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Original Article

Relationship between systemic inflammatory response index, systemic immune inflammation index and neutrophil-lymphocyte ratio in patients undergoing intracranial aneurysm surgery

Yildiz Yigit[1], Julide Hazneci[2], Suheyla Abitagaoglu[3], Arzu Yildirim Ar[4]

ABSTRACT

Objectives: We aimed to investigate the relationship between Systemic Inflammatory Response Index (SIRI), Systemic Immune Inflammation Index (SII), Neutrophil Lymphocyte Ratio (NLR) and mortality in intracranial aneurysm surgery patients, and evaluate their predictive value for mortality.

Methodology: Patients who underwent intracranial aneurysm surgery between April 2013 and April 2022 at a single center were retrospectively included with the approval of the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (2022/55). Demographics, aneurysm characteristics, intensive care and mechanical ventilation requirements, and mortality status were recorded. SIRI, SII, and NLR were recorded preoperatively, on the 7th postoperative day, and at discharge. The predictive value for mortality was assessed with logistic regression and ROC analysis.

Results: In 286 included patients, the mortality rate was 13.3%. Patients with mortality had higher SIRI, SII, and NLR than survivors at all time points. NLR on postoperative day seven had the highest predictive power for mortality, followed by SIRI and SII. Logistic regression analysis showed postoperative day seven NLR, SIRI, and SII as significant predictors of mortality. NLR and SIRI were strong prognostic indicators, increasing mortality risk by 5.57 and 4.97 times above their cut-off values, respectively. Inflammatory markers were higher in ruptured aneurysm patients across all time periods.

Conclusion: SIRI, SII, and NLR were associated with mortality in intracranial aneurysm surgery patients. NLR on postoperative day seven emerged as a strong predictor of mortality. These accessible and non-invasive inflammatory indices could be useful for risk assessment in clinical practice.

KEYWORDS: Aneurysm surgery, Indices, Mortality.

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1. Yildiz Yigit, MD
Clinic of Anesthesiology and Reanimation,
2. Julide Hazneci, MD
Clinic of Neurosurgery,
3. Suheyla Abitagaoglu, MD
Associate Professor,Clinic of Anesthesiology and Reanimation,
University of Health,Sciences, Sultan Abdulhamid Han,
Teaching and Research Hospital, Istanbul, Turkey.
4. Arzu Yildirim Ar, MD
Professor, Clinic of Anesthesiology and Reanimation,
1,2,4: University of Health Sciences, Fatih Sultan Mehmet,
Teaching and Research Hospital, Istanbul, Turkey.

Correspondence:

Yildiz Yigit
Clinic of Anesthesiology and Reanimation,
University of Health Sciences, Fatih Sultan Mehmet,
Teaching and Research Hospital, Istanbul, Turkey.
Email: yildizyigityigit@gmail.com

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INTRODUCTION

Intracranial aneurysms can be detected incidentally with a symptom such as headache, but more commonly present with severe complications of intracerebral hematoma (ICH), subarachnoid hemorrhage (SAH) or hydrocephalus. Intracranial aneurysms are the most common cause of non-traumatic SAH.[1] While unruptured aneurysms may undergo elective surgery, ruptured cases require urgent intervention.

Following aneurysmal SAH, red blood cell breakdown products lead to the release of inflammatory cytokines, potentially causing cognitive decline, delayed cerebral ischemia (DCI), and cerebral vasospasm (CVS).[2-4] These complications can impair the patient's quality of life, resulting in disability or mortality. Prediction and timely treatment of these complications in advance is important in preventing complications, disability, and mortality associated with SAH.[5]

The Systemic Inflammatory Response Index (SIRI) (monocytes × neutrophils/lymphocytes) and the Systemic Immune Inflammation Index (SII) (platelets × neutrophils/lymphocytes) are novel inflammatory markers.[6,7] SIRI, SII, and the Neutrophil Lymphocyte Ratio (NLR) are reported as important markers for prognosis and mortality.[8-11] These indices can predict complications associated with cerebrovascular events while evaluating inflammatory responses. Additionally, they represent a non-invasive, easily accessible, reliable, and objective method for these purposes.[5]

