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ORIGINAL ARTICLE **ARAŞTIRMA YAZISI**

NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PROGNOSIS OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE

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ABSTRACT

INTRODUCTION: Neutrophil to Lymphocyte Ratio (NLR) is suggested to predict functional outcomes and mortality at admission of patients with intracerebral hemorrhage (ICH). However, effect of timing of NLR measurement on prediction of mortality and expansion in ICH has not been clarified.
METHODS: From admission and 24th-hour blood samples, admission NLR (NLR-adm) and 24th-hour NLR (NLR-24th) was calculated as "absolute neutrophil count/lymphocyte count". Hematoma expansion was evaluated with the volume (ABC/2) difference from admission cranial CT to follow-up one.
RESULTS: A total of 383 patients (41.7% female, age, 65±13) were assessed. Of them, 251 (65.5%) were discharged. The average hematoma volume was 32.8 cc and 35.3 cc in the first and second CT, respectively. The mean NLR was 8.2±10.3 at admission and 16.6 ± 15.7 at 24th hour. Only NLR-24th (β=0.035, OR: 1.036 (1.002-1.071), p=0.04), hematoma volume at first CT (β=0.012, OR 1.012 (0.999-1.024) p=0.067) and Hemphill score (β=0.689, OR 1.992 (1.402-2.832) p<0.001) were found to be significantly related with mortality after adjusted to age (decade), atrial fibrillation, anticoagulant use and NLR-adm. An exploratory logistic regression analysis indicated that hematoma expansion greater than 12.5 cc correlated to, albeit borderline, NLR-24th (β=0.038, OR=1.038 (95%CI: 1.008-1.069) but not NLR-adm.
DISCUSSION and CONCLUSION: We found NLR-24th to be associated with higher mortality and greater hematoma expansion rate. This NLR increment, probably secondary to the stress response, in ICH can be considered as an epiphenomenon of worse prognosis.
Keywords: Stroke, adrenal, stress, complete blood count, pneumonia.

NÖTROFİL-LENFOSİT ORANI VE SPONTAN İNTRASEREBRAL KANAMA PROGNOZU

ÖZET

GİRİŞ ve AMAÇ: İntraserebral kanamalı (İSK) hastaların başvuru esnasında ölçülen "nötrofil lenfosit oranının (NLR)" fonksiyonel sonuçları ve mortaliteyi öngörmede kullanılabileceği belirtilmiştir. Bununla birlikte, NLR ölçümünün zamanlamasının, İSK'daki mortalite ve erken genişleme tahmini üzerindeki etkisi tam olarak netleşmemiştir.
YÖNTEM ve GEREÇLER: Giriş ve 24. saat kan örneklerinden, giriş NLR ("NLR-adm") ve 24 saatlik NLR ("NLR-24"), "mutlak nötrofil sayısı / lenfosit sayısı" olarak hesaplandı. Hematom volümetrik genişlemesi, "geliş" ve 24. saatte çekilen "kontrol" BT arasındaki" ABC/2 formülü" ile hesaplanan hacimler arasındaki fark olarak alındı.
BULGULAR: Toplam 383 hasta (Kadın: 41.7%, yaş, 65±13) incelendi. Bunların 251 (65.5%)'i taburcu edilebildi. Ortalama İSK hacmi ilk BT'de 32,8 cc ve kontrol BT'de 35,3 cc idi. Ortalama NLR-adm 8,2±10,3 iken NLR-24 16,6±15,7 idi. Yaş (on yıl), atriyal fibrilasyon ve antikoagülan kullanımına göre uyarlanarak yapılan regresyon analizinde NLR-24 (β=0,035, OR: 1,036 (1,002-1,071), p=0,04), ilk BT'deki İSK hacmi (β=0,012, OR 1,012 (0,999-1,024) p=0,067) ve Hemphill skoru (β=0.689, OR 1,992 (1,402-2,832) p<0,001) mortalite ile doğrudan bağlantılı bulunmuştur. Deneysel lojistik regresyon analizi ile 12,5 cc'den büyük hematom genişlemesinin, sınırda olsa da NLR-24 (β=0,038, OR=1,038 (95%CI: 1,008-1,069)

