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Do early neutrophil to eosinophil ratio and the levels of neutrophil and white blood cells predict intra-hospital mortality in patients with spontaneous intracerebral hemorrhages?

Erken nötrofil/eozinofil oranı ile nötrofil ve beyaz kan hücrelerinin seviyeleri spontan intraserebral hemorajili hastalarda hastane içi mortaliteyi öngörüyor mu?

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Abstract
Aim: In recent years, inflammatory markers such as red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), and C-reactive protein to albumin ratio (CAR) have been investigated in spontaneous intracerebral hemorrhage (ICH). However, they were not analyzed together in ICH. In the present study, we examined whether neutrophil, neutrophil to eosinophil ratio (NER), and white blood cell (WBC) levels along with the above-mentioned markers predict the intrahospital mortality in patients diagnosed with spontaneous ICH at admission.
Methods: We conducted this retrospective cohort study by examining spontaneous ICH patients hospitalized in our clinic between April 2015 and March 2019. We divided patients into two groups, as survivors and non-survivors. The receiver operating characteristics (ROC) curve analysis test was used to evaluate the predictive value of laboratory variables for mortality and to calculate cut-off values.
Results: A total of 130 patients, 82 survivors and 48 non-survivors, were included in the study. The patients who were non-survivors at the hospital had significantly higher median hemorrhage volume, WBC, and neutrophil levels compared to those of survivors ($P<0.001$, $P=0.001$ and $P=0.003$, respectively). There was no significant difference between the two groups in terms of median CAR, NLR, NER, and RDW-SD values ($P=0.216$, $P=0.237$, $P=0.229$, and $P=0.215$, respectively). The area under the ROC curve was 0.676 (95% CI, 0.57-0.78) for WBC and 0.659 (95% CI, 0.56-0.76) for neutrophil.
Conclusion: Our results showed that the elevated neutrophil and WBC levels at the acute phase of spontaneous ICH predict the intrahospital mortality of the patients. Further studies are required for the predictive value of NER.
Keywords: White blood cell, Spontaneous intracerebral hemorrhage, Neutrophil, Inflammatory parameters, Red blood cell distribution width, Neutrophil to lymphocyte ratio, Neutrophil to eosinophil ratio

Öz
Amaç: Son yıllarda, spontan intraserebral hemorajide (ICH) kırmızı kan hücresi dağılım genişliği (RDW), nötrofil/lenfosit oranı (NLO) ve C-reaktif protein/albümin oranı (CAO) gibi inflamatuar belirteçler araştırılmıştır. Ancak, bunlar ICH'de birlikte incelenmemiştir. Bu çalışmada, spontan ICH tanısı alan hastalarda başvuru sırasında yukarıda belirtilen belirteçlerle birlikte nötrofil, nötrofil/eozinofil oranı (NEO) ve beyaz kan hücresi (WBC) düzeylerinin hastane içi mortaliteyi tahmin edip etmediğini araştırdık.
Yöntemler: Bu retrospektif kohort çalışmasını, Nisan 2015 - Mart 2019 tarihleri arasında kliniğimizde yatan spontan ICH hastalarını inceleyerek gerçekleştirdik. Hastaları hayatta kalanlar ve hayatta kalmayanlar olarak iki gruba ayırdık. Mortalite için laboratuvar değişkenlerinin prediktif değerini değerlendirmek ve kesme değerlerini hesaplamak için, alıcı çalışma karakteristikleri (ROC) eğrisi analizi kullanılmıştır.
Bulgular: Çalışmaya, 82'si hayatta kalan ve 48'i hayatta kalmayan olmak üzere 130 hasta dahil edildi. Hastanede ölen hastaların medyan hemoraji hacmi, WBC ve nötrofil değerleri yaşayanlara göre anlamlı olarak yüksekti (sırasıyla $P<0,001$; $P=0,001$ ve $P=0,003$). Medyan CAO, NLO, NEO ve RDW-SD değerleri açısından iki grup arasında fark yoktu (sırasıyla $P=0,216$; $P=0,237$; $P=0,229$ ve $P=0,215$). ROC eğrisi altındaki alan: WBC için 0,676 (% 95 CI; 0,57-0,78) ve nötrofil için 0,659 (% 95 CI; 0,56-0,76) idi.
Sonuç: Sonuçlarımız, spontan ICH'nin akut evresinde daha yüksek nötrofil ve WBC düzeyleri hastaların hastane içi mortalitesini öngörmüştür. NEO'nın predikdif değeri için ileri çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Beyaz kan hücresi, Spontan intraserebral hemoraji, Nötrofil, İnflamatuvar parametreler, Kırmızı kan hücresi dağılım genişliği, Nötrofil/lenfosit oranı, Nötrofil/eozinofil oranı

