Systemic Immune-Inflammation Index Predicts Delayed Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

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BACKGROUND: Delayed cerebral vasospasm is a feared complication of aneurysmal subarachnoid hemorrhage (SAH).

OBJECTIVE: To investigate the relationship of systemic inflammation, measured using the systemic immune-inflammation (SII) index, with delayed angiographic or sonographic vasospasm. We hypothesize that early elevations in SII index serve as an independent predictor of vasospasm.

METHODS: We retrospectively reviewed the medical records of 289 SAH patients for angiographic or sonographic evidence of delayed cerebral vasospasm. SII index [(neutrophils × platelets/lymphocytes)/1000] was calculated from laboratory data at admission and dichotomized based on whether or not the patient developed vasospasm. Multivariable logistic regression and receiver operating characteristic (ROC) analysis were performed to determine the ability of SII index to predict the development of vasospasm.

RESULTS: A total of 246 patients were included in our study, of which 166 (67.5%) developed angiographic or sonographic evidence of cerebral vasospasm. Admission SII index was elevated for SAH in patients with vasospasm compared to those without ($P < .001$). In univariate logistic regression, leukocytes, neutrophils, lymphocytes, neutrophil-lymphocyte ratio (NLR), and SII index were associated with vasospasm. After adjustment for age, aneurysm location, diabetes mellitus, hyperlipidemia, and modified Fisher scale, SII index remained an independent predictor of vasospasm (odds ratio 1.386, $P = .003$). ROC analysis revealed that SII index accurately distinguished between patients who develop vasospasm vs those who do not (area under the curve = 0.767, $P < .001$).

CONCLUSION: Early elevation in SII index can independently predict the development of delayed cerebral vasospasm in aneurysmal SAH.

KEY WORDS: Subarachnoid hemorrhage, Inflammation, Vasospasm, Aneurysm, Systemic immune-inflammation index

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Subarachnoid hemorrhage (SAH) is a life-threatening neurological event commonly resulting from ruptured intracranial aneurysms. SAH accounts for 5% of strokes annually with high rates of mortality and long-term disability.[1] One of the feared complications of SAH is delayed cerebral vasospasm, defined as arterial narrowing of large cerebral vessels typically occurring between 3 and 14 d after SAH in up to 70% of patients.[2,3] In those who survive the initial rupture, vasospasm is a major cause of morbidity and mortality. Vasospasm can be diagnosed through transcranial Doppler ultrasonography (TCD), digital subtraction angiography (DSA), or computed tomography angiography (CTA). However, despite the ability to identify vasospasm when it has already developed, we lack specific, objective biomarkers to predict this damaging consequence.

ABBREVIATIONS: ALC, absolute lymphocyte count; **ANC,** absolute neutrophil count; **CNS,** central nervous system; **DND,** delayed neurological deterioration; **EBI,** early brain injury; **NLR,** neutrophil-lymphocyte ratio; **PLT,** platelet count; **SII,** systemic immune-inflammation; **STROBE,** Strengthening the Reporting of Observational Studies in Epidemiology; **TCD,** transcranial Doppler ultrasonography

Although no longer recognized as the sole contributor to delayed neurological deterioration (DND), the prevention and treatment of vasospasm after SAH remain an important therapeutic goal.[3] Recent investigations have shown an association between inflammatory responses after SAH and poor functional outcomes.[4,5] This inflammatory response is most pronounced during the early brain injury (EBI) period up to 72 h following SAH.[4-7] Crosstalk between the brain and immune systems during SAH may be one potential mechanism contributing to brain injury, complications, and outcome.

The systemic immune-inflammation (SII) index is a novel biomarker of systemic inflammatory response underexplored in SAH. The SII index has been described in the oncology literature as an independent predictor of poor prognosis in gastrointestinal, pancreatic, cervical, and bladder cancers.[8-10] In the central nervous system (CNS), SII index helps differentiate between high- and low-grade gliomas.[11,12] More recently, SII index was shown to predict poor outcome following intracerebral hemorrhage.[13] While similar to other indices such as the neutrophil-lymphocyte ratio (NLR),[14] the SII index also incorporates changes in platelets into a single index. Given the strong interaction between inflammation and thrombosis,[3,15] the SII index may serve as a superior tool to NLR and other laboratory measures for predicting complications after SAH. Here, we hypothesized that elevated SII index at admission predicts the development of delayed angiographic or sonographic vasospasm in aneurysmal SAH (aSAH).