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ile bağlantılı olduğu ama NLR-adm'in belirleyici rolü olmadığını göstermiştir. Yani, bu tam kan parametreleri ile gelişte hematom genişlemesi öngörülemez.
TARTIŞMA ve SONUÇ: 24. saatte bakılan NLR intraserebral kanama bağlamında mortalite artışı ve belki hematom genişlemesi ile ilişkilidir. Bu olasılıkla İSK'nın yarattığı stres reaksiyonunun derecesini yansıtan bir epifenomendir.
Anahtar Sözcükler: İnme, adrenal, stres, tam kan sayımı, pnömoni.

INTRODUCTION

Intracerebral Hemorrhage (ICH) is a devastating type of stroke with high rate of disability and mortality (1). It is known that both local and systemic inflammatory response are immediately triggered after stroke (2). Neutrophil to Lymphocyte Ratio (NLR) is an inexpensive and ready-to-use method to evaluate individual inflammatory status; and this method has been shown to be a marker for prediction of functional outcomes and mortality in coronary syndrome (3), ischemic stroke (4, 5), cancer (6), and ICH (7), as well. However, the association between NLR and intracerebral hematoma expansion has yet to be clarified. We herein aimed to document the effects of NLR, and its changes, on survival of patients with ICH and to explore whether there is an association between NLR and ICH expansion.

MATERIAL AND METHODS

Patients, data, measurements, scores: Socio-demographic, clinical and imaging data were extracted retrospectively with chart review, along with prospectively-gathered institutional stroke database running for the last ten years. Age <18 years and patients with secondary ICH were excluded. Clinical stroke severity was assessed with National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) at admission. Hemphill score (8) and STICH-2 prognosis score (STICH-2 PS) (9) were calculated. Of 413 patients detected via chart review, 334 had admission CT and 271 had 24th-hour follow-up cranial CT ready-to-our-review. Reasons for not performing follow-up CT may be early mortality, very good or moribund clinical status, or contraindication to transfer to CT suits. Exact duration of time intervals between symptom onset and first/second CTs could be obtained in only 133 patients. There was no significant difference between the main demographic variables of patients with and without follow-up CT (data not shown). Hematoma volume was calculated by the "AxBxC/2 formula" (10). NLR value was calculated as the absolute neutrophil count divided by the absolute lymphocyte count at the admission (NLR-adm) and 24th hour (NLR-24th). NLR-adm and NLR-24th were available in 389 and 270 patients, respectively. The institutional review board approved the study protocol and the database.

Outcomes: Major outcome measures were "survival" at discharge and "hematoma expansion" on the first day. The survival status at discharge was tallied as "survived" and "expired". The hematoma expansion was calculated as the blood volume difference ("cubic centimeter-cc or milliliter" and percentage) between second and first CTs. Significant hematoma volume growth thresholds were set at "12.5 cc" and "33%".

Blood samples, hematological data: First blood samples were almost invariably obtained at the time of admission to emergency department while the second samples (at the end of the first day of ictus) were obtained at discretion of the treating physician. Complete blood count (CBC) results were collected via electronic chart review. Studied parameters and their normal ranges were: lymphocyte count, 1.2-3.6 (10^3/μL); neutrophil count, 1.8-6.4 (10^3/μL); monocyte count, 0.3-0.9 (10^3/μL); hemoglobin, 11.7-15.5 (gr/dL) and hematocrit 34.5-46.3 (%). Normal limits of NLR were calculated as 0.5 to 5.3.

Statistics: All values are represented as mean ± standard deviation, 95% confidence intervals (95% CI), percentages, medians with interquartile ranges (IQR) as appropriate. Distribution normality was analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests properly. Differences were tested with Mann-Whitney U / Student's t, paired t and Chi-square / Fisher's exact tests appropriately. Exploratory multivariate models to detect importance of NLR and other CBC parameters on survival and hematoma expansion were constructed. In these models, factors with p value less than 0.1 in the univariate phase were included into the multivariate steps. $P<0.05$ was set as the statistical significance level. SPSS version 22 was used for all calculations.