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Introduction

Stroke is still one of the major causes of death around the world [1]. Although the spontaneous intracerebral hemorrhages (ICH) account for the 10-20% of all strokes, mortality and disability risk of spontaneous ICH can be much higher than ischemic stroke type [2]. Unfortunately, spontaneous ICH patients are not as lucky as ischemic stroke patients as there are few therapeutic strategies for ICH treatment, and their benefits are limited [3]. Factors such as age, hemorrhage volume, infratentorial localization, intraventricular hemorrhage, and initial Glasgow Coma Scale score are important indicators of the prognosis in spontaneous ICH [4]. High arterial blood pressure in the early phase was also associated with the prognosis of ICH [5]. Surely, it is important to know the prognostic factors not only for fighting against the neurological and systemic complications of ICH (e.g., antibiotic treatment in case of a systemic infection, decompression surgery and/or evacuating hemorrhage if shift develops, external ventricle drainage for ventricle hemorrhages, etc.) but also for informing the patients' relatives properly. Knowing the prognostic factors may contribute to clinician's ICH management. Therefore, researchers have been trying to identify new prognostic factors that may affect the prognosis of ICH. In recent years, neutrophil to lymphocyte ratio (NLR) [6,7], C-reactive protein (CRP) [8], C-reactive protein to albumin ratio (CAR) [9], and red blood cell distribution width (RDW) have been investigated in ICH [10]. However, these markers were not investigated together in spontaneous ICH. In our study, we aimed to investigate whether neutrophil to eosinophil ratio (NER), neutrophil, and white blood cell (WBC) levels, along with the abovementioned inflammatory markers, predict the intrahospital mortality. To that end, we carried out the present study based on the laboratory results of patients collected during the first admission to the hospital.

Materials and methods

Study population

We retrospectively identified the spontaneous ICH patients who were followed and treated at the Aksaray University Education and Research Hospital between April 2015 and March 2019. The patients included in the study were those who applied to the hospital within 24 hours from the onset of symptoms and either died in hospital while being treated for spontaneous ICH or discharged upon a partial or complete recovery. Patients older than 18 years were included in the study. Patients who have subarachnoid hemorrhage and secondary ICHs (trauma, vascular malformation, brain tumor, etc.), acute or chronic infection, blood disease, liver and renal failure, electrolyte abnormalities, receive immunomodulatory or immunosuppressive therapy, had a hemorrhagic infarction, and are younger than 18 years of age were excluded.

Initially, the medical history of the patients, who are brought to the emergency room of our hospital with stroke pre-diagnosis, was collected from themselves or their relatives. Vital signs (pulse, blood pressure, arterial oxygen saturation, fever, etc.) are quickly recorded; blood sugar level is measured from a finger. During the rapid neurological examination, blood samples are collected for hemogram, international normalized ratio, activated partial thromboplastin time, and biochemical evaluation. Brain computed tomography (brain CT) or magnetic resonance imaging (brain MRI) for parenchymal imaging, and vascular imaging of the brain (brain CT angiography or brain MR angiography) for vascular abnormalities were performed routinely. The location and the volume of the hematoma are determined based on the parenchymal and vascular imaging results and treatment is planned accordingly. All the included patients received standard treatment according to up to date stroke guidelines [3]. Laboratory analysis was conducted in the hematology laboratory of our institution. Venous blood samples were taken from patients, centrifuged, and blood cell counts were performed at our hematology center using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan). NER was calculated by dividing the neutrophil count by eosinophil count, while CAR was calculated by dividing the amount of C-reactive protein (mg/dL) by albumin amount (g/L), and NLR was calculated by dividing the neutrophil count by lymphocyte count.

Clinical findings and laboratory results, brain parenchymal and vascular imaging results, risk factors, and other demographic characteristics of patients during the initial emergency room admission was collected from our database and used for statistical analysis. The study was approved by the Aksaray University Human Research Ethics Committee (6/22/2020, 2020/06-57) and carried out in accordance with the Helsinki Declaration.

