

## Can neutrophil/lymphocyte ratio and mean platelet volume values be used as early markers in assessing the prognosis of patients with aneurysmal subarachnoid hemorrhage?

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Inflammation plays an important role in cerebrovascular diseases, including intracerebral hemorrhage. Assessing the prognosis of such hemorrhage at early stage adds significance to treatment outcome. In this study, for the first time, we used neutrophil/lymphocyte (N/L) ratio and mean platelet volume (MPV) values as early markers in assessing the prognosis of patients with aneurysmal subarachnoid hemorrhage (SAH). This retrospective study included 50 patients with aneurysmal SAH who were diagnosed, hospitalized, treated, and follow-up with angiography between 2015 and 2016 (Gr. I). Blood count parameters and their clinical status after application (the first-arrival Glasgow coma score [GCS]) and at discharge (Glasgow outcome score [GOS]) were examined. The MPV value and N/L ratio were compared with that of the nonaneurysmatic control group (group 2, n = 50). The N/L ratio of Gr. I (median: 10.80) was significantly higher than that of the control group (median: 2.20) ( $P < 0.05$ ). The GCS (median: 10.0) and GOS (median: 3.0) of Gr. I were significantly lower than those of the control group (median GCS: 15.00, median GOS: 5.00) ( $P < 0.05$ ). MPV values were not different between the two groups ( $P > 0.05$ ). In the aneurysm group, the higher the N/L ratio, the lower the GCS and GOS, while the lower the N/L ratio, the higher the GCS and GOS. In patients with aneurysmal SAH, the inflammation level was associated with disease severity, which can be considered as an early treatment and prognostic marker. The initial application of the N/L ratio may be important in assessing the prognosis, and a lower N/L ratio may be used as a simple, effective, and important marker to estimate the better prognosis of patients with aneurysmal SAH.

**Keywords:** Cerebral angiography, Cerebral hemorrhage, Cerebrovascular diseases, Vasospasm

Although subarachnoid hemorrhage (SAH) constitutes 5% of all cerebrovascular diseases, it requires careful close follow-up and treatment due to the high mortality and morbidity potential<sup>1</sup>. Intracranial aneurysms (approximately 75-80%, saccular aneurysms) being the most common reason<sup>2</sup>. After SAH, 50% of patients were lost during the first month, and at least 50 of the survivors have a permanent disability<sup>3</sup>. Inflammation play an important role in cerebrovascular diseases (CVD), including intracerebral hemorrhage<sup>4,5</sup>. Hence, biochemical and hematological markers are used during the follow-up and treatment in such pathologies<sup>6</sup>.

In recent years, the neutrophil/lymphocyte (N/L) ratio is considered as a parameter that combines the deterioration of overall health conditions and negative effects reflecting physiological stress, indicating an acute inflammatory response<sup>7</sup>. The mean platelet volume (MPV) is a platelet function marker and is an

indication of increased MPV platelet reactivation<sup>8</sup>. Inflammation is associated with the pathogenesis of aneurysmal subarachnoid hemorrhage (aSAH), and N/L ratio as well as MPV value are considered as new inflammatory markers<sup>9-11</sup>.

Therefore in this study, we retrospectively compared the N/L ratio and MPV values between patients with aneurysm induced SAH and the control group. Further, we evaluated the effects of these inflammatory markers on the prognosis and their usability as early markers.

### Materials and Methods

This retrospective study was conducted at Faculty of Medicine, Kırıkkale University and got the approval of the Ethics Committee of Noninvasive Research at the Kırıkkale University (No.: 20/03-19, Date: 08/11/2016). Information was obtained from the database of Kırıkkale University Faculty of Medicine, Neurosurgery Department. As the data used are retrospective, informed consent was considered not required.

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### Participants

This retrospective study included patients with SAH who were diagnosed, hospitalized, treated, and followed-up with angiography at the Faculty of Medicine Neurosurgery Clinic, Kirikkale University between 2015 and 2016. Among these patients, 50 patients with aneurysms using angiography who were monitored and treated at our hospital were included in the study group (Gr. I) with mean age  $61.04 \pm 12.75$  (range, 25-88) years. A total of 50 healthy participants who did not have any problems with cranial or blood diseases and without aneurysms were included in the control group (Gr. II). Mean age of this group was  $33.52 \pm 16.46$  (range, 18-72) years. The age, gender, N/L ratio<sup>12</sup>, MPV values<sup>13</sup>, first-arrival Glasgow coma score (GCS) and Glasgow outcome scores (GOS) of both the groups were analyzed to determine the clinical condition, and aneurysmal locations in angiography of Gr. I were retrospectively examined.