METHODS

This study was approved by the local Institutional Review Board (#2015-0559), which determined that informed consent was unnecessary. All recorded data were anonymized. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patient Population

We identified cases of aSAH admitted to the University of Illinois Hospital & Health Sciences System, a large comprehensive stroke center located in Chicago, Illinois. Subjects were identified using

International Classification of Diseases (ICD)-9 (430) and ICD-10 (I60.XX) discharge codes. We included all patients admitted between January 2013 and July 2019 with aSAH above 18 yr old. SAH was confirmed by head computed tomography (CT) and/or lumbar puncture based on clinical guidelines.[2] DSA or CTA was performed to confirm the presence of cerebral aneurysms.

Study Design

Electronic medical records were reviewed and demographic, clinical, and laboratory data were collected into a secure database. The primary outcome was evidence of angiographic and/or sonographic cerebral vasospasm. Vasospasm was defined as evidence of cerebral arterial narrowing, regardless of clinical symptoms, based on DSA findings and impression of the neurointerventionalist performing the procedure as well as daily TCD performed by registered vascular technologists and interpreted by board-certified neurosonologists. TCD diagnosis of vasospasm was done using published, standardized criteria based on mean flow velocities $>$ 120 cm/s and Lindegaard ratio $>$ 3.[2,16,17] At our center, angiographic vasospasm is documented as mild (decreased vessel caliber up to 25% decrease), moderate (25%-50%), or severe (>50%). Follow-up angiography is performed 7 d after SAH in all patients who undergo surgical clipping, and all patients who experience clinical deterioration or worsening TCD. Those who do not receive follow-up angiography are followed through daily TCD only. Any patient for which the presence or absence of vasospasm could not be confirmed was excluded. We additionally assessed for symptomatic vasospasm based on the presence of angiographic vasospasm and DND, the latter defined as new focal neurological deficits and/or decreased consciousness (persistent drop in Glasgow Coma Scale [GCS] by $\geq$ 2 points).[17] Baseline characteristics collected were age, sex, race, ethnicity, aneurysm location (anterior or posterior circulation), and past medical history of cardiovascular disease and/or stroke. We collected clinical and radiographic scores obtained on admission including the modified Fisher scale, Hunt-Hess classification, and GCS.[18-19] These scores were obtained in all patients as standard protocol by neurosurgeons blinded to SII index data. We further collected laboratory data within 24 h of admission, including total leukocyte count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), NLR, and platelet count (PLT). SII index was calculated using the following equation: SII = [(PLT $\times$ ANC/ALC)/1000].

Statistical Analysis

Descriptive variables are presented as number of patients with percentages or median and interquartile range. Fisher's exact test or Pearson's Chi-squared test was used to compare nominal variables, while the Mann-Whitney test or Kruskal-Wallis test was used to compare continuous variables based on data distribution. Logistic regression was used to identify laboratory predictors of cerebral vasospasm. We performed univariate logistic regression for each laboratory variable. Variables with $P < .10$ on univariate analysis were entered into a multivariable logistic regression model, whereby each laboratory value was adjusted by covariates. The presence of multicollinearity among independent variables, defined as variance inflation factor $\geq$5 or tolerance of $<$0.20, was assessed using weighted linear regression.[20] Receiver operating characteristic (ROC) analysis was performed to assess ability of SII index, modified Fisher scale, and the multivariable model for SII index to distinguish between patients who did or did not develop vasospasm. Youden's index was calculated to determine optimal test cutoffs. A P-value of $< .05$ was considered statistically significant unless otherwise indicated. Statistical Package for the Social Sciences (Version 27, IBM® SPSS®, Chicago, Illinois) software was used to conduct the analysis. Figures were made using GraphPad Prism (Version 9, La Jolla, California).