Statistical analysis

The results are presented as mean (standard deviation) for normally distributed data, median (min-max) for non-normally distributed data and percentage (%). Kolmogorov-Smirnov normality test was used to investigate the distribution pattern. Red blood cell (RBC) and platelet data, which distributed normally, were compared using Student's independent samples T test. The other blood test parameters with non-normal distribution, were compared using Mann Whitney U test. Categorical variables were investigated using the Chi- square test. The factors affecting mortality were investigated using univariate and multivariate logistic regression analysis. The variables with a *P* value of primary comparison under 0.25 were included in the univariate logistic regression model and the variables with a *P* value of univariate logistic regression analysis under 0.1 were included in the multivariate logistic regression model. The model fit was assessed using Hosmer-Lemeshow goodness of fit statistics. The assessment of consistency between the variables was performed using Cox and Snell pseudo-R^2 and Nagelkerke pseudo-R^2 tests. To evaluate the predictive value of variables, and to calculate the cut- off values, receiver operating characteristics (ROC) curve analysis test was used. If the area under the ROC curve is 0.5, the model does not discriminate; 0.5-0.7, the model has poor to fair discrimination; 0.7-0.8, the model has acceptable discrimination; 0.8-0.9, the model has excellent discrimination; and 0.9-1.0, is a very rare outcome [11]. For statistical analysis of all data, we used SPSS 23.0 software for Windows (SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

130 patients with spontaneous ICH were included in the study. There were 82 survivors [43 males and 39 females, median age: 69 (25-89) years] and non-survivors consisted of 48 patients [20 males and 28 females, median age: 68.5 (42-93)]. The median age (*P*=0.334) and gender distribution (*P*=0.236, X^2=1407) were not different between the non-survivors and survivors.

The comparison of hematological parameters between the groups (survivors and non-survivors) is given in detail in Table 1. According to the Student's T test, the mean RBC was not significantly different between the non-survivors and survivors (*P*=0.674). Mann Whitney U test revealed that the median CRP, albumin, CAR, lymphocyte, NLR, eosinophil, NER, hemoglobin, hematocrit, RDW-CV, RDW-SD and mean corpuscular volume (MCV) values did not significantly differ between the non-survivors and survivors (*P*=0.377, *P*=0.396, *P*=0.216, *P*=0.739, *P*=0.237, *P*=0.708, *P*=0.229, *P*=0.504, *P*=0.94, *P*=0.43, *P*=0.215 and *P*=0.152, respectively). However, the median volume of hemorrhage, WBC and neutrophil values were significantly higher in non-survivors, compared with the survivors (*P*<0.001, *P*=0.001 and *P*=0.003, respectively).

The Chi-square test revealed that in terms of shift, opening to the ventricle and the presence of congestive heart failure were significantly higher in non-survivors, compared with the survivors (*P*<0.001, *P*=0.001 and *P*<0.011, respectively) (Table 2). However, the rates of diabetes mellitus, arterial hypertension, hyperlipidemia, and coronary artery disease did not significantly differ between the non-survivors and survivors (*P*=0.132, *P*=0.579, *P*=0.396, and *P*=0.834, respectively).

Table 3 represents the distribution of hemorrhage localizations, which were similar between the non-survivors and survivors (*P*=0.783, X^2=3.97).

In Table 4, the univariate and multivariate logistic regression analysis results were presented. The univariate logistic regression model revealed that the volume of hemorrhage, WBC, neutrophil, the presence of shift, ventricular opening, and congestive heart failure were found to affect mortality (*P*=0.002, *P*=0.002, *P*=0.003, *P*<0.001, *P*=0.003 and *P*=0.017, respectively). However, the multivariate logistic regression model revealed that only the presence of ventricular opening affected mortality (*P*=0.006).

Table 1: Comparison of routine hematological parameters between survivors and non-survivors

	Survivor patients (n=82)	Non-survivor patients (n=48)	*P*-value
Age, year	69 (26-89)	68.5 (42-93)	0.334
Red blood cell (10^{12}/L)	4.36 (5.55)	4.67 (6.85)	0.674
The volume of hemorrhage (cm^3)	7.16 (0.28-142.2)	26.14 (0.6-170)	<0.001
C- reactive protein (mg/dL)	5.07 (0.27-297)	7.15 (0.29-190)	0.377
Albumin (g/L)	41.15 (24.3-50.1)	40.3 (4.37-51)	0.396
CAR	0.16 (0.1-8.48)	0.21 (0.1-10.58)	0.216
WBC (10^9/L)	8.63 (3.70-22.37)	10.72 (1.88-20.31)	0.001
Neutrophil (10^9/L)	5.54 (2.41-17.95)	7.22 (1.16-18.1)	0.003
Lymphocyte (10^9/L)	1.83 (0.32-5.63)	1.52 (0.23-7.74)	0.739
NLR	3.28 (0.6-82.4)	3.93 (0.7-44.39)	0.237
Eosinophil (10^9/L)	0.1 (0.005-2.16)	0.085 (0.01-0.55)	0.708
NER	50.14 (1.70-1795)	61.43 (5.4-1709)	0.229
Hemoglobin (g/dL)	13.85 (7.5-19.6)	13.8 (5.18-18.7)	0.504
Hematocrit (%)	41.3 (25.6-56.4)	41.05 (22.9-80.4)	0.94
RDW-CV (%)	13.5 (1.8-19.1)	13.56 (11.20-44.6)	0.43
RDW-SD (fL)	42.6 (27.8-63.7)	43.8 (13.9-65.8)	0.215
MCV (fL)	86.05 (30.2-114)	87.55 (77.7-98.6)	0.152