RESULTS

The mean age of entire study population was 65±13 years and 41.7% were female. Symptom onset to first CT duration was 259±240 minutes. The average hematoma volume was 32.8±37.1 cc in the first CT. Mean duration from the initial to control CTs was 1663±1639 minutes. The average hematoma volume was 35.3±38 cc in the second CT.

Mean age, atrial fibrillation (AF), anticoagulant use, admission ICH volume (by approximately 20cc) and its enlargement during the first day (16.74 cc vs. 2.25 cc), admission SBP, NIHSS, GCS, Hemphill score and STICH-2 PS were significantly higher in 132 patients who died of ICH during hospital stay than those of251 (65.5%) who were successfully discharged (Table I).

Average NLR was 8.2±10.3 at admission, and significantly increased to 16.6±15.7 at the end of the first day. The increase in NLR was due to the increase of neutrophil count and, and perhaps more decisively, the more significant reduction in lymphocyte count. The decrease in lymphocyte was more pronounced in patients who died in comparison to survivors (Figure). The number of neutrophils increased from 7.81±4.17 to 9.39±4.17 in surviving patients, and increased from 8.98±4.93 to 12.1±4.92 in deceased patients (p=0,001). Lymphocyte count decreased from 1.68±1.8 to 1.1±0.73 in surviving patients, whereas this decrease was more pronounced in patients who died: from 1.87±1.31 to 0.79±0.52 (p<0.001). As a result, the increase in NLR was much more pronounced in patients who died because of changes in these opposite directions. NLR value increased from 7.21±7.46 to 12.46±10.83 in survivors and from 10.37±14.61 to 22.25±19.73 in those who died (p <0.001).

Survival, or mortality, was not found to be significantly correlated with admission NLR, but definitely found to be linked to NLR at the 24th of the event. This univariate finding (Table I) was tested in a multivariate environment with two models. In the first model, NLR-24th (β=0.035, OR 1.036 (1.002-1.071), p=0.040), hematoma volume at first CT (β=0.012, OR 1.012 (0.999-1.024), p=0.067) and Hemphill score (β=0.689, OR 1.992 (1.402-2.832) p<0.001) were found to be significantly and independently related to in hospital mortality after adjusted to age (decade), AF, anticoagulant use and NLR-adm. In a second model in which STICH-2 PS was added instead of Hemphill's score, again NLR-24th (β=0.034, OR 1.034 (1.009-1.060) p=0.008), in addition to STICH-2 PS (β=0.022, OR 1.022 (1.015-1.029), p<0.001), were found to be as independent predictors of mortality.

Intracranial hematoma volume expansion greater than 12.5 cc was detected in 46 (17%) patients. In 60 patients (22,2%), ICH volume increase was higher than 33%. Features of patients with significant ICH expansion (either 12.5 cc or 33% increase) were summarized in Table II. In patients with >12.5 cc ICH expansion, aspirin use, anticoagulant use, initial ICH volume, lobar location, both Hemphill and STICH-II PS, and mortality rate were higher. In patients with >33 percent ICH expansion, anticoagulant use, aPTT, INR and ICH admission volume were higher and survival rate was lower (Table II).

Correlation between numerical NLR changes and ICH volume changes from admission to the end of the first day was, albeit weak, significantly positive (r=0.273, p two-tailed <0.001). Patients with a hematoma expansion greater than 12.5 cc had marginally lower lymphocyte count decrease (average change: -1.05±0.88 vs. -0.74±1.02, p=0.08) and significantly higher neutrophil count increase (4.85±5.56 vs. 1.33±4.05, p=0.001). Similarly, those with hematoma expansion greater than 33% had significantly higher neutrophil increase (3.85±5.49 vs. 1.43±4.13, p=0.01) and borderline lymphocyte count decrease (-1.05±1.0 vs. -0.72±0.99, p=0.07).