RESULTS

Of 289 screened SAH patients, 256 (88.6%) had aSAH. Of these, 246 (96.1%) met our inclusion criteria (Figure 1). Ten patients with aSAH were excluded from the study as vasospasm diagnosis was uncertain based on review of medical records and imaging data. Of these 10, 8 were deceased within 3 d of admission while the remaining 2 were high-grade aSAH patients

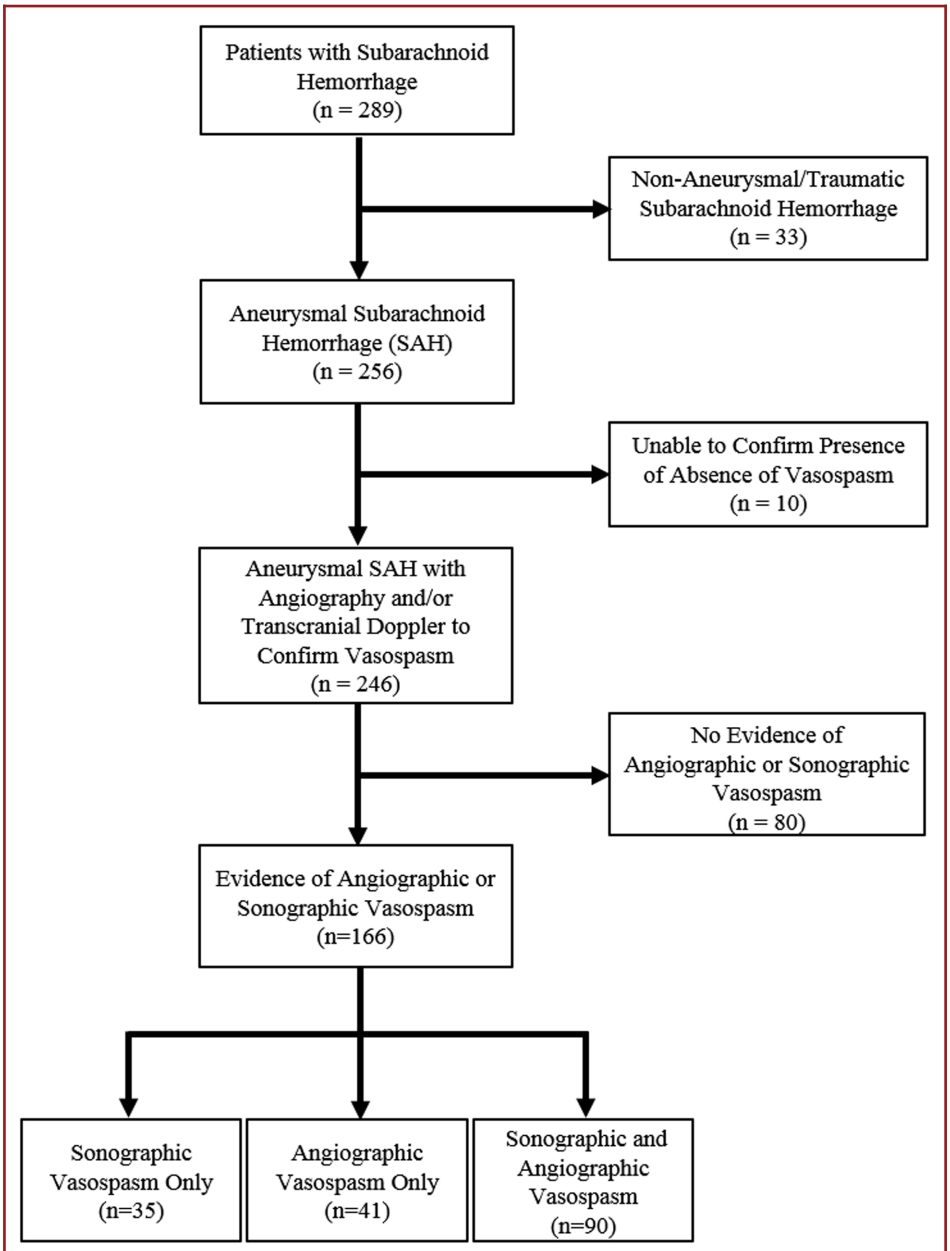

FIGURE 1. *Study design with inclusion and exclusion criteria for aSAH patients. Of 289 consecutive patients with SAH, 256 (88.6%) had an intracranial aneurysm as the confirmed source of hemorrhage. From these 256 patients, 246 (96.1%) were included in the study based on available transcranial Doppler ultrasound and angiography findings to confirm the presence or absence of delayed cerebral vasospasm. Of these, 166 (67.5%) had angiographic or sonographic evidence of vasospasm.*

of advanced age who did not receive follow-up angiography and had suboptimal TCD due to poor bone windows.