In patients with unruptured intracranial aneurysms, an early increase in SII at admission and within the first 24 hours of hospitalization has been associated with aneurysmal wall enhancement (AWE). Even in patients without clear symptoms or significant AWE, SII values above certain thresholds have been considered an early clinical warning sign that the aneurysm may be at risk of rupture, highlighting the ability of SII to identify high-risk cases before aneurysm rupture.[12] Furthermore, recent studies have demonstrated a relationship between inflammatory responses after SAH and patient prognosis.[13,14]

In our study, we aimed to investigate the relationship between SIRI, SII, and NLR and mortality in patients undergoing surgery for unruptured and ruptured intracranial aneurysms.

METHODOLOGY

We retrospectively evaluated 300 patients who underwent intracranial aneurysm surgery between April 2013 and April 2022 at University Fatih Sultan Mehmet Training and Research Hospital, Turkey.

Ethical approval: Clinical Research Ethics Committee was approved (Ref No. 2022/55; dated June 9, 2022) by Health Sciences University Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey.

A total of 14 patients under the age of 18, with hematological malignancy, coagulation disorder, infection, or insufficient data were excluded from the study, and the remaining 286 patients were evaluated. Age, gender, comorbidities, number of aneurysms and their locations were recorded.

Rupture status, SIRI, SII, and NLR values at preoperative, postoperative day seven, and discharge timepoints, intensive care unit (ICU) admission and length of stay, invasive mechanical ventilation requirements and duration, hospital length of stay, and mortality were documented.

Patients who were observed to have died while hospitalized were classified as in-hospital deaths. There were two patients who experienced mortality before the 7th day (on the 5th and 6th days). The data for these patients were recorded at the 7th day and at the time of discharge.

For patients in whom mortality was observed, the data at the time of mortality were defined as laboratory measurements taken at the time of discharge.

Statistical analysis: The NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) was used for statistical analyses. Quantitative variables were presented using descriptive statistical methods such as mean, standard deviation, median, minimum, and maximum values, while qualitative variables were presented using frequency and percentage. The Shapiro-Wilk test and Box Plots were used to assess the normal distribution of data. The Mann Whitney U test was used for two-group comparison of variables without normal distribution. The Friedman test and the Dunn Bonferroni post-hoc test were used for within group comparisons. Qualitative data were evaluated using sensitivity, specificity, positive predictive value, and negative predictive value. ROC Curve analysis was carried out to the cut-off values for SIRI, SII, and NLR. The Binomial Exact test was used to compare ROC Curve levels between groups. Significance was set at $p<0.05$.

RESULTS

Of the 286 study patients, 57.7% (n=165) were female, with a mean age of 52±11, ranging from 21 to 82 years. 95.1% of aneurysms were located in the anterior

Table-I: Baseline Characteristics and Outcomes of Study Patients.

		n (%)
Gender	Female	165 (57.7)
	Male	121 (42.3)
Age	Mean±SD	52.41±11.15
	Median (Min-Max)	52 (21-82)
Aneurysm	Unruptured	93 (32.5)
	Ruptured	193 (67.5)
Need for intensive care		153 (53.5)
Length of ICU stay	Mean±SD	5.88±19.72
	Median (Min-Max)	2 (0-294)
Need for IMV		114 (39.9)
IMV duration	Mean±SD	4.60±19.42
	Median (Min-Max)	0 (0-294)
Length of hospital stay	Mean±SD	18.41±20.60
	Median (Min-Max)	15 (5-300)
Mortality		38 (13.3)

ICU: Intensive Care Unit,
IMV: Invasive Mechanical Ventilation.

Table-II: Comparison of SIRI, SII, and NLR values according to mortality.