An exploratory logistic regression analysis indicated that hematoma expansion greater than 12.5 cc correlated to, albeit borderline, NLR-24th (β=0.038, OR=1.038 (95%CI: 1.008-1.069, p=0.012) but not NLR-adm. The other determiners of hematoma expansion were aspirin use (β=1.036, OR=2.819 (95%CI: 1.136-6.996), p=0.025); anticoagulant use (β=1.127, OR=3.086 (95%CI: 1.171-8.133), p=0.023); lobar location (β=1.304, OR=3.682 (95%CI: 1.456-9.311), p=0.006); Hemphill score (β=0.427, OR=1.532 (95%CI: 1.058-2.218), p=0.024).No correlation between NLR-adm or NLR-24th and percental hematoma expansion (<33% or >33%) was observed. None of the univariate-significant determiners of hematoma expansion greater than 33% such as anticoagulant use, admission aPTT and 24th INR persisted in any exploratory multivariate modeling.

Table I. Comparison of survived and expired ICH patients.

		Survived	Expired	*p*
Age, years		64±13	68±13	*0.003*
Female		42%	41%	*0.803*
Hypertension		72%	77%	*0.357*
Diabetes		17%	25%	*0.067*
Hyperlipidemia		15%	15%	*0.850*
Atrialfibrillation		4%	11%	*0.007*
Smoking		16%	12%	*0.301*
Aspirin use		28%	36%	*0.128*
Clopidogreluse		4%	7%	*0.283*
Anticoagulantuse		9%	20%	*0.003*
Statinuse		8%	9%	*0.623*
Time-to-CT, minute		244±246	267±204	*0.609*
Admission ICH volume, cc		23.02±28.14	53.21±45.22	*<0.001*
Follow-up ICH volume, cc		21.51±24.18	64.29±46.4	*<0.001*
Volume increase, cc		2.25±8.38	16.74±36.11	*<0.001*
Volume increase, %		19.09±91.79	239.03±1169.83	*0.020*
ICH location	Lobar	32%	36%	*0.328*
	Putamen	23%	23%	
	Thalamus	31%	26%	
	Cerebellar	6%	5%	
	Pons	2%	5%	
	Other	6%	5%	
Admission SBP, mmHg		176±41	185±47	*0.097*
Admission DBP, mmHg		102±23	105±24.7	*0.331*
Admission heart rate		77±21	82±26	*0.061*
Admission NIHSS		11.4±10.1	24.9±13.1.	*<0.001*
Admission GCS		12.99±2.94	8.7±4.31	*<0.001*
Hemphillscore		1.27±1.12	2.66±1.22	*<0.001*
STICH-2 prognosis score		36.76±42.14	-17.69±59.49	*<0.001*
Length of stay		19.81±25.31	21.6±31.33	*0.557*
Hematological parameters				
Admission lymphocyte		1.68±1.08	1.87±1.31	*0.144*
Admission neutrophil		7.81±4.17	8.98±4.93	*0.018*
Admission NLR		7.21±7.46	10.37±14.61	*0.007*
Admission leukocyte		10.42±4.05	11.75±4.87	*0.005*
Admission hematocrit		41±4.92	40.34±6.25	*0.257*
Admission platelet		244.49±71.82	235.38±93.09	*0.289*
Admission INR		1.32±1.9	1.55±1.65	*0.252*
Admission aPTT		27.17±4.39	29.34±8.35	*0.001*
Follow-uplymphocyte		1.1±0.73	0.79±0.52	*<0.001*
Follow-upneutrophil		9.39±4.17	12.1±4.92	*<0.001*
Follow-up NLR		12.46±10.83	22.25±19.73	*<0.001*
Follow-upleukocyte		11.58±4.57	14.07±5.11	*<0.001*
Follow-uphematocrit		38.18±5.5	39.5±26.19	*0.555*
Follow-upplatelet		229.1±64.16	219.31±82.48	*0.002*
Follow-up INR		1.15±0.21	1.45±0.44	*<0.001*
Follow-up aPTT		27.57±5.16	29.04±5.88	*0.270*

Abbreviations: Ad.: Admission, Afib: Atrial fibrillation, aPTT: activated partial thromboplastin time, CT: Computerized tomography of head, DBP: Diastolic blood pressure, FU: Follow-up, GCS: Glasgow Coma Scale Score, ICH: Intracranial hemorrhage, INR: international normalized ratio, NIHSS: The National Institutes of Health Stroke Scale, NLR: Neutrophil-to-lymphocyte ratio, SBP: Systolic blood pressure, STICH-2 PS: STICH-II prognostic score.