Baseline characteristics of patients are shown in Table 1. Of 246 aSAH patients, 240 (97.6%) had initial DSA and 168 (70.0%) had follow-up DSA within 5 to 7 d. Of these 168, 131 (78.0%) had angiographic vasospasm. A total of 245/246 (99.6%) patients had TCD studies, and 125/245 (51.0%) had sonographic evidence of vasospasm. Of these patients, 90 had both angiographic and sonographic evidence of vasospasm, 41 had only angiographic evidence, while 35 had

TABLE 1. Baseline Characteristics of aSAH Patients With and Without Delayed Cerebral Vasospasm

Variable	All, N = 246	No vasospasm, N = 80	Vasospasm, N = 166	*P*-value
Demographics				
Age, years	55.2 (46.1-63.0)	60.8 (52.5-70.8)	52.2 (44.1-59.2)	**<.001***
Female sex	158 (64.2)	53 (66.3)	105 (63.3)	.673§
Race				.798§
Black	77 (31.3)	26 (32.5)	51 (30.7)	
White	51 (20.7)	18 (22.5)	33 (19.9)	
Other	118 (48.0)	36 (45.0)	82 (49.4)	
Hispanic ethnicity	53 (21.5)	21 (26.3)	32 (19.3)	.247§
Aneurysm location				**.015**§
Anterior circulation	208 (84.6)	61 (76.3)	147 (88.6)	
Posterior circulation	38 (15.4)	19 (23.8)	19 (11.4)	
Past medical history				
Hypertension	130 (54.6)	48 (62.3)	82 (50.9)	.126§
Diabetes mellitus	29 (12.2)	14 (18.2)	15 (9.3)	.058§
Hyperlipidemia	41 (17.2)	20 (26.0)	21 (13.0)	**.017§**
Ischemic stroke	6 (2.5)	2 (2.6)	4 (2.5)	>.999§
SAH	14 (5.9)	5 (6.5)	9 (5.6)	.774§
Intracerebral hemorrhage	2 (0.8)	1 (1.3)	1 (0.6)	.543§
Clinical scores on admission				
Modified Fisher scale				**.039**§
0	3 (1.2)	2 (2.5)	1 (0.6)	
1	13 (5.3)	8 (10.0)	5 (3.0)	
2	28 (11.4)	13 (16.3)	15 (9.0)	
3	87 (35.4)	24 (30.0)	63 (38.0)	
4	109 (44.3)	33 (41.3)	76 (45.8)	
Unknown	6 (2.4)	0 (0.0)	6 (3.6)	
Hunt and Hess classification				.193§
1	20 (8.1)	11 (13.8)	9 (5.4)	
2	86 (35.0)	30 (37.5)	56 (33.7)	
3	55 (22.4)	18 (22.5)	37 (22.3)	
4	28 (11.4)	6 (7.5)	22 (13.3)	
5	32 (13.0)	10 (12.5)	22 (13.3)	
Unknown	25 (10.2)	5 (6.3)	20 (12.0)	
GCS				.369§
3-8	64 (26.0)	17 (21.3)	47 (28.3)	
9-12	19 (7.7)	6 (7.5)	13 (7.8)	
13-15	163 (66.4)	57 (71.3)	106 (63.9)	
Laboratory data on admission				
Leukocytes, $10^3/\mu L$	12.7 (10.3-16.1)	11.7 (9.2-14.2)	13.6 (10.6-17.1)	**<.001***
Neutrophils, $10^3/\mu L$	10.6 (8.1-14.1)	9.2 (6.2-12.2)	11.8 (8.8-14.4)	**<.001***
Lymphocytes, $10^3/\mu L$	1.2 (0.9-1.7)	1.4 (0.9-1.9)	1.2 (0.8-1.6)	**.049***
NLR	9.1 (5.4-13.8)	7.0 (4.4-11.4)	10.8 (6.2-15.2)	**<.001***
Platelets, $10^3/\mu L$	236.0 (198.0-285.0)	229 (185.3-285.0)	240 (202.0-288.0)	.165*
SII index, $10^3/\mu L$	2.1 (1.3-3.4)	1.6 (0.8-2.6)	2.3 (1.5-3.8)	**<.001***