		SIRI			*SII*			*NLR*		
		Survivors (n=248)	*Mortality (n=38)*	[a] *p*	*Survivors (n=248)*	*Mortality (n=38)*	[a]*p*	*Survivors (n=248)*	*Mortality (n=38)*	[a]*p*
Preoperative	Mean±SD	2.57±2.82	6.08± 7.04	0.001**	1512.41±1 695.36	2522.07± 2535.97	0.021*	6.16±7.07	9.27±8.25	0.021*
	Median (Min-Max)	1.5 (0-18.5)	3.5 (0.4-28.8)		851 (73.3-13011.4)	1785.7 (134.1-11050)		3.4 (0.5-62.9)	7.2 (0.8-34)	
Postoperative Day seven	Mean±SD	3.68±4.38	6.83± 7.59	0.001**	1346.28± 1259.15	1953.08± 1733.28	0.006**	5.18±5.43	9.38±7.69	0.001**
	Median (Min-Max)	2.4 (0-35.5)	4.3 (0-35.8)		1012.1 (116.4-14697)	1415.3 (261.3-9181.3)		3.9 (0.6-71)	7 (2.6-36.5)	
Discharge	Mean±SD	1.98±2.49	6.08± 8.76	0.001**	1005.39± 797.74	2662.71± 5074.09	0.001	3.45±3.09	14.27±27.36	0.001**
	Median (Min-Max)	1.3 (0.2-24.4)	2.9 (0-42.4)		816.6 (107.6-5301)	1261.8 (68.9-30690)		2.7 (0.5–30.5)	7.5 (1.5–165)	
Δ Change	[b]p	0.001**	0.224		0.001**	0.899		0.001**	0.474	
Preop-Postop Day seven	Mean±SD	1.10±4.28	0.75± 9.21	0.720	-166.12± 1836.44	-569.00± 2671.67	0.362	-0.97±8.37	0.11±10.44	0.640
	[bb]p	0.001**	0.187		0.001**	0.819		0.001**	0.251	
Preop- Discharge	Mean±SD	-0.59±3.47	0.00± 11.07	0.624	-507.02± 1784.9	140.64± 5826.65	0.827	-2.71±7.72	5.00±28.66	0.036*
	[bb]p	0.046*	0.774		0.097	0.646		0.001**	0.819	
Postoperative Day seven - Discharge	Mean±SD	-1.70±4.22	-0.75± 10.03	0.319	-340.89± 1200.16	709.64± 5304.99	0.397	-1.73±5.26	4.89±28.16	0.137
	[bb]p	0.001**	0.108		0.001**	0.819		0.001**	0.359	

SIRI: Systemic inflammatory response index, SII: Systemic immune inflammation index, NLR: Neutrophil-Lymphocyte Ratio a: Mann-Whitney-U Test, b: Friedman Test, bb: Dunn test with Bonferroni correction, **p<0.01, *p<0.05

circulation. There was a single aneurysm present in 74.8% of cases. 32.5% of the patients (n=93) had unruptured aneurysms and 67.5% (n=193) had ruptured aneurysms. 49.6% of the patients had hypertension and 8.3% of the patients had diabetes. Postoperative complications included vasospasm in 32.9%, postoperative cerebral ischemia in 33.2%, and postoperative hydrocephalus in 5.5% of the patients.

In the postoperative period, 53.5% of patients (n=153) required ICU admission and 39.9% (n=114) required IMV. The mean ICU length of stay was 5.88±19.72 days and mean IMV duration was 4.60±19.42 days. The mean hospital length of stay was 18.41±20.60 days. Overall mortality was 13.3% (n=38). The descriptive characteristics of the patients are presented in Table-I.

No significant differences were found between preoperative, postoperative day seven, and discharge SIRI values in patients with mortality (p=0.224). In surviving patients, significant differences were found between the preoperative, postoperative day seven, and discharge SIRI values (p=0.001). Surviving patients showed an increase in SIRI values on the 7th postoperative day compared to the preoperative value (p=0.001), a decrease in SIRI values at discharge compared to the preoperative value (p=0.046), and a decrease in SIRI values at discharge compared to the 7th postoperative day (p=0.001). The preoperative, postoperative day seven, and discharge SIRI values of patients with mortality were significantly higher than those of survivors (p=0.001).

No significant differences were found between the preoperative, postoperative day seven, and discharge SII values in patients with mortality (p=0.889). In surviving patients, significant differences were observed between preoperative, postoperative day seven, and discharge SII values (p=0.001). Surviving patients showed a significant decrease in SII values on the 7th postoperative day compared to the preoperative value and at discharge compared to the 7th postoperative day (p=0.001, p=0.001). The preoperative, postoperative day seven, and discharge SII values of patients with mortality were significantly higher than those of survivors (p=0.021, p=0.006, and p=0.001, respectively).