Table II. Intracerebral hematoma (ICH) expansion.

	ICH expansion			ICH expansion		
	≥12.5 cc	**<12.5cc**	**p**	**≥33%**	**<33%**	***p***
Age, years	69±10	65±13	*0.061*	65±14	66±13	*0.928*
Female	44%	43%	*0.894*	50%	41%	*0.188*
Hypertension	74%	75%	*0.917*	80%	73%	*0.304*
Diabetes	26%	21%	*0.433*	25%	21%	*0.438*
Hyperlipidemia	30%	18%	*0.060*	27%	18%	*0.139*
Afib	11%	7%	*0.368*	12%	6%	*0.168*
Smoking	15%	15%	*0.972*	10%	17%	*0.207*
Aspirin use	44%	28%	*0.040*	34%	30%	*0.554*
Clopidogreluse	9%	7%	*0.602*	7%	7%	*0.961*
Anticoagulant	31%	11%	*0.001*	31%	10%	*<0.001*
Statinuse	13%	10%	*0.583*	12%	10%	*0.758*
Time-to-CT, min	276±231	256±242	*0.729*	220±204	270±249	*0.289*
ICH volume, cc	41.4±31.8	25.2±28.7	*0.001*	20.3±18.5	30.2±32.1	*0.024*
Lobar ICH	48%	27%	*0.006*	27%	32%	*0.438*
Putamen ICH	26%	23%	*0.676*	23%	24%	*0.939*
Thalamus ICH	22%	33%	*0.146*	35%	30%	*0.418*
Admission SBP	179±38	184±42	*0.537*	186±47	182±40	*0.642*
Admission DBP	102±20	104±24	*0.699*	107±26	102±23	*0.153*
Hemphill score	2.05±1.23	1.53±1.24	*0.015*	1.55±1.17	1.64±1.27	*0.644*
STICH-2 PS	12.54±49.36	37.33±49.3	*0.002*	37.4±41.3	31.88±52.36	*0.453*
ength of stay, day	24±32	24±35	*0.873*	26±32	23±35	*0.572*
Survival	30%	73%	*<0.001*	42%	71%	*<0.001*
Ad. lymphocyte	2±1.56	1.78±1.12	*0.283*	2.1±1.45	1.74±1.12	*0.051*
Ad. neutrophil	6.13±3.84	7.88±4.14	*0.014*	6.09±4.16	8±4.04	*0.003*
Ad. NLR	8.56±16.26	7.26±8.28	*0.450*	5.39±8.73	8.03±10.23	*0.087*
Ad. leukocyte	8.92±3.64	10.68±4.71	*0.018*	9.01±4.31	10.77±4.6	*0.008*
Ad. hematocrit	39±5.5	41±5.6	*0.042*	39.6±5.7	41±5.5	*0.114*
Ad. Platelet	228±89	231±75	*0.794*	235±83	230±76	*0.619*
Admission INR	1.78±1.39	1.38±2.13	*0.228*	1.63±1.01	1.4±2.24	*0.448*
Admission aPTT	31.68±8.6	26.99±5.68	*<0.001*	30.57±8.15	26.99±5.72	*0.002*
FU lymphocyte	0.81±0.53	1.07±0.74	*0.060*	0.87±0.55	1.06±0.75	*0.141*
FU neutrophil	11.26±5.15	9.35±4.09	*0.022*	10.45±5.47	9.47±3.98	*0.208*
FU NLR	20.73±22.63	12.97±11.62	*0.005*	16.21±10.52	13.83±15.3	*0.357*
FU leukocyte	12.78±5.51	11.57±4.86	*0.206*	12.25±5.66	11.65±4.8	*0.499*
FU hematocrit	43.61±46.35	37.76±6.03	*0.129*	42.71±42.16	37.72±5.94	*0.163*
FU platelet	226±76	212±70	*0.533*	224±71	218±71	*0.675*
FU INR	1.58±0.4	1.2±0.29	*<0.001*	1.45±0.43	1.19±0.26	*0.002*
FU aPTT	30.59±5.35	26.82±4.53	*0.008*	30.39±6.1	26.26±3.64	*0.453*

Abbreviations: Ad.: Admission, Afib: Atrial fibrillation, aPTT: activated partial thromboplastin time, CT: Computerized tomography of head, DBP: Diastolic blood pressure, FU: Follow-up, ICH: Intracranial hemorrhage, INR: international normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, SBP: Systolic blood pressure, STICH-2 PS: STICH-II prognostic score.