NLR: Neutrophil to lymphocyte ratio, CAR: C- reactive protein to albumin ratio, NER: Neutrophil to eosinophil ratio, RDW: Red blood cell distribution width, WBC: White blood cell, MCV: Mean corpuscular volume

Table 2: Comparison of categorical variables between survivors and non-survivors

	Survivor patients (n=82)	Non-survivor patients (n=48)	*P*-value	X^2-value
Gender (M/F)	43/39	20/28	0.236	1.407
Presence of shift	21 (25.6%)	28 (58.3%)	<0.001	13.805
IVH (cm^3)	20 (24.4%)	25 (52.1%)	0.001	10.259
DM, n (%)	24 (29.3%)	22 (45.8%)	0.132	4.05
HT, n (%)	56 (68.3%)	35 (72.9%)	0.579	0.308
HL, n (%)	4 (4.9%)	3 (6.25%)	0.396	1.853
CHF, n (%)	4 (4.9%)	9 (18.75%)	0.011	6.474
CAD, n (%)	6 (7.3%)	4 (8.3%)	0.834	0.044

IVH: Intraventricular hemorrhage, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CHF: Congestive heart failure, CAD: Coronary artery disease

Table 3: The distribution of hemorrhage localizations

Localization	Survivor patients	Non-survivor patients
Pons	3 (3.66%)	4 (8.3%)
Mesencephalon	1 (1.22%)	0 (0%)
Cerebellum	10 (12.2%)	6 (12.5%)
Basal Ganglia	13 (15.85%)	6 (12.5)
Thalamus	22 (26.8%)	13 (26.8%)
Caudate nucleus	0 (0%)	1 (2.08)
Putamino- capsular	9 (10.97%)	4 (8.3%)
Lobar	24 (29.3%)	14 (29.16%)
Total	82 (%100)	48 (100%)

Table 4: The logistic regression analysis results of the study

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
The volume of hemorrhage	1.029 (1.011-1.048)	0.002	1.015 (0.995-1.036)	0.139
CAR	1.186 (0.963-1.46)	0.109	-	-
WBC	1.192 (1.067-1.331)	0.002	1.089 (0.811-1.464)	0.57
Neutrophil	1.186 (1.058-1.329)	0.003	1.104 (0.788-1.546)	0.566
NLR	1.01 (0.971-1.051)	0.609		
NER	1.001 (1-1.002)	0.092	1 (0.999-1.002)	0.436
RDW-SD	1.024 (0.972-1.079)	0.37	-	-
MCV	1.037 (0.981-1.098)	0.202	-	-
Gender	1.544 (0.752-3.168)	0.237	-	-
Shift	4.067 (1.905-8.682)	<0.001	1.93 (0.712-5.231)	0.196
Ventricular opening	3.157 (1.487-6.702)	0.003	3.479 (1.418-8.535)	0.006
Diabetes Mellitus	1.929 (0.923- 4.032)	0.081	1.826 (0.723-4.612)	0.202
Congestive Heart Failure	4.5 (1.304- 15.534)	0.017	2.988 (0.679-13.154)	0.148
			Cox and Snell pseudo-R^2 = 0.258 Nagelkerke pseudo-R^2 = 0.352 Hosmer- Lemeshow *P* = 0.305	

Figure 1 shows the ROC curve representing the predictive value of WBC and neutrophil for mortality. The area under the ROC curve was 0.676 (95% CI, 0.57-0.78) for WBC and 0.659 (95% CI, 0.56-0.76) for neutrophil. The cut-off value of WBC and neutrophil were 9.63 (sensitivity: 66% and specificity: 67%) and 6.67 (sensitivity: 58% and specificity: 65%), respectively.

