scale (mRS) scores, and the length of hospital stay (LHS) were recorded on a data collection form. The clinical outcome was assessed by the NIHSS score on admission, mRS scores at discharge, and on the number of days of hospitalization. Blood samples were analyzed by optical laser light scatter analysis methods (Abbott, cell-dyn Ruby 3700, USA).

Results: Among the study cohort, 134 patients were discharged with a status of cured or surviving, whereas 30 patients did not survive. NLR ratios were higher among the patients who later expired than among the patients who were discharged (p=0.011). Mortality was the highest among cases with an undetermined origin. The WBC and neutrophil count differed significantly among the stroke subtype classifications (p=0.009 and 0.008, respectively), although NLR did not vary significantly among the stroke subtypes (p=0.070). The median LHS was 5 (1–116) days and did not differ significantly among the subtype groups (p=0.877).

Conclusion: Higher NLR is associated with an increased mortality rate in patients with AIS but is not a good predictor for AIS subtypes.
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Keywords: Neutrophil to lymphocyte ratio, acute ischemic stroke, mortality

Introduction

A stroke is generally defined as any disease process that results in a loss of blood flow to the brain, causing permanent (1) focal neurologic syndromes. Strokes are the second most common cause of death after coronary artery disease (2) and are a major cause of disability worldwide (3-6) and a major contributor to the global burden of disease in western countries (7). Acute ischemic stroke (AIS) is one of the most common types of stroke presenting at emergency departments (EDs).

Disruption of the blood–brain barrier causes leukocyte infiltration and a release of pro-inflammatory cytokines following AIS. Recent studies have demonstrated that peripheral leukocyte levels increase following cerebrovascular ischemia. The initial peripheral leukocyte count following a stroke can help predict stroke severity, disability rates at discharge, and final infarct volume (2). Some publications suggest that the leukocyte count at the time of admission is predictive of the likelihood of ischemic stroke and the impact of any resulting neurologic disability on daily living activity (8).

Recent studies suggest that peripheral white blood cells and other inflammatory processes play an important role in the pathophysiology of AIS (3, 9). The neutrophil-to-lymphocyte ratio (NLR) is a parameter of inflammation (2, 10) that is easy to obtain, economical (2), and widely available (11) and has emerged recently as an independent useful prognostic marker to predict the mortality and prognosis of some cardiovascular and neurologic diseases (2, 9-12).

In recent years, several studies have been published investigating the relationship between NLR and stroke (ischemic or hemorrhagic) mortality and prognosis. No previous study, however, has evaluated the relationship between AIS and NLR in the cases of stroke stratified by subtype in ED patients. We examined the relationship between NLR at the time of ED presentation and the short-term mortality in patients with AIS and its diagnostic subtypes.

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Materials and Methods

This study is a retrospective cross-sectional investigation conducted with 164 AIS patients presenting to the University Education and Research Hospital ED with AIS between July 2015 and February 2016 who were eligible for participation in the study.

The study data were reviewed retrospectively from hospital records using the International Classification of Diseases-10 (ICD-10) codes for AIS. The demographic characteristics of the patients, hemogram test results on admission, co-morbidities, AIS subtype diagnosis, arrival time at the ED [time between the start of symptoms and arrival at the ED (hours)], National Institutes Of Health Stroke Scale (NIHSS) scores, modified Rankin Scale (mRS) scores, length of hospital stay (days), etiology, the "trial of org 10172 in acute stroke treatment" (TOAST) classification, definitive diagnosis, and clinical outcome were recorded retrospectively on a data collection form in accordance with the Declaration of Helsinki. The outcome was assessed by the NIHSS score on admission, mRS (mRS, 0=no symptoms at all, 6=death) scores at discharge, and the length of hospitalization. Patients were referred for the study by the attending emergency physician. The patients with incomplete or missing data such as medical, demographic, clinical, laboratory, and radiologic data; a history of prior stroke attack or who had already been receiving treatment for stroke from another center; all types of hemorrhagic stroke, such as subarachnoid, subdural, epidural, intraparenchymal, and intraventricular hemorrhages; fever at presentation; any malignancy; chronic inflammatory disease, for example connective tissue disorders such as vasculitis, rheumatoid arthritis, systemic lupus erythematosus, renal, and hepatic insufficiency; pancreatitis; organ transplantation; immunosuppressive etiologies; and hemoglobinopathies were excluded from the study because NLR may be affected.

Blood samples were evaluated using optical laser light scatter analysis methods (Abbott, cell-dyn Ruby 3700, USA).

