RESEARCH

Blood inflammatory biomarkers predict in-hospital pneumonia after endovascular treatment of aneurysm in patients with aneurysmal subarachoid hemorrhage

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Abstract

The systemic inflammatory response index (SIRI) is a well-known marker of systemic inflammation reflecting the body's inflammatory/immune state. The study aimed to evaluate the relationship between the SIRI on admission and aneurysmal subarachnoid hemorrhage (aSAH)-associated pneumonia and compare with other currently used bio-markers. We reviewed 562 successive patients with aneurysmal SAH who underwent endovascular treatment between January 2019 and September 2021. ASAH-associated pneumonia was diagnosed using the modified Centers for Disease Control and Prevention criteria. The SIRI on admission was calculated as monocyte count×neutrophil count / lymphocyte count. Multiple logistic regression models were used for data analysis. A total of 158 (28.11%) patients developed aSAH-associated pneumonia. Using the Multiple logistic regression analysis, a notable dose–response association was found between the elevated SIRI (fourth quartile) and aSAH-associated pneumonia (adjusted odds ratio=6.759; 95% confidence interval [CI], 3.280–13.930; $p < 0.001$ [p for trend < 0.001]). The SIRI (0.701, 95% CI: 0.653–0.749) presented a higher area under the curve (AUC) than systemic immune- inflammation index (SII) (0.669, 95% CI: 0.620–0.718) ($p = 0.089$); neutrophil-to-lymphocyte ratio (NLR) (0.665, 95% CI: 0.616–0.714) ($p = 0.035$) and platelet-lymphocyte ratio (PLR) (0.587, 95% CI: 0.534–0.641) ($p < 0.001$). A higher SIRI on admission was associated with aSAH-associated pneumonia, which may guide further clinical trials of prophylactic antibiotic therapy.

Keywords Systemic inflammatory response index · Aneurysmal subarachnoid hemorrhage · Inflammation · aSAH-associated pneumonia

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH)-associated pneumonia accounts for approximately 13.2–29.4% of patients with aSAH [1–4], which worsens patient prognosis and prolongs the duration of hospitalization [5, 6]. Endovascular treatment is currently considered an effective therapeutic option for aneurysmal subarachnoid hemorrhage, which is associated with less injury compared to surgical clipping. We hypothesized that there might be differences in the inflammatory status between these two treatments. And a previous study by Li R et al. showed variations in the risk of pneumonia formation between the two treatments [7]. However, the risk factors and predictors of pneumonia

after aSAH treated with endovascular coiling have not yet been reported.

Previous studies have shown that subarachnoid hemorrhage rapidly activates an inflammatory cascade [8, 9], leading to leukocytosis, platelet aggregation, and lymphocyte apoptosis [10, 11]. There is mounting evidence indicating that aSAH-associated immunosuppression may contribute to the development of infections [9] and potentially influence outcomes in patients with aSAH. Therefore, it is necessary to identify bio-markers that can represent the body's inflammatory response to predict the occurrence of aSAH-associated pneumonia. However, only lactate dehydrogenase and IL-6 have been reported as independent risk factors for post-stroke prognosis [2, 12, 13].

The systemic inflammatory response index (SIRI) is a well-known marker of systemic inflammation where the immune state of the body can be calculated by quantifying the absolute count of neutrophils, monocytes, and

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lymphocytes in the peripheral blood of patients. To date, SIRI has been widely used in tumor research [14, 15], and is performed immediately after admission. However, the predictive value of the SIRI for aSAH after endovascular treatment-associated pneumonia remains unclear.

Therefore, this study intends to evaluate the relationship between the SIRI and pneumonia after aneurysmal subarachnoid hemorrhage by endovascular treatment and compare it with other biomarkers.

Methods

Study design and patients

From January 2019 to September 2021, aSAH patients who received endovascular treatment at three large centers in China were recruited (Beijing Tiantan Hospital; Beijing Tongren Hospital; The Third Xiangya Hospital, Central South University). Written informed consent was obtained from all the patients. This study was reviewed and approved by the hospital review committees, and complied with the principles of the Declaration of Helsinki.

Considering the impact of systemic inflammation, and the dynamic changes in inflammation over time, we enrolled patients with aSAH aged 18 years or older, and had a time interval of symptom onset to hospital admission of less than 3 days and excluded those with additional aneurysms (e.g., blood bubble, dissection, fusiform, infectious, cerebrovascular or Moyamoya malformation), incomplete data, history of neurosurgical interventions or those who had cancer, inflammatory diseases, autoimmune diseases, or admission accompanied by infectious disease. The diagnosis of aneurysm by digital subtraction angiography (DSA), computed tomographic angiography (CTA), and magnetic resonance angiography (MRA), and SAH by computed tomographic(CT).