Values are median (interquartile range) or number of patients (%) unless otherwise indicated. Boldface type indicates statistical significance with $P < .05$. *Mann-Whitney test; §Chi-squared or Fisher's exact test.

only sonographic evidence, due to lack of follow-up angiogram. In total, 166 (67.5%) aSAH patients developed evidence of angiographic or sonographic vasospasm. Of patients with angiographic or sonographic vasospasm, 83 (50.0%) had DND or symptomatic vasospasm. Given the smaller sample with symptomatic vasospasm, we focused on patients with angiographic or sonographic vasospasm. Average time to develop vasospasm across patients was 5.5 ± 2.8 d. Compared to those without vasospasm, patients who developed vasospasm were younger ($P < .001$), had anterior circulation aneurysms ($P = .015$), were less likely to have hyperlipidemia ($P = .017$), and had higher modified Fisher scales ($P = .039$; Table 1).

TABLE 2. Univariate Logistic Regression Analysis of Admission Laboratory Values to Predict Delayed Cerebral Vasospasm

		Unadjusted	
Variable	**Beta (SE)**	**OR (95% CI)**	***P*-value**
Leukocytes, $10^3/\mu$L	0.123 (0.035)	1.131 (1.056-1.212)	**<.001**
Neutrophil, $10^3/\mu$L	0.134 (0.036)	1.143 (1.066-1.225)	**<.001**
Lymphocytes, $10^3/\mu$L	−0.377 (0.183)	0.686 (0.479-0.983)	**.040**
NLR	0.089 (0.025)	1.093 (1.041-1.148)	**<.001**
Platelets, $10^3/\mu$L	0.002 (0.002)	1.002 (0.998-1.006)	.259
SII Index, $10^3/\mu$L	0.381 (0.103)	1.464 (1.196-1.793)	**<.001**

SE, Standard Error.
Boldface type indicates $P < .05$.

We next investigated differences in laboratory data on admission. Compared to those without vasospasm, patients who developed vasospasm had higher median total leukocytes (13.6 vs 11.7 $10^3/\mu$L, $P < .001$), ANC (11.8 vs 9.2 $10^3/\mu$L, $P < .001$), NLR (10.8 vs 7.0, $P < .001$), and SII index (2.3 vs 1.6 $10^3/\mu$L, $P < .001$) in addition to lower ALC (1.2 vs 1.4 $10^3/\mu$L, $P = .049$). While a statistical difference was observed in those with moderate-to-severe vasospasm compared to those without vasospasm ($P = .018$), no difference was observed in SII index between those with mild vasospasm and those without vasospasm ($P = .276$). Additionally, SII was elevated in patients with symptomatic ($P = .002$) and asymptomatic vasospasm ($P < .001$) compared to those without vasospasm; however, there was no statistical difference between those with symptomatic vs asymptomatic vasospasm (2.2 vs 2.3 $10^3/\mu$L, $P = .354$). Univariate logistic regression for laboratory variables revealed similar ability to predict development of cerebral vasospasm (Table 2). After adjusting for baseline differences in age, aneurysm location, diabetes mellitus, hyperlipidemia, and modified Fisher scale in multivariable logistic regression, total leukocyte count, ANC, NLR, and SII index predicted vasospasm (all $P < .05$). However, SII index had the highest odds ratio (OR) of 1.386 (95% CI 1.006-1.603, $P = .003$; Table 3). Three other factors

TABLE 3. Multivariable Logistic Regression Analysis of Admission Laboratory Values as Predictors of Delayed Cerebral Vasospasm