Statistical analysis

The study data were analyzed using MedCalc Statistical Software version 12.7.0.0. The Shapiro–Wilk test was used to determine normality. Continuous variables are shown as the mean ± SD or median (min-max) where applicable. Categorical data are reported as the number of cases and percentages. Mean differences among the groups were analyzed by one-way ANOVA, and the Kruskal–Wallis test was used to compare medians. Categorical data were analyzed by the Pearson's chi-square or Fisher's exact test, where appropriate. A p value <0.05 was considered statistically significant.

Results

The study included 164 [79 females (48.2%) and 85 males (51.8%)] AIS patients. The mean age of the study participants was 71.9±9.3 years (min: 52 years, max: 89 years). Demographic characteristics, co-morbidities, TOAST classification, mRS scores, median NIHSS scores, and median arrival time at the ED are given in Table 1.

Among the patients, 134 were discharged as cured or surviving, while 30 patients died. The mean age of the dead subjects was 76.1±10.9 years, and the mean age of the surviving patients was 70.8±13.3 years; this difference was statistically significant (p=0.044). The mean NIHSS score among the dead patients was significantly elevated relative to the surviving patients (p<0.001). The WBC, neutrophil count, and NLR ratios were elevated among the dead patients compared to the surviving patients (p=0.009, p<0.001, and p=0.011, respectively), whereas the lymphocyte count was higher among the surviving patients than among the dead subjects (p=0.005). The highest rate of mortality occurred in cases of AIS of an undetermined origin (UDO) according to the TOAST classification (p<0.001). There were no statistically significant differences between the groups according to gender, co-morbidity, or length of hospital stay. The clinical characteristics of the subjects including death and survival status are summarized in Table 1.

According to the TOAST classification of the subjects, 15 (9.1%) were diagnosed with large-artery disease (LAD), 15 (9.1%) were diagnosed with cardioembolism (CE), 25 (15.2%) had small-artery disease (SAD), and 109 patients (66.5%) were classified as UDO. Mortality occurred in UDO (n=28) and CE stroke subtypes (p=0.000). The WBC and neutrophil count differed significantly among AIS subgroups (p=0.009 and p=0.008, respectively), but NLR was not significantly different among the AIS subtypes (p=0.070) (Table 2).

Discussion

This study examined the association between the NLR and mortality in ED patients with AIS and its subtype. Elevated NLR was associated with increased hospital mortality rates in cases of AIS but was not correlated with specific AIS subtypes. Elevated leukocyte and neutrophil counts and decreased lymphocyte counts were found in the deceased subjects compared to surviving subjects.

Recently, a number of scoring systems and biochemical markers have been developed to predict stroke prognosis and mortality (5, 11). Currently, the NLR is one of most widely used inflammatory markers (2, 10). The neutrophil count, lymphocyte count, and NLR can be easily obtained from the WBC count (5). The NLR is a simple, inexpensive, and easily available prognostic marker for some inflammatory diseases (11, 13).

Inflammatory activity develops within 6–24 h after the vascular pathology and plays an important role in ischemic damage (4). High NLR ratios may be associated with vascular inflammation in both acute coronary diseases and in AIS, and the size of the infarct volume is proportional to the NLR ratio, independent of the etiology (2, 4, 9, 13). In one study, an NLR threshold value of 5.0 was found to be predictive of mortality (4, 9). Another study conducted among intracerabral hemorrhagic patients demonstrated that patients with an NLR of 7.35 had a higher rate of mortality (11). In the present study, the mean NLR value was 2.7±1.5 for surviving patients and 12.1±4.5 among non-surviving subjects.

Neutrophils may contribute to indirect cerebral injury by occluding cerebral microvessels, leading to an extension of the infarct or by the release of neurotoxic substances and inflammatory mediators into the penumbra and focal ischemic brain (8, 9, 11, 14). Similar to earlier publications, WBC and neutrophil counts were elevated among dead subjects compared to surviving patients, with the greatest elevation occurring in CE subtype AIS. In general, increased serum WBC and neutrophil counts have been associated with poor outcomes in many disease conditions (5, 8). An elevated neutrophil count is an early indicator of ischemic brain damage (9) and is associated with a poor prognosis at 3 months, larger infarct volumes, and increased stroke severity in the early stage of ischemia (4, 14). The neutrophil response to vascular injury occurs within approximately 6–12 h in rat models (14) and

Table 1. Demographic and clinical characteristics of subjects regarding death and survival status

