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Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack

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Abstract. – OBJECTIVES: This investigation was conducted to test the value of Neutrophil Lymphocyte Ratio (NLR), which has been shown in some recent studies to be a prognostically important and an easy-to-measure inflammatory marker, in patients presenting to Emergency Service with stroke (ischemic and hemorrhagic) and transient ischemic attack.

MATERIALS AND METHODS: A total of 868 patients were enrolled, who presented to our Emergency Service with cerebrovascular accident (stroke and transient ischemic attack) and admitted to Neurology Clinic. Demographic characteristics and comorbidities of patients were recorded. The patients were divided into 3 groups as acute ischemic stroke (AIS), acute hemorrhagic stroke (AHS) and transient ischemic attack (TIA). Patients with AIS were classified into subgroups in terms of TOAST (trial of 10172 stroke treatment) criteria. Admission NLR levels were compared across all groups.

RESULTS: A total of 868 patients were enrolled, 51.6% of which were male and 48.4% were female. AIS rate was 75.3%, AHS rate was 14.3% and TIA rate was 10.7%. In all of patients, mortality rate was 10.7%. NLR was significantly higher in patients who died ($p < 0.001$). NLR level in patients with TIA was significantly lower than those of AIS and AHS groups ($p < 0.001$). Among AIS subgroups, NLR level was significantly higher in group with great artery atherosclerosis or atherothrombosis compared to other groups ($p < 0.001$).

CONCLUSIONS: NLR may be used as a simple and easy-to-measure marker for prediction of short-term prognosis and in-hospital mortality in both ischemic and hemorrhagic stroke patients.

Key Words:
Neutrophil lymphocyte ratio, Stroke, Transient ischemic attack.

Introduction

Stroke (ischemic or hemorrhagic)[1,2] is the third leading cause[3,4] of death worldwide and the most limiting condition of daily activities of elderly[5]. Stroke forms the most important part of emergent neurologic cases[1,6]. TIA lasts less than 24 hours and greatly increases stroke risk[7].

NLR is an inflammatory marker recently introduced and used in many studies, which is both simple and of low cost[8-12].

We could not retrieve any studies in which NLR is studied in patients with TIA and stroke. Thus, we aimed to explore the relationship between prognosis, stroke subtype, and in-hospital mortality and NLR measured prior to any specific therapy in patients presenting to Emergency Department with stroke and TIA.

Materials and Methods

This investigation was conducted on 868 patients presenting to Diyarbakır Research and Education Hospital Emergency Service between 2009 and 2011 and eligible for study enrollment. The inclusion and exclusion criteria are given in Table I.

Medical, demographic, clinical, laboratory, and radiologic data of patients were recorded on pre-prepared standard study forms. These data were assessed by a single neurologist who grouped patients by determining TIA, stroke (ischemic and hemorrhagic), and AIS subtypes. AIS patients were etiologically classified according to Trial of Org 10172 Stroke Treatment (TOAST) criteria[13]. AIS is etiologically grouped into 5 subtypes which are; great artery atherosclerosis or atherothrombosis (GAA), cardioembolic (CE), small artery occlusion or lacunar (LAC), unknown origin (UO), and rare stroke types. In-hospital mortality and hospital stay of patients were recorded. NLR were calculated from complete blood counts obtained at admission.

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Table I. Inclusion and exclusion criteria.

Inclusion criteria
• Patients with stroke proven by clinical picture, CT, or MRI
• Patients presenting with TIA
Exclusion Criteria
• Patients with trauma, surgery, neoplasm, active infection, immunosuppressive agent use, hematologic disease, inflammatory disease, severe hepatic and renal disease, acute metabolic disease, and intoxication
• Patients referred to a different health facility
• Patients with incomplete or lacking medical, demographic, clinical, laboratory, and radiologic data
• Patients with previous stroke and TIA

Statistical Analysis

The results of the study were presented as mean ± SD. Univariate analyses were performed with chi-square test for categorical variables and with Student test for continuous variables. In-group analyses were performed with Kruskal Wallis one-sided analysis of variance and Mann-Whitney U test for multiple groups when groups were non-normally distributed and sample sizes were unequal. A p value < 0.01 was considered significant for in-group analyses and a p value < 0.05 for other comparisons. Step-wise Logistic regression analysis was used in multivariate analyses of significant variables of univariate analyses to determine independent risk factors for mortality.

Results

A total of 868 patients were enrolled. Patients were classified into 3 groups in terms of diagnosis of AIS 75.3% (n=654), AHS 14.3% (n=124), and TIA 10.4% (n=90).