Models	**Variable**	**Beta (SE)**	**Adjusted OR (95% CI)**	***P*-value**
1	Age, yr	−0.053 (0.014)	0.948 (0.923-0.974)	<.001
	Anterior aneurysm	0.878 (0.417)	2.407 (1.062-5.453)	.035
	Diabetes mellitus	−0.364 (0.469)	0.695 (0.277-1.743)	.437
	Hyperlipidemia	−0.313 (0.422)	0.732 (0.320-1.6710	.458
	Modified Fisher scale	0.478 (0.184)	1.613 (1.124-2.314)	.009
	Leukocytes, $10^3/\mu$L	**0.095 (0.040)**	**1.100 (1.018-1.189)**	**.017**
2	Age, yr	−0.052 (0.014)	0.949 (0.924-0.974)	<.001
	Anterior aneurysm	0.878 (0.418)	2.406 (1.061-5.457)	.036
	Diabetes mellitus	−0.365 (0.470)	0.694 (0.276-1.744)	.437
	Hyperlipidemia	−0.303 (0.422)	0.738 (0.323-1.689)	.472
	Modified Fisher scale	0.451 (0.186)	1.569 (1.091-2.258)	.015
	Neutrophils, $10^3/\mu$L	**0.108 (0.040)**	**1.114 (1.029-1.206)**	**.007**
3	Age, yr	−0.055 (0.013)	0.947 (0.922-0.972)	<.001
	Anterior aneurysm	0.955 (0.417)	2.598 (1.146-5.888)	.022
	Diabetes mellitus	−0.149 (0.466)	0.862 (0.346-2.149)	.750
	Hyperlipidemia	−0.268 (0.408)	0.765 (0.344-1.701)	511
	Modified Fisher scale	0.545 (0.182)	1.724 (1.206-2.464)	.003
	Lymphocytes, $10^3/\mu$L	**−0.387 (0.208)**	**0.679 (0.452-1.021)**	**.063**
4	Age, yr	−0.057 (0.014)	0.945 (0.919-0.971)	<.001
	Anterior aneurysm	1.091 (0.434)	2.977 (1.272-6.970)	.012
	Diabetes mellitus	−0.226 (0.472)	0.798 (0.316-2.013)	.633
	Hyperlipidemia	−0.178 (0.418)	0.837 (0.369-1.900)	.670
	Modified Fisher scale	0.485 (0.186)	1.625 (1.128-2.341)	.009
	NLR	**0.085 (0.027)**	**1.088 (1.032-1.147)**	**.002**
5	Age, yr	−0.054 (0.014)	0.947 (0.922-0.973)	<.001
	Anterior aneurysm	1.008 (0.430)	2.739 (1.180-6.359)	.019
	Diabetes mellitus	−0.205 (0.480)	0.815 (0.318-2.087)	.669
	Hyperlipidemia	−0.229 (0.419)	0.795 (0.350-1.809)	.585
	Modified Fisher scale	0.511 (0.185)	1.667 (1.159-2.397)	.006
	SII index, $10^3/\mu$L	**0.327 (0.110)**	**1.386 (1.118-1.719)**	**.003**

SE, Standard Error.
Boldface type used for all white blood cell count multivariable logistic regression results.

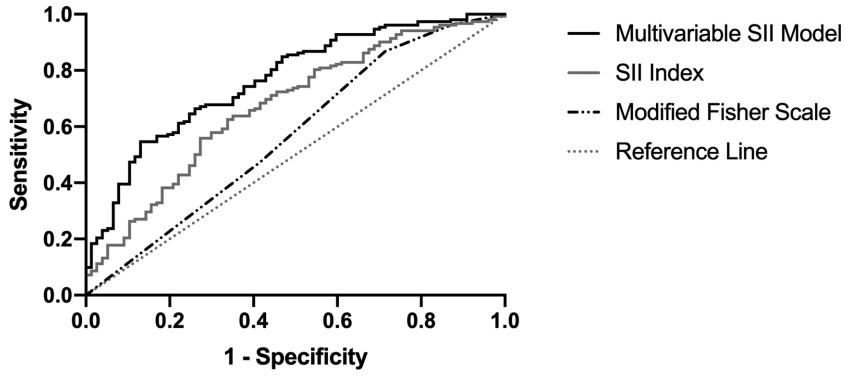

FIGURE 2. *ROC curve for admission SII index to identify patients with cerebral vasospasm. ROC analysis was performed to determine the association of SII index with the development of delayed cerebral vasospasm. SII index is compared to modified Fisher scale, a measure routinely used in clinical practice to predict vasospasm. Predicted probabilities from the multivariable logistic model, whereby SII was adjusted by age, aneurysm location, diabetes mellitus, hyperlipidemia, and modified Fisher scale, were also plotted. Adjusted SII identified patients at risk of vasospasm (AUC = 0.767, P < .001). The optimal predictive cut-off value for adjusted SII from the multivariable model's predicted probabilities based on Youden's index was a 0.764, corresponding to a sensitivity of 54.6% and specificity of 87.0%.*

that remained independent predictors of vasospasm across each model included age, anterior circulation aneurysms, and modified Fisher scale (all $P < .05$; Table 3). Multicollinearity was not observed between the independent variables and development of vasospasm.