No significant differences were found between the preoperative, postoperative day seven, and discharge NLR values in patients with mortality (p=0.474, p>0.05). In surviving patients, significant differences were found between preoperative, postoperative day seven, and discharge NLR values (p=0.001). In surviving patients, significant decreases were observed in NLR values between preoperative and postoperative 7th day, preoperative and discharge, and postoperative 7th day and discharge (p=0.001; p=0.001; p=0.001). NLR values at preoperative, postoperative day seven, and discharge were higher in patients with mortality than those of survivors (p=0.021, p=0.001, p=0.001, respectively) (Table-II).

The predictive power of inflammatory indices measured on postoperative day seven for mortality was evaluated using ROC analysis and logistic regression (odds ratio). NLR (AUC: 0.742) had the highest predictive power for mortality with postoperative day seven values (SIRI AUC: 0.671, SII AUC: 0.639). When the AUC of the indices were compared in pairs, NLR showed better prediction than SII (p=0.008), while no difference was found between the AUC of SIRI and SII (p=0.483) and between SIRI and NLR (p=0.099).

Elevated postoperative day seven SIRI, SII, and NLR values were associated with an increased mortality risk. SIRI >5.6 was associated with a 4.974-fold increased risk of mortality (95% CI: 2.410–10.264). SII >1016 was associated with a 2.846-fold increased risk of mortality (95% CI: 1.326–6.107). An NLR value above 5.13 was associated with a 5.566-fold increased risk of mortality (95% CI: 2.581–12.006) (Table-III). NLR, SIRI, and SII values measured on postoperative day seven were found to be significant biomarkers for predicting mortality. Specifically, NLR and SIRI cut-off values emerged as strong prognostic indicators, increasing mortality risk by 5.57 and 4.97 times, respectively.

Patients with ruptured aneurysms had higher preoperative and postoperative day seven SIRI, SII, and NLR than those with unruptured aneurysms (p=0.001). At discharge, only SII remained higher in ruptured cases (Table-IV).

DISCUSSION

Our study evaluated the relationship between preoperative and postoperative SIRI, SII, and NLR values and mortality in patients undergoing intracranial surgery for ruptured and unruptured aneurysms. All three indices

Table III: ROC Curve Analysis with Postoperative Day seven Measurements for Mortality.

	Cut-off	*Sensitivity*	*Specificity*	*Positive Predictive Value*	*Negative Predictive Value*	*AUC*	*95% CI*	*p*
SIRI	≥5.60	47.37	84.27	31.58	91.27	0.671	0.570–0.772	0.001*
SII	≥1016	73.68	50.40	18.54	92.59	0.639	0.547–0.731	0.006*
NLR	≥5.13	73.68	66.53	25.23	94.29	0.742	0.664–0.821	0.001*

SIRI: Systemic inflammatory response index, SII: Systemic Immune Inflammation Index,
NLR: Neutrophil Lymphocyte Ratio *p<0.01

Table-IV: Comparison of SIRI, SII, and NLR values according to aneurysm status.