448 (51.6%) of patients were male and 420 were female (48.4%). The mean age was 67.87±11.13 years. Mean hospital stay was 11.16±5.57 days. 775 (89.3%) patients were discharged whereas 93 (10.7%) died during hospital stay. Clinical and demographic data of patients are given in Table II.

When mortality rate in subgroups of AIS investigated, the highest mortality was observed in the group with great artery atherosclerosis (16.1% (55 patients out of 342) whereas lacunar group had the lowest mortality (1.4% (2 patients out of 144) ($p < 0.001$). Patients who died were compared with those who survived in terms of comorbid diseases, revealing that diabetes as a comorbid disease significantly increased mortality (16.8% (63/376) ($p < 0.001$). Neutrophil, lymphocyte counts and NLR were significantly higher in patients who died ($p < 0.001$). Demographic, clinical, and laboratory data of dead and surviving patients are given in Table III.

TIA group had a higher mean age compared to AIS and AHS groups ($p = 0.027$). Furthermore, AIS group had a significantly higher congestive heart failure rate compared to other groups ($p = 0.002$). Comparison of neutrophil, lymphocyte counts and NLR levels revealed that TIA group had a significantly lower levels than other 2 groups ($p < 0.001$). Demographic, clinical, and laboratory data of patients in terms of stroke type are given in Table IV.

Among subtypes of AIS, NLR levels were significantly higher in patients with GAA compared to other 3 groups ($p < 0.001$ for 3 groups). NLR levels were significantly lower in patients with CE compared to GAA, LAC, and UO ($p < 0.001$, $p < 0.001$, p 0.041, respectively). NLR levels did not significantly differ in LAC and UO ($p = 0.562$). NLR levels in terms of AIS subtypes are given in Table V.

NLR levels were significantly higher in both AIS and AHS patients who died compared to both groups of patients who survived. This situation suggests that NLR level is valuable in predicting mortality whatever the stroke type is. NLR levels of our dead patients and surviving patients in terms of stroke type are given in Table VI.

Discussion

We confirmed that there is a relationship between short-term prognosis, stroke subtype, and

Table II. Clinical and demographic characteristics.

Patient characteristics (n=868)	
Age (mean ± SD; y)	67.87 ± 11.13
Male/Female	448/420
Hospital Stay (mean ± SD; day)	11.16 ± 5.57
Comorbidity	
Hypertension	568 (65.4%)
Diabetes mellitus	376 (43.3%)
Hyperlipidemia	284 (32.7%)
Congestive heart failure	338 (38.9%)
Stroke type	
Acute ischemic stroke	654 (75.3%)
Acute hemorrhagic stroke	124 (14.3%)
Transient ischemic attack	90 (10.4%)
Outcome	
Cure	775 (89.3%)
Exitus	93 (10.7%)

Table III. Demographic, clinical and laboratory differences between dead patients and surviving patients.

Variable	Surviving patients n = 775	Dead patients n = 93	p
Age (years; mean ± SD)	67.63 ± 11.14	69.83 ± 10.97	0.073
Gender			
Male	396	52	0.442
Female	379	41	
Stroke Type			
Acute Ischemic Stroke	583	71	0.899
Acute Hemorrhagic Stroke	102	22	0.011
Transient Ischemic Attack	90	-	< 0.001
AIS Subtype			
Great Artery Atherosclerosis	287	55	< 0.001
Cardioembolic	98	11	1.000
Lacunar	142	2	< 0.001
Unknown origin	56	3	0.191
Co-morbid disease			
Hypertension	499	69	0.065
Diabetes mellitus	313	63	< 0.001
Hyperlipidemia	255	29	0.815
Congestive Heart Failure	296	42	0.216
Neutrophil (hours; mean ± SD)	6.20 ± 2.28	8.77 ± 2.83	< 0.001
Lymphocyte (days; mean ± SD)	1.87 ± 0.78	1.22 ± 0.73	< 0.001
NLR (µmol/l; mean ± SD)	3.97 ± 2.36	9.92 ± 6.32	< 0.001

first 30-day in-hospital mortality and NLR measured in patients presenting to Emergency Service with stroke and TIA.

Many previous studies showed that leukocyte, neutrophil, and lymphocyte counts play a role in peripheral inflammatory response and atherosclerotic processes[14-17]. Neutrophils, in particular, may cause neutrophil invasion and plaque rupture by secreting some mediators (proteolytic enzymes, arachidonic acid, elastase, free oxygen radicals)[18-20]. Lymphocytes, are more involved in regulation of immune responses[18]. However, some studies found lower lymphocyte counts in acute myocardial infarction[21] and advanced heart failure[22].