### Devices

An automatic blood counter (CELL-DYN 3700, Abbott, IL, USA) was used for the full blood count, and the blood received was examined in approximately 60 min. Cranial computed tomography (CT) scans were used to diagnose SAH obtained in the supine position. Images were obtained by a 64-slice CT (Siemens Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) using the following parameters: tube voltage, 120 kV; effective mAs, 350; slice thickness, 0.67 mm; scanning area, 180 mm, and the image matrix,  $768 \times 768$ .

### Cerebral angiography

Cerebral angiography was performed at Kirikkale University, Faculty of Medicine, Angiography Unit on all patients with SAH. Contrast was used for the process, and sedation was performed.

### Statistical analysis

The statistical package for the social sciences for Windows 16.0 (SPSS, INC, an IBM Company, Chicago, Illinois) was used for statistical analysis. Chi-square test, Mann-Whitney U-test, independent samples t-test, Kruskal-Wallis variance analysis test, and Spearman's correlation rho-efficient test were used. A  $P$  value  $< 0.05$  was considered statistically significant.

### Results

Our study had 23 (46%) males and 27 (54%) females in Gr. I and 19 (38%) males and 31 (62%)

females in the control group (Gr. II) ( $p = 0.418$ ,  $\chi^2 = 0.657$ ). It was observed that the number of women was higher in the control group. In the experimental group (Gr. I), the aneurysm was located in the anterior communicating artery (23 patients, 46%), middle cerebral artery (MCA) (21 patients, 42%), internal carotid artery (2 patients, 4%), basilar artery (2 patients, 4%), anterior cerebral artery (ACA) (1 patient, 2%), and anterior choroidal artery (1 patient, 2%). Cerebral angiography was definitely performed in SAH cases detected by CT scan (Figs 1 and 2).

Blood parameters and clinical condition (on the first arrival and outcome) scores in both groups are shown in Table 1.



Fig. 1 — In axial cranial tomography cross section, aneurysmatic subarachnoidal hemorrhage is seen in the areas indicated by black arrow.



Fig. 2 — Cerebral angiography shows an aneurysm indicated by a black arrow in the anterior communicating artery.

**Blood parameters**

*MPV and N/L ratio*

No significant difference was observed between the Mean platelet volume (MPV) of both the groups ( $P > 0.05$ ). However, the neutrophil/lymphocyte (N/L) ratio of Gr. I (median: 10.80) was significantly higher than that of the control group (median: 2.20) ( $P < 0.05$ ) (Table 1).

**Clinical condition scores**

*GCS and GOS*

The Glasgow coma score (GCS) of Gr. I (median: 10.0) was significantly lower than that of the control group (median: 15.00) ( $P < 0.05$ ). Similarly, the Glasgow outcome score (GOS) of Gr. I (median: 3.0) was also significantly lower than that of the control group (median: 5.00) ( $P < 0.05$ ) (Table 1).

The blood parameters and clinical condition (on the first arrival and outcome) scores based on the aneurysm localization in the Gr. I are shown in Table 2. No significant differences between MPV and N/L ratios and GCS and GOS among six different localizations of aneurysms (anterior communicating artery, MCA, internal carotid artery, basilar artery, ACA, and anterior choroidal artery) were observed.

As Spearman's correlation test results, we observed inverse correlation, i.e., higher the N/L ratio, the lower GCS and GOS in the aneurysm group ( $P < 0.05$ ); and lower the N/L ratio, the higher the GCS and GOS in the aneurysm group ( $P < 0.05$ ). (Table 3). Glasgow coma score (GCS) was positively

correlated with GCS and the Glasgow outcome score (GOS) in the aneurysm group ( $P < 0.05$ ). No significant correlations were observed between age, gender, MPV, N/L ratio and clinical condition scores (GCS and GOS) ( $P > 0.05$ ).