Variables	Surviving (n=134)	Dead (n=30)	p	Total (n=164)
Age (years) ±SD	70.8±13.3	76.1±10.9	0.044†	71.9±9.3
Gender, n (%)				
Female	63 (79.7)	16 (20.3)	0.551$	79 (48.2)
Male	71 (83.5)	14 (16.5)		85 (51.8)
Co-morbid conditions, n (%)				
Hypertension	104 (77.6)	18 (60.0)	0.063$	122 (74.4)
Diabetes mellitus	48 (36.4)	6 (20.0)	0.132$	67 (40.6)
Coronary artery disease	58 (43.3)	9(30.0)	0.220$	54 (33.3)
Congestive heart failure	23(17.2)	8 (35.4)	0.300$	31 (18.9)
Chronic obstructive pulmonary disease	10 (7.5)	3 (10.0)	0.708$	13 (7.9)
Multiple conditions	70 (52.2)	16 (53.3)	1.000$	86 (52.4)
NIHSS, median (min-max)	4 (1–16)	14 (4–18)	<0.001¶	6 (1–18)
Length of hospital stay (day), median (min-max)	4 (2–22)	4 (2–101)	0.877¶	5 (1–116)
Arrival time of ED (h), median (min-max)	0 (0–65)	0 (0–16)	0.954¶	0 (0–57)
WBC, 10^3/UL, mean±SD	10.0±3.1	12.1±3.8	0.009†	10.4±3.3
Neutrophil, 10^3/UL, mean±SD	6.9±3.01	9.7±3.9	<0.001†	7.4±3.4
Lymphocytes, 10^3/UL, mean±SD	2.3±1.5	1.5±0.9	0.005†	2.3±1.4
Monocytes, 10^3/UL, mean±SD	0.7±0.3	0.8±0.4	0.101†	1.9 ±0.7
NLR	2.7±1.5	12.1±4.5	0.011†	5.8±9.2
TOAST, n (%)				
Large-artery disease	15 (11.2)	-	<0.001$	15 (9.1)
Cardioembolism	13 (9.7)	2 (6.7)		15 (9.1)
Small-artery disease (lacune)	25 (18.7)			25 (15.2)
Undetermined origin	81 (60.4)	28 (93.3)		109 (66.5)
mRS score				
No significant disability	21 (12.8)	-		21 (12.8)
Slight disability	67 (40.9)	-		67 (40.9)
Moderate disability	26(15.9)	-		26(15.9)
Moderate-severe disability	14 (8.5)	-		14 (8.5)
Severe disability	6 (3.7)	-		6 (3.7)
Dead	-	30 (18.3)		30 (18.3)

†Student's t test, ¶Mann–Whitney U test, $Fisher's Exact Test. SD: standard deviation; min: minimum; max: maximum; n: number of cases; ED: emergency department; NIHSS: National Institutes of Health Stroke Scale; NLR: neutrophil-to-lymphocyte ratio; TOAST: The Trial of Org 10172 in Acute Stroke Treatment; WBC: white blood cell

6–24 h in human patients (9). In the present study, WBC counts were significantly elevated among non-surviving patients.

Lymphopenia, including decreased T cells, is an early indicator of AIS and emerges within a few days following stroke initiation (3, 7, 15). Serum lymphocyte levels may be inversely associated with poor outcomes (8). The decreased serum levels of lymphocytes in AIS may be directly related to the increase in NLR ratios (5, 7, 8). Lymphocytes increase 3–6 days after AIS onset and peak around 7 days after stroke (4, 13). We observed that non-surviving patients had significantly reduced lymphocyte counts. This NLR increase may be the result of an invasion of the edematous penumbra by immune cells and an associated decrease in serum lymphocytes associated with the infarct volume.

An earlier study reported that the degree of inflammatory activation is higher in subjects with the CE subtype than in subjects with other TOAST subtypes of stroke (16). Another study demonstrated significantly higher NLR levels in patients with LAD AIS (10). However, our study found no significant differences in NLR between stroke subtypes.

Table 2. Acute ischemic stroke subtypes and peripheral immunocell distribution

	Large-artery disease	Cardioembolism	Small-artery disease (lacune)	Undetermined origin	p
WBC, 10^3/UL mean±SD	8.3±1.6	11.7±3.8	9.04±1.9	10.1±3.6	0.009
Neutrophil 10^3/UL mean±SD	5.3±1.5	8.9±4.01	6.1±2.0	7.1±3.6	0.008
Lymphocytes 10^3/UL mean±SD	1.7±0.5	1.6±0.8	1.5±0.8	1.7±1.6	0.089
Monocytes 10^3/UL mean±SD	0.3±0.2	0.3±0.1	0.2±0.3	0.7±0.9	0.233

WBC: white blood cell; SD: standard deviation

Immune-inflammatory activation during AIS is associated with stroke volume and severity and is graded using the NIHSS score. A strong correlation between NLR and the NIHSS score has been shown in previous clinic trials (9, 16). Similarly, our results supported these reports that both a median NIHSS score [14 (4–18)] and NLR ratio were higher in non-surviving subjects than in surviving patients.