Recent clinical trials suggested that higher leukocyte and subtype counts as well as higher NLR levels have predictive power in prognosis, severity, and mortality rates of atherosclerosis and cardiovascular diseases[9,23-25].

Although there are reports in literature on leukocytes and their subtypes[26-28], we could retrieve only one study[29] investigating NLR levels. Balestrino et al[30] referred that higher leukocyte and neutrophil counts are observed during the

Table IV. Demographic, clinical, and laboratory data in terms of stroke type.

Variable	AIS n = 654	AHS n = 124	TIA n = 90
Age (years; mean ± SD)	67.74 ± 11.01	66.56 ± 11.86	70.60 ± 10.66*
Gender			
Male	338	64	46
Female	316	60	44
Co-morbid disease			
Hypertension	399	112	57
Diabetes mellitus	302	50	24
Hyperlipidemia	212	42	30
Congestive Heart Failure	274[a]	31	33
Neutrophil (hours; mean ± SD)	6.68 ± 2.44	6.71 ± 2.66	4.68 ± 1.64[b]
Lymphocyte (days; mean ± SD)	1.71 ± 0.72	1.80 ± 0.90	2.42 ± 0.91[b]
NLR (umol/l; mean ± SD)	4.87 ± 3.48	5.02 ± 4.30	2.14 ± 1.14[b]
Hospital Stay (mean ± SD; day)	12.41 ± 5.18[b]	10.25 ± 4.63[b]	3.33 ± 1.33[b]

*$p = 0.027$, [a]$p = 0.002$, [b]$p < 0.001$.

Table V. NLR levels in terms of AIS subtypes

AIS subtype	NLR (ratio; mean ± SD)	AIS Subtype	NLR (ratio; mean ± SD)	p
GAA	6.67 ± 3.74	CE	1.74 ± 0.40	< 0.001
		LAC	3.75 ± 1.74	< 0.001
		UO	3.00 ± 1.49	< 0.001
CE	1.74 ± 0.40	GAA	6.67 ± 3.74	< 0.001
		LAC	3.75 ± 1.74	< 0.001
		UO	3.00 ± 1.49	0.041
LAC	3.75 ± 1.74	GAA	6.67 ± 3.74	< 0.001
		CE	1.74 ± 0.40	< 0.001
		UO	3.00 ±1.49	0.562
UO	3.00 ± 1.49	GAA	6.67 ± 3.74	< 0.001
		CE	1.74 ± 0.40	0.041
		LAC	3.75 ± 1.74	0.562

acute period of ischemic stroke and this value is also related with poor prognosis. Christensen et al[31]. found similar results. We also found significantly higher neutrophil, lymphocyte counts as well as higher NLR levels in patients with both acute ischemic and hemorrhagic stroke compared to transient ischemic attack. Therefore, our findings support the hypothesis that there is a strong correlation between severity of cerebrovascular accident and NLR levels.

Rodriguez et al[32] found the lowest leukocyte count in lacunar group among patients presenting with acute stroke. Buck et al[33] found the lowest neutrophil count in lacunar group. Elkind et al[34] found higher leukocyte counts in cardioembolic and atherosclerotic stroke subtypes. Güven et al[14] found both higher leukocyte and neutrophil counts in great artery atherosclerosis while the counts were lower in lacunar group. Our study revealed that among acute ischemic stroke subtypes, great artery atherosclerosis had a significantly higher NLR compared to other 3 groups. Cardioembolic ischemic stroke group had a significantly lower NLR compared to other 3 groups. We believe that this phenomenon stems from the fact that thrombi are more important than atherosclerotic inflammation in pathophysiology of cardioembolic strokes.

Table VI. NLR levels of our dead patients and surviving patients in terms of stroke type.

	NLR (ratio; mean ± SD)		
	Dead patients n = 93	Surviving patients n = 685	p
AIS	9.66 ± 6.30	4.30 ± 2.39	< 0.001
AHS	10.80 ± 6.48	3.78 ± 2.24	< 0.001

Higher leukocyte counts have been related to short-term mortality, especially in studies on ischemic stroke[26,27]. We also found a significantly higher neutrophil, lymphocyte counts and NLR in patients who died. Moreover, patients of both ischemic and hemorrhagic stroke groups who died had a significantly higher NLR.

Conclusions

NLR may be used as a simple and easy-to-use marker to predict short term prognosis and mortality in both ischemic and hemorrhagic stroke.

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