**Discussion**

Currently, the neutrophil/lymphocyte (N/L) ratio is accepted as a parameter that provides information about the relationship between the systemic inflammatory environment and physiological stress. Furthermore, systemic inflammation prevention and brain damage reduction should be considered in the treatment method<sup>14-16</sup>. It has been reported that increased neutrophil count in cerebrovascular diseases is associated with ischemic damage<sup>17</sup>. Moreover, an increased N/L ratio is valuable in predicting the clinical outcomes of patients with aneurysmal subarachnoid hemorrhage (aSAH), and is associated with the risk of complications such as rebleeding<sup>18</sup>.

Cellular DNA damage is associated with interleukin-6 (IL-6) expression and various proinflammatory cytokines<sup>19</sup>. Furthermore, apoptosis and functional deactivation of peripheral lymphocytes are also indicative of an interrupted important role in

Table 1 — Blood parameters and clinical condition (first arrival and outcome) scores in both groups

	Group I (n=50)			Group II (n=50)			P
	Mean	Median	SD	Mean	Median	SD	
Age	61.04	62.00	12.75	33.52	25.50	16.46	0.000*
MPV (fl)	10.09	9.83	1.14	9.89	10.05	1.14	0.392**
N/L ratio	13.39	10.80	7.92	2.35	2.20	1.21	0.000*
GCS	10.08	10.00	3.53	15.00	15.00	0.00	0.000*
GOS	3.06	3.00	1.78	5.00	5.00	0.00	0.000*

[MPV, ; N/L, neutrophil/lymphocyte; GCS, Glasgow coma scores and GOS, Glasgow outcome scores. \*P value of Mann Whitney U test; \*\*P value of independent samples t-test]

Table 3 — Correlation test results in Group I\*

		MPV (fl)	N/L ratio	GKS	GOS
MPV (fl)	r		0.107	-0.024	0.034
	p		0.460	0.869	0.814
N/L ratio	r	0.107		-0.291	-0.286
	p	0.460		0.041	0.044
GCS	r	-0.024	-0.291		0.795
	p	0.869	0.041		0.000
GOS	r	0.034	-0.286	0.795	
	p	0.814	0.044	0.000	
Age	r	-0.040	-0.070	-0.235	-0.268
	p	0.783	0.630	0.100	0.060
Gender (Code 1: Male, Code 2: Female)	r	-0.099	0.056	-0.172	-0.181
	p	0.495	0.701	0.233	0.209

[\*P value shows the results of Spearman's correlation rho efficient test]

Table 2 — Blood parameters and clinical condition (first arrival and outcome) scores according to the aneurysm localization in Group I

	Localization of aneurysm												P*
	Anterior communicating artery (n=23)		Middle cerebral artery (n=21)		Internal carotid artery (n=2)		Anterior cerebral artery (n=1)		Basillar artery (n=2)		Anterior choroidal artery (n=1)		
	Median	SD	Median	SD	Median	SD	Median	SD	Median	SD	Median	SD	
MPV (fl)	10.10	1.44	9.70	0.83	10.45	0.07	11.00	-	9.30	0.98	9.87	-	0.640
N/L ratio	11.67	7.71	10.18	7.66	14.10	5.51	21.60	-	20.92	17.35	9.20	-	0.569
GCS	10.00	3.30	10.00	3.68	14.00	1.41	4.00	-	10.50	4.94	10.00	-	0.329
GOS	2.00	1.78	4.00	1.79	4.50	0.70	1.00	-	2.50	2.12	5.00	-	0.377

[\*P value of Kruskal Wallis variance analysis test]

host defense<sup>20</sup>. Moreover, red blood cell parameters are associated with outcomes following an aSAH. Zhao *et al.*<sup>21</sup> reported that postoperative red cell distribution width (RDW) is independently associated with poor functional outcomes in patients with aSAH undergoing surgical clipping.

In this study, the N/L ratio and mean platelet volume (MPV) values were compared in patients with SAH and the nonaneurysmatic control group. The effects of these inflammatory markers on the prognosis and availability as an early marker were also evaluated. Previous studies have reported that increased inflammatory response in patients with intracranial hemorrhage is caused by both trauma and bleeding. Moreover, developing brain damage leads to decreased cerebral autoregulation and increased cell pressure<sup>22,23</sup>. We found that the higher the N/L ratio, the lower the Glasgow coma score (GCS) on admission<sup>24</sup>. Guo *et al.*<sup>25</sup> concluded that elevated NLR is an independent predictor of poor outcome and delayed cerebral ischemia occurrence in aSAH.