Finally, ROC analysis was performed to determine ability of SII index to distinguish between aSAH patients who did or did not develop vasospasm (Figure 2). We compared the ROC curves for SII index and the multivariable SII model to that of the modified Fisher scale, used clinically for predicting vasospasm. Modified Fisher scale showed modest ability to distinguish between patients with and without vasospasm (area under the curve [AUC] = 0.569, 95% CI 0.487-0.650, $P = .089$). Optimal cutoff for modified Fisher scale was 2, whereby those with a score >2 would be likely to develop vasospasm (Youden's index = 0.154, sensitivity 86.8%, specificity 28.6%). However, SII index significantly differentiated between groups (AUC = 0.672, 95% CI 0.698-0.747, $P < .001$). The optimal cutoff for SII level was 1.924 $10^3/\mu$L, whereby those with SII index above this level would be likely to develop vasospasm (Youden's index = 0.287, sensitivity 63.8%, specificity 64.9%). After covariate adjustment, the multivariable SII model demonstrated significant improvement in distinguishing between patients with or without vasospasm (AUC = 0.767, 95% CI 0.703-0.831, $P < .001$). The optimal predicted probability cutoff determined from the multivariable SII model was 0.764 (Youden's index = 0.416, sensitivity 58.9%, specificity 80.6%).

DISCUSSION

Systemic inflammation is common after aSAH and may contribute to feared complications such as delayed cerebral vasospasm. Here, we show for the first time that SII index is elevated in aSAH patients who develop vasospasm compared to those who do not. Admission SII index independently predicted development of vasospasm, which peaks around 1 wk after aSAH with an optimal cutoff of 1.924 $10^3/\mu$L (sensitivity 63.8%, specificity 64.9%). The predictive power of the SII index was improved when age, aneurysm location, diabetes mellitus, hyperlipidemia, and modified Fisher scale were included as covariates (Table 3 and Figure 2) with an optimal predicted probability cutoff of 0.764 (sensitivity 58.9%, specificity 80.6%). The combination of these measurements resulted in improved specificity for predicting vasospasm.

While approaches such as TCD and DSA exist to diagnose patients actively experiencing vasospasm, we lack specific, objective methods to predict its development prior to onset. The modified Fisher scale is a useful radiographic tool to stratify risk of developing vasospasm based on admission CT; however, despite sufficient sensitivity, there is modest specificity and inter-rater reliability.[21-23] Thus, SII index, which integrates changes in peripheral neutrophils, lymphocytes, and platelets, is a novel, readily available, and noninvasive biomarker with added specificity to help identify patients at high risk of developing vasospasm and guide early management.

Differences in SII index observed in this study suggest a potential role for early inflammatory responses in driving delayed sequelae after aSAH.[5] Our study expands upon previous studies demonstrating changes in circulating leukocytes after aSAH. Several studies have investigated the relationship between systemic inflammatory response syndrome and outcome after aSAH.[24-28] Elevated total leukocytes and neutrophils were shown to be independently associated with vasospasm after adjusting for age and clinical severity.[29-31] Decreased serum lymphocytes

plays a role in infectious complications of aSAH, although the association with vasospasm is unclear.[31,32] Elevated NLR independently predicts DND and functional outcome, although predictive ability for vasospasm has not been fully established.[14,33,34] Further, evidence supports the role of platelet activation in driving poor outcomes after aSAH.[3,35-39] Platelet activation and aggregation occur during the period of EBI within the cerebral microvasculature[35,38] but can also be observed peripherally.[36,37,39] In this study, we show that by integrating changes in neutrophils, lymphocytes, and platelets into a single measurement, the SII index is superior in predicting vasospasm compared to its individual components.

Two other variables that remained significant predictors of vasospasm in multivariable analysis included age and aneurysm location. These findings are consistent with previous literature showing increased incidence of vasospasm in patients less than 60 yr old.[40] Data on aneurysm location and incidence of vasospasm are less clear, although some studies have shown increased incidence with anterior circulation aneurysms.[41] Taken together, early identification of patients at higher risk of vasospasm may guide clinical management, including earlier or more frequent monitoring. Future studies should also assess the relationship of SII index to DND, neurological, and cognitive outcomes.