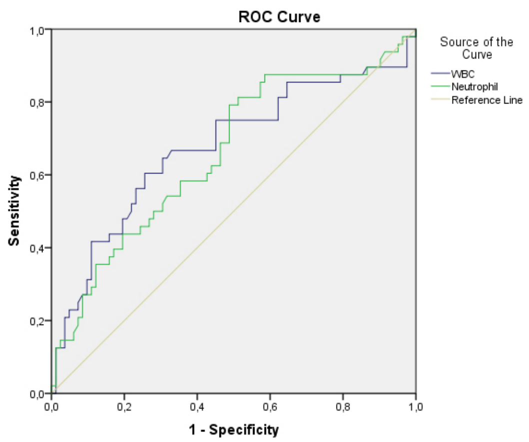

Figure 1: The receiver operating characteristic (ROC) curve expressing the ability of white blood cell (WBC) and neutrophil to predict in-hospital mortality

Discussion

The significant findings of our study were that the elevated neutrophil and WBC levels at the hospital admission have a predictive value for intrahospital mortality in spontaneous

ICH patients. These results suggest that neutrophil-mediated severe inflammation during the acute phase of ICH increases mortality by contributing to secondary brain damage.

An increase in the neutrophil, NLR, CAR, RDW, CRP, and WBC levels reflects systemic inflammation. In recent years, the significance of these parameters has been emphasized in ICH prognosis [6-10]. However, NER has not been investigated together with these parameters. Therefore, we analyzed all these parameters together to examine their predictive value for ICH mortality.

It is emphasized that high neutrophil levels at the time of application are associated with poor prognosis in ICH [12]. In our study, we found that elevated neutrophil levels during admission (acute phase) predict intrahospital mortality in ICH patients. Secondary brain damage in ICH occurs with a chain of inflammatory pathophysiological events. Neutrophils play an important role in this type of damage [13,14]. Immediately after the stroke onset, microglia activation starts with hematoma components within minutes [13,15,16]. Free oxygen radicals, chemokines, and pro-inflammatory cytokines released by the excessive microglia activation initiate inflammatory signaling [13]. Then, the neutrophils produced in the blood begin to accumulate around the hematoma approximately 4 hours after the ICH, reaching peak within 2-3 days [13,14]. Neutrophils, accumulated around and within the hematoma in the brain, lead to excessive regulation of the matrix metalloproteinase-9 (MMP-9), macrophage activation, and the secretion of pro-inflammatory cytokines such as IL-1beta and TNF-alpha [13,17]. The result of this chain of pathophysiological events is secondary brain damage caused by the blood-brain barrier (BBB) breakdown, hemorrhage growth, and increased edema around hemorrhage [17,18]. It was shown in a neutrophil depletion study carried out with the anti-polymorphonuclear leukocyte antibody that the BBB breakdown, MMP-9 expression in perihematomal neutrophils, axon injuries, the number of perihematomal microglia/macrophages, and glial scar formation was reduced with the reduced neutrophil levels [18]. These findings reveal the significant role played by neutrophils in secondary brain damage developed in ICH. In the present study, we aimed to emphasize the significance of neutrophils in ICH once more.

WBC is considered a reliable biomarker for inflammation [19]. It was found that the elevated WBC count in blood predicts the poor outcome occurring within the first 3 days after ICH [20]. Similarly, we found that high WBC levels at hospital admission predict the intrahospital mortality in ICH patients.

In previous studies, NLR, CAR, and RDW-SD were associated with mortality in spontaneous ICH patients. These markers also reflect the systemic inflammation, just as neutrophils [6,9,10]. In the present study, deceased patients had higher NLR, CAR, RDW-SD, and NER levels than alive patients, yet the difference between the two groups was not statistically significant. The reason for this might be the fact that the study groups consisted of a small number of patients or that we analyzed the patients' laboratory parameters obtained during the acute phase. NER, which expresses the increase of neutrophils and the decrease of eosinophils in the blood, can be easily calculated by dividing the number of neutrophils by the number of eosinophils. As we analyzed the blood parameters obtained in the acute phase of ICH in the present study, the changes in these blood parameters may have not been reflected in NER yet. Analyzing the laboratory parameters collected after the 4th or, ideally, the 24th hour of ICH may reflect changes to NER better. The significance of NER in ICH can be clarified in the future with more detailed and extensive studies by addressing the current findings and issues.

Limitations

Although the present study was carried out to determine whether hematological inflammatory parameters at the time of admission have a predictive value for the intrahospital mortality of spontaneous ICH patients and emphasize the significance of neutrophils in ICH, it has some limitations. These include small number of patients, working with laboratory parameters obtained during the acute phase of the disease (at the admission), and carrying out a retrospective analysis can be considered as the limitations of the present study.

Conclusion

As a result, elevated neutrophil and WBC levels at the hospital admission predicted the intrahospital mortality of patients in the acute phase of ICH. Further studies with larger patient groups are needed to define NER as a new inflammation parameter.

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