DISCUSSION

In this study, we demonstrated that only NLR values obtained at the end of the first day were associated with in-hospital mortality. However, admission NLR values were not linked to in-hospital mortality. In previous researches, albeit not all (11), admission NLR has been shown to be associated with both mortality and early or late functional outcomes (7, 12, 13). There may be various mechanisms for positive association between NLR and short-term mortality in the patients with acute ICH. Intracerebral hematoma-mediated immunodepression, or neurogenic immunodepression in brief term, is the first mechanism that comes to mind. Decrease of

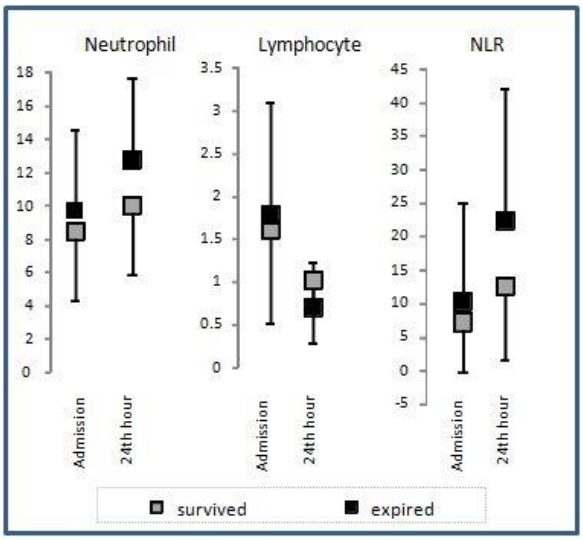

Figure. Changes of Neutrophil count, lymphocyte count and NLF from admission to 24th hour.

lymphocyte count, resulting in proportional increase of NLR, is a characteristic feature of neurogenic immunodepression and closely related to stroke-associated pneumonia which is one of the major contributors of mortality in this population (14). The second mechanism is early systemic inflammatory response triggered by ICH components (15). The resulting neutrophilia, which will lead to an increase in NLR, can enhance secondary tissue damage in the hemorrhagic brain. The third, and perhaps more credible, mechanism is hypothalamic-pituitary-adrenal axis hyperactivity occurring in patients with ICH after hyperacute phase (16). The stress reaction triggered by increased levels of cortisol or catecholamines result in typical neutrophilia and lymphocytopenia, causing significant NLR increase. Increased stress response is connected to poor prognosis. This may be because both the stress reaction correlates with excess tissue damage, which already is associated with poor prognosis. That is, it is an epiphenomenon with poor prognosis. Or, the stress reaction exerts a direct negative effect on the course of the event.

In our study, we found that NLR increase was parallel to hematoma volume increase. But, the relationship wasn't very robust. It only showed a weak, but independent, link between NLR at 24th hour and ICH enlargement of more than 12.5 cc. In the literature, there is no direct and supportive potent data on association between expansion of hematoma and NLR. In a previous study (17), intracerebral hematoma expansion was found inversely correlated with higher admission leukocyte and neutrophil counts, whereas there was no correlation with lymphocyte count. But, NLR was not examined in this study. In a more recent study (18), it was found that NLR was associated with 'Island Sign', which reflects increased risk of intracerebral hematoma expansion. However, a multivariate analysis did not document an independent connection of NLR to hematoma expansion.

Our study has some minor limitations. First of all, its retrospective nature caused exclusion of some patients due to inadequacy of data. No data about infectious status were collected. Moreover, cause of death was not pursued. Without these, further interpretation of the results would have perhaps been possible. Now, this is up to future work on this issue.

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