Data collection

Baseline data were evaluated, including modified Fisher grades, general information (age, sex, weight, height, body temperature, respiratory rate, heart rate), past medical history (hypertension, hyperlipidemia, diabetes, previous cerebral ischemia/cerebral hemorrhage), personal history (smoking and drinking history), and occurrence
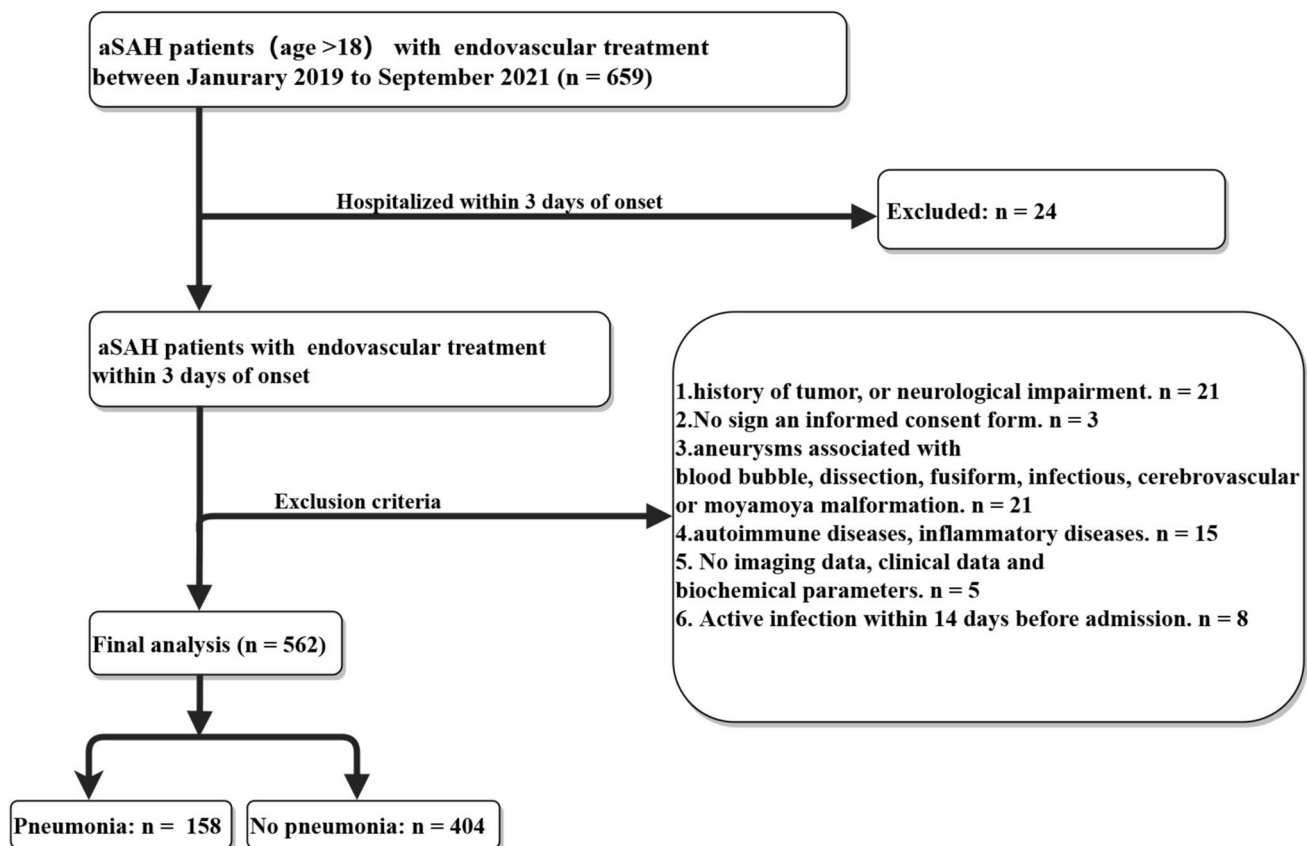
Fig. 1 Flow chart of Patients of the study. aSAH, aneurysmal subarachnoid hemorrhage

Table 1 Baseline characteristics of aneurysmal SAH patients who received endovascular treatment with pneumonia and non-pneumonia