It has become increasingly clear that SAH is a disease not exclusively limited to the CNS. SAH affects the cardiac and respiratory systems in addition to systemic inflammatory responses.[6,7,42,43] Most studies investigating inflammatory responses and immune dysregulation after aSAH have suggested a prominent role of the autonomic nervous system, involving overactive sympathetic tone from the hypothalamic-pituitary-adrenal axis.[44] This promotes systemic inflammation, as major reservoirs of immune cells respond to catecholamines and cortisol.[7,44] Despite this, clinical studies of anti-inflammatory agents in aSAH patients have been conflicting.[3] A systematic review of corticosteroids for preventing poor outcome after aSAH revealed no evidence of beneficial or adverse effects.[45] However, a randomized, open-label, single-blinded study administering subcutaneous interleukin-1 receptor antagonist demonstrated efficacy in reducing inflammatory markers.[46] While not powered to investigate clinical efficacy, a trend for improved functional outcome at 6 mo was observed, supporting the need for a phase III study.[46] Our observations, combined with data obtained in animal models, suggest that inflammation may modulate vascular tone after aSAH, offering a potential therapeutic target for intervention. While it has been established that nonspecific immunomodulation after aSAH (through use of corticosteroids) does not offer benefit,[45] future studies may use more specific immunomodulatory agents to identify targeted subpopulations who may benefit. Additionally, studies in experimental SAH have demonstrated that reducing circulating leukocytes improves microvascular function, microthrombosis, and neurological outcome.[3,15,47-49]

Limitations

Limitations to this study include its single-center, retrospective nature. Follow-up angiography studies were not performed in all patients and, therefore, we also relied on TCD evidence of vasospasm. Though both TCD and DSA are validated ways to assess vasospasm, DSA is the gold standard.[2,16,17] Based on the results of a meta-analysis, the sensitivity and specificity of TCD for detecting vasospasm are approximately 70% and 100%, respectively.[50] Most studies included in this meta-analysis used the same TCD cutoffs used in our study. Only 10 patients with aSAH were excluded as we could not confirm the presence or absence of vasospasm. We also used vasospasm regardless of symptoms as our primary endpoint. Thus, we cannot comment on the effect of SII on symptomatic vasospasm. Future prospective, multicenter studies are required to assess the prognostic value of SII index for the diagnosis of symptomatic vasospasm in aSAH patients. This would also permit incorporation of additional prospective metrics including the Hijdra sum score.[51] Finally, measurement of admission SII does not account for the few patients who may present in a delayed fashion; therefore, differences observed here in SII index may be an underestimate, as acute inflammatory responses normalize over time.

CONCLUSION

In summary, early elevation in SII index after aSAH assists in the prediction of delayed cerebral vasospasm measured via angiography and TCD. Systemic inflammation is common after SAH and SII index offers a reliable, objective, specific, and noninvasive method of assessing systemic inflammatory responses that prognosticate cerebrovascular complications.

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COMMENT

In this study, the authors present a single center series of 246 patients with aneurysmal subarachnoid hemorrhage and compare admission laboratory markers with development of delayed vasospasm. The authors conclude that early elevation in the systemic immune-inflammation (SII) index is predictive of cerebral vasospasm in patients with ruptured aneurysms. This evidence is based on elevations in SII in predicting outcomes in patients with various cancers as well as glioma and intracranial hemorrhages.

In the study, the authors carefully note that statistically significant differences in SII were present between those with moderate and severe vasospasm and those without vasospasm, yet no difference was found between those with mild and those without vasospasm. Furthermore, regarding clinical vasospasm, there were differences between symptomatic and asymptomatic vasospasm compared to patients without vasospasm, while no difference was observed between patients with or without clinical symptoms. This suggests a possible association with systemic inflammation and vascular spasm, but the SII cannot be used to determine clinical consequences of this spasm. Furthermore, as the authors note, other signs of inflammation can be used to predict the same consequence (radiographic spasm as noted on transcranial doppler or angiogram, with or without symptoms), such as total leukocyte count, neurotrophil count (ANC), and neutrophil-lymphocyte ratio (NLR). Given these considerations, SII is likely somewhat limited for application to this purpose. While the SII might be used to help indicate possible spasm, the inability to distinguish between symptomatic and asymptomatic vasospasm may lead to unnecessary treatment or invasive monitoring.

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