In our study, the N/L ratio was higher in the aSAH group than that in the control group. However, the N/L ratio is within the normal range in the aSAH group. When the rate decreased, patients were found to have high Glasgow outcome scores (GOS) due to a low inflammatory response. This demonstrated that the inflammatory response was very closely associated with the clinics of patients with aSAH about the proliferation of the N/L ratio. Moreover, the high N/L ratio was associated with lower GCS and GOS, whereas the low N/L ratio was associated with higher GCS and GOS in the aSAH group, which was directly related to patient morbidity, mortality, and prognosis. Consistent with the literature, a high N/L ratio was found to be associated with early neurological deterioration and increased short-term mortality rates. Remarkably, inflammation was significantly associated with negative outcomes.

Further, the N/L ratio of patients with intracerebral hematoma (ICH) rate represents an independent parameter associated with increased mortality. Patients with increased N/L at post-admission should be more intensively examined and these patients represent a population at risk of infectious complications and increased mortality<sup>26-28</sup>.

Mean platelet volume (MPV) is a parameter that shows platelet function and activation. In general,

large platelets are considered more reactive. In the literature, it has been reported that MPV values increase in acute ischemic events, such as coronary artery disease and stroke, and MPV values decrease during activation periods of inflammatory diseases, such as familial Mediterranean fever, ulcerative colitis, and rheumatoid arthritis<sup>29-32</sup>.

Different opinions about MPV have been reported in the literature. Chen & Zhang<sup>33</sup> reported that MPV is a dynamic variable occurring during aSAH, and a high MPV at 3-5 days after hemorrhage is associated with ischemia development. Rzeplinski *et al.*<sup>34</sup> demonstrated that increased MPV measured in the acute phase of aSAH may identify patients at risk for unfavorable neurological outcomes. Beyan & Beyan<sup>35</sup> concluded that the time from blood collection to measurement causes a 2-50% variation in MPV results. Therefore, MPV may not be a marker for poor clinical outcomes in patients with aSAH. A study comparing the healthy control group with patients with ICH reported no significant changes in the MPV value<sup>15</sup>. In our present study, no statistically significant difference was found in the MPV values of both the control and aSAH groups. When this situation was evaluated on basis of anesthesia management, MPV appears to be not affected in the aSAH group; Therefore, the risk of ischemia or bleeding was not increased which could be due to possible platelet dysfunction in patients with aSAH.

Additionally, other inflammatory biomarkers that have already been involved in the pathophysiology of stroke, for example, C-reactive protein, metalloproteinases, or interleukins, may be correlated with poor outcomes of aSAH<sup>36-38</sup>. As a readily available biochemical indicator, assessing the N/L ratio on admission for patients with aSAH can assist clinicians in making more appropriate treatment decisions and more active hospital monitoring<sup>39,40</sup>.

The correlation study has revealed an inverse correlation that the higher the N/L ratio, the lower GCS and GOS, while the lower the N/L ratio, the higher the GCS and GOS in the aneurysm group. The lower N/L ratio in correlation with the increased GCS and GOS in the aneurysm group, indicates a better prognosis in patients with aSAH.

Given the complex inflammatory process, our above study had several limitations. Firstly, its retrospective nature is a limitation. Additionally, since

no localized bleeding was observed in the subarachnoid area in patients with aSAH, bleeding amounts could not be calculated, and an assessment could not be made between the bleeding volume and N/L ratio.

### Conclusion

The retrospective analysis of patients with aneurysmal subarachnoid hemorrhage (aSAH) as detailed above, has demonstrated the inflammation level to have some association with the disease severity, and hence, it can be considered as early markers of the treatment and prognosis.

### Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. This retrospective study was conducted at the Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey with the approval of the Ethics Committee of Non-Invasive Research at Kırıkkale University (No.: 20/03-19, Date: 08/11/2016)

### Conflict of interest

Authors declare no competing interests.

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