This study has several limitations because of its retrospective design nature. Data extraction from hospital records has a limited ability to accurately identify health conditions and includes a substantial amount of missing data. Another limitation is the lack of a direct comparison between neutrophil and lymphocyte counts and the levels of other inflammatory markers. Also, many co-morbidities and environmental factors that might have affected the inflammatory marker levels were not taken into account. We were unable to evaluate the correlation between the infarct volume and NLR because no infarct volume measurement was made. Finally, the absence of systemic infection was determined by patient history and body temperature measurement alone; therefore, we do not know if infection may have contributed to changes in the inflammatory parameters measured in this study cohort.

Conclusion

The NLR is a simple, widely accessible, and inexpensive marker that may be used as an independent predictor of short-term mortality in AIS patients during ED presentation, but it is not a good predictor for AIS subtypes. However, additional large-scale studies are necessary to support these results.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Patient conset for this retrospective study has not been received.

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References

1. Ortega SB, Noorbhai I, Poinsatte K, Kong X, Anderson A, Monson NL, et al. Stroke induces a rapid adaptive autoimmune response to novel neuronal antigens. Discov Med 2015; 19: 381-92.
2. Saliba W, Barnett-Griness O, Elias M, Rennert GK. Neutrophil to lymphocyte ratio and risk of a first episode of stroke in patients with atrial fibrillation: a cohort study. J Thromb Haemost 2015; 13: 1971-9. [CrossRef]
3. Oh SH, Kim OJ, Shin DA, Song J, Yoo H, Kim YK, et al. Alteration of immunologic responses on peripheral blood in the acute phase of ischemic stroke: blood genomic profiling study. J Neuroimmunol 2012; 249: 60-5. [CrossRef]
4. 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: 2163-8. [CrossRef]
5. Köklü E, Yüksel İÖ, Arslan S, Bayar N, Çağırcı G, Gencer ES, et al. Is elevated neutrophil-to-lymphocyte ratio a predictor of stroke in patients with intermediate carotid artery stenosis? J Stroke Cerebrovasc Dis 2016; 25: 578-84. [CrossRef]
6. Seyhanli ES, Lok U, Gulacti U, Buyukaslan H, Atescelik M, Yildiz M, et al. Assessment of serum and urine ghrelin levels in patients with acute stroke. Int J Clin Exp Med 2015; 8: 722-9.
7. Urra X, Cervera A, Villamor N, Planas AM, Chamorro A. Harms and benefits of lymphocyte subpopulations in patients with acute stroke. Neuroscience 2009; 158: 1174-83. [CrossRef]
8. Kumar AD, Boehme AK, Siegler JE, Gillette M, Albright KC, Martin-Schild S. Leukocytosis in patients with neurologic deterioration after acute ischemic stroke is associated with poor outcomes. J Stroke Cerebrovasc Dis 2013; 22: e111-7. [CrossRef]
9. Tokgoz S, Kayrak M, Akpinar Z, Seyithanoğlu A, Güney F, Yürüten B. Neutrophil lymphocyte ratio as a predictor of stroke. J Stroke Cerebrovasc Dis 2013; 22: 1169-74. [CrossRef]
10. Gökhan S, Ozhasenekler A, Mansur Durgun H, Akil E, Ustündag M, Orak M. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. Eur Rev Med Pharmacol Sci 2013; 17: 653-7.
11. Wang F, Hu S, Ding Y, Ju X, Wang L, Lu Q, et al. Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage. J Stroke Cerebrovasc Dis 2016; 25: 182-7. [CrossRef]
12. Li Z, Cui L, Ma J, Ma X, Li G. Association between neutrophil to lymphocyte ratio and atrial fibrillation. Int J Cardiol 2015; 187: 361-2. [CrossRef]
13. Hyun S, Kwon S, Cho S, Park S, Jung W, Moon S, et al. Can the neutrophil-to-lymphocyte ratio appropriately predict carotid artery stenosis in patients with ischemic stroke? A retrospective study. J Stroke Cerebrovasc Dis 2015; 24: 2646-51. [CrossRef]
14. Zhao L, Dai Q, Chen X, Li S, Shi R, Yu S, 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: 739-44. [CrossRef]
15. Kraft P, Drechsler C, Schuhmann MK, Gunreben I, Kleinschnitz C. Characterization of peripheral immune cell subsets in patients with acute and chronic cerebrovascular disease: a case-control study. Int J Mol Sci 2015; 16: 25433-49. [CrossRef]
16. Tuttolomondo A, Pecoraro R, Casuccio A, Di Raimondo D, Buttà C, Clemente G, et al. Peripheral frequency of CD4+ CD28- cells in acute ischemic stroke: relationship with stroke subtype and severity markers. Medicine (Baltimore) 2015; 94: e813. [CrossRef]