	SIRI				*SII*			*NLR*		
		Unruptured Aneurysm (n=93)	*Ruptured aneurysm (n=193)*	[a]*p*	*Unruptured aneurysm (n=93)*	*Ruptured aneurysm (n=193)*	[a]*p*	*Unrup-tured aneurysm (n=93)*	*Ruptured aneurysm (n=193)*	[a] p
Preop	Mean±SD	1.30±1.05	3.88± 4.38	0.001**	694.27± 469.42	2105.43± 2086.95	0.001**	2.94± 2.48	8.32±8.17	0.001**
	Median (Min-Max)	1.1 (0.2-8)	2.5 (0-28.8)		603.1 (73.3-2889.3)	1514.3 (134.1-13011.4)		2.1 (0.5–14.7)	5.9 (0.7–62.9)	
Postoperative Day seven	Mean±SD	2.32±2.15	4.95± 5.75	0.001**	1095.03± 913.24	1586.82± 1484.28	0.001**	4.50±3.58	6.33±6.71	0.001**
	Median (Min-Max)	1.8 (0.2-15.5)	3.2 (0-35.8)		810.6 (116.4-5934.9)	1185.5 (154.2-14697)		3.4 (0.6–18.7)	4.7 (0.9–71)	
Discharge	Mean±SD	2.15±3.20	2.70± 4.54	0.251	908.81± 835.8	1378.24± 2417.61	0.001**	3.64± 3.81	5.49±12.98	0.063
	Median (Min-Max)	1.3 (0.2-24.4)	1.5 (0-42.4)		671.3 (107.6-5301)	917.1 (68.9-30690)		2.7 (0.5–30.5)	3 (0.9–165)	
Δ Change	[b] p	0.001**	0.001**		0.001**	0.001**		0.001**	0.001**	
Preoperative-Postop Day seven	Mean±SD	1.02±2.31	1.07± 6.11	0.430	400.77± 983.02	-518.61± 2236.65	0.001**	1.56± 4.32	-1.98±9.91	0.001**
	[bb] p	0.001**	0.002**		0.001**	0.799		0.001**	0.780	
Preoperative-Discharge	Mean±SD	0.85±3.29	-1.17± 5.71	0.001 **	214.54± 906.82	-727.19± 3166.85	0.001**	0.69± 4.32	-2.83± 15.23	0.001**
	[bb]p	0.002**	0.001**		0.048*	0.001**		0.164	0.001**	
Postoperative Day seven - Discharge	Mean±SD	-0.17±3.51	-2.25± 5.93	0.001	-186.23± 939.58	-208.58± 2653.79	0.085	-0.87± 3.91	-0.85±13.73	0.010*
	[bb]p	0.001**	0.001**		0.001**	0.001**		0.001**	0.001**	

SIRI: Systemic inflammatory response index, SII: Systemic Immune Inflammation Index, NLR: Neutrophil-Lymphocyte Ratio.
[a] Mann-Whitney-U Test, [b]Friedman Test, [bb]Dunn test with Bonferroni-correction **p<0.01, *p<0.05

were higher in patients with mortality than in survivors at preoperative, postoperative day seven, and discharge timepoints. Among the indices, NLR on postoperative day seven demonstrated the highest predictive power for mortality. Patients with ruptured aneurysms had higher SIRI, SII, and NLR at admission and in the postoperative period compared to patients with unruptured aneurysms.

Geraghty et al. investigated SII in predicting delayed CVS after aneurysmal SAH in a retrospective study of 246 patients, finding that 84.6% of aneurysms were located in the anterior circulation, and reported that these indices could assess inflammatory responses and predict complications associated with cerebrovascular events.[5] In a study by Chen et al. involving 333 patients, SII was an independent predictor of DCI and helpful in identifying patients at high risk for DCI.[15]

Zhao et al. retrospectively studied 869 critically ill patients with intracerebral hemorrhage (ICH) and reported that inflammatory markers NLR, SIRI, and lymphocyte-monocyte ratio are predictors of mortality risk in ICU patients with ICH, and that NLR demonstrated superior predictive performance.[16] Zhang et al. conducted a retrospective study on 6041 patients observing that high neutrophil count at admission was associated with increased mortality in patients with aneurysmal SAH.[17] A retrospective study on 240 patients with aneurysmal SAH and meta-analysis by Guo et al. associated elevated NLR with poor functional outcomes. NLR had an AUC of 0.805 for poor outcome in the meta-analysis.[18] Lukito PP et al., in a retrospective study of 63 patients hospitalized due to aneurysmal SAH, found that NLR predicted cerebral infarction and poor functional outcome at discharge, concluding that inflammatory responses with aneurysmal SAH may lead to poor outcomes including cognitive decline, delayed cerebral ischemia, and cerebral vasospasm.[19]

Arslan et al. investigated the prognostic value of SII, NLR, and platelet-lymphocyte ratio (PLR) in 161 critically ill patients with moderate to severe traumatic brain injury in their retrospective study, reporting higher SII and NLR but lower PLR in the mortality group. In multivariate regression analysis, SII and PLR were independent predictors of mortality.[20] Similarly, in our aneurysm surgery patients, patients with mortality had higher preoperative, postoperative day seven, and discharge SIRI, SII, and NLR compared to survivors. NLR had the highest predictive power for mortality with postoperative day seven values in our cohort.

Peng et al. conducted a retrospective study on 122 patients with unruptured intracranial fusiform aneurysms (IFA) finding early increased SII at admission associated with aneurysmal wall enhancement (AWE). An elevated SII index at the patient's initial blood tests upon presentation identified high-risk cases before aneurysm rupture. They determined that an early rise in the SII index could independently predict AWE in IFAs and proposed SII as a potential new biomarker for predicting IFA instability. Furthermore, the study noted that inflammatory markers were lower in patients with unruptured aneurysms compared to those with ruptured aneurysms, and that SII has been identified as a potential tool for predicting aneurysm wall instability, particularly in unruptured fusiform aneurysms.[12]

Wu et al. prospectively examined 125 patients finding that NLR at admission was higher in patients with ruptured intracranial aneurysms versus unruptured intracranial aneurysms, and that high-resolution vascular wall magnetic resonance imaging was associated with circumferential AWE in unruptured intracranial aneurysms. Furthermore, they stated that AWE with high-resolution vascular wall magnetic resonance imaging is an inflammation marker for intracranial aneurysm.[21] In parallel, our study showed higher SIRI, SII, and NLR in patients with ruptured aneurysms at the time of initial presentation and in the postoperative period compared to patients with unruptured aneurysms.

Geng et al. examined SIRI in 916 patients with esophageal squamous cell carcinoma (ESCC) and found SIRI to be an independent index for prognosis in ESCC patients after radical resection.[22] Chen JH et al. evaluated SII in the preoperative period to predict the prognosis of colorectal cancer in their retrospective study on 1383 patients and stated that SII is a powerful tool for predicting survival outcomes in patients with colorectal cancer.[23]

Wang et al. investigated the clinical value of NLR, SII, PLR, and SIRI in 320 patients with intracerebral hemorrhage to predict the onset and severity of stroke-associated pneumonia (SAP). In their prospective observational study, they found that NLR was the best predictor of SAP and poor outcomes at discharge in patients with ICH among the four indices.[24]

In a retrospective study of 75 patients evaluating the results of surgical clipping in anterior circulation aneurysms, Sajid et al. reported a postoperative vasospasm rate of 17.33%, a hydrocephalus rate of 6.66%, and a mortality rate of 2.66%. In our study, postoperative vasospasm was observed in 32.9%, hydrocephalus in 5.5%, and mortality in 13.3%. We believe that the higher mortality rate in our study is due to the fact that 53.5% (n=153) of our patients were treated in the intensive care unit, and our patient group was clinically more critical.[25]

Limitations: *It is a retrospective, single-center study. The number of patients is limited, and potential confounding factors may have affected the results.* AWE measurements were not available. Additionally, the inclusion of both ruptured and unruptured aneurysms may have introduced heterogeneity into the patient group.

Strengths: The assessment of inflammatory markers at different time points and the investigation of the association between easily accessible laboratory data (NLR, SIRI, SII, etc.) and mortality in patients with aneurysms. Furthermore, we believe that the results obtained from our study may contribute to future studies examining the relationship between inflammatory markers and prognosis and mortality.

We believe that it would be beneficial to investigate the relationship between mortality and various, easily accessible, non-invasive laboratory data in future studies.

CONCLUSION

In our patients who underwent aneurysm surgery, SIRI, SII, and NLR measured at baseline and in the postoperative period were higher in patients with mortality compared to survivors. We showed that SIRI, SII, and NLR are useful to predict mortality, and that NLR had high predictive power based on the ROC analysis of values measured on the 7th postoperative day.

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Authors' Contribution:

YY, JH, AYA: Surgical and Medical Practices.
YY, SA, AYA: Concept. Critical review
YY, JH, SA, AYA: Design, Analysis or Interpretation, Literature Search, Writing.
YY, JH, AYA: Data Collection and interpretation
All authors have read and approved the final version and they are also responsible for the accuracy and integrity of the data and analyses in this study.