Characteristics	Total (n=562)	Pneumonia (n=158)	Non-pneumonia (n=404)	P value
Sex, female	362 (64.4)	96(60.8)	266(65.8)	0.258
Age, years	58 (49–66)	62.50(52–71)	56(47–64)	<0.001
Admission vital signs				
BMI	24.23(22.04–26.57)	24.33(21.96–26.88)	24.23(22.05–26.54)	0.917
Temperature, ℃	36.50(36.40–36.80)	36.70(36.50–37)	36.50(36.30–36.70)	<0.001
Respiration rate breaths/minute	19(18–20)	20(17–20)	19(18–20)	0.381
Heart rate/minute	78(70–82)	80(71.75–88.25)	76(70–80)	<0.001
SAP, mm Hg	145.50(131–160.25)	152(134–165)	143(130–160)	0.022
DAP, mm Hg	86(79–95)	87(79–98)	85(79–94)	0.277
MAP, mm Hg	106.67(97–115.67)	109.67(98–118.08)	105.67(97–114.92)	0.051
Admission clinical grade				
Modified Fisher scale				<0.001
1–2	335(59.6)	48(30.4)	287(71)	
3–4	227(40.4)	110(69.6)	117(29)	
Hunt-Hess scale				<0.001
1–3	511(90.9)	129(81.6)	382(94.6)	
4–5	51(9.1)	29(18.4)	22(5.4)	
Medical history				
Hypertension	344(61.2)	121(76.6)	223(55.2)	<0.001
Diabetes	70(12.5)	29(18.4)	41(10.1)	0.008
Hyperlipidemia	132(23.5)	50(31.6)	82(20.3)	0.004
Previous stroke	103(18.3)	48(30.4)	55(13.6)	<0.001
Heart disease	87(15.5)	43(27.2)	44(10.9)	<0.001
Previous or current smoking, n (%)	160(28.5)	56(35.4)	104(25.7)	0.022
Previous or current drinking, n (%)	117(20.8)	42(26.6)	75(18.6)	0.035
Aneurysm characteristics				
Multiple aneurysms	136(24.2)	44(27.8)	92(22.8)	0.207
Aneurysm size, median (IQR), mm	5.19(3.79–7.04)	5.31(3.91–7.16)	5.14(3.68–6.95)	0.201
Maximum height, median (IQR), mm	4.92(3.47–6.57)	5.01(3.79–6.85)	4.84(3.32–6.51)	0.155
Neck width, median (IQR), mm	3.01(2.26–4.22)	3.08(2.24–4.55)	2.99(2.29–4.12)	0.243
Maximum width, median (IQR), mm	3.83(2.83–5.71)	4.11(2.95–6.24)	3.78(2.79–5.49)	0.060
AR, median (IQR)	1.58(1.16–2.04)	1.58(1.16–2.05)	1.57(1.16–2.05)	0.709
SR, median (IQR)	1.98(1.43–3.01)	2.22(1.53–3.16)	1.91(1.41–2.96)	0.038
Parent vessel diameter, median (IQR), mm	2.63(1.93–3.39)	2.44(1.95–3.33)	2.67(1.91–3.41)	0.220
Irregularity, n (%)	242(43.1)	72(45.6)	170(42.1)	0.453
Daughter sac, n (%)	78(13.9)	27(17.1)	51(12.6)	0.169
Location, n (%)				0.034
ICA	176(31.3)	45(28.5)	131(32.4)	0.365
AComA	133(23.7)	32(20.3)	101(25)	0.234
PComA	102(18.1)	24(15.2)	78(19.3)	0.255
ACA	27(4.8)	9(5.7)	18(4.5)	0.536
MCA	37(6.6)	11(6.9)	26(6.4)	0.821
PC	87(15.5)	37(23.4)	50(12.4)	0.001
Treatment				0.656
Coiling only	269(47.9)	78(49.4)	191(47.3)	
Stents assist coiling	293(52.1)	80(50.6)	213(52.7)	
Admission laboratory				
LY, median (IQR), 10^9/L	1..06(0.75–1.48)	0.98(0.69–1.37)	1.11(0.79–1.54)	0.008
PLT, median (IQR), 10^9/L	222(181–269)	223(186.75–278.25)	221(179–268)	0.358

Table 1 (continued)

Characteristics	Total (n = 562)	Pneumonia (n = 158)	Non-pneumonia (n = 404)	P value
NEUT, median (IQR), 10^9/L	9.98(6.99–13.11)	12.22(9.84–14.99)	8.80(6.22–12.08)	< 0.001
EO, median (IQR), 10^9/L	0.01(0–0.03)	0.01(0–0.02)	0.01(0–0.03)	0.165
LEUC, median (IQR), 10^9/L	11.44(8.65–14.62)	13.72(11.33–16.78)	10.40(8.19–13.81)	< 0.001
RBC, median (IQR), 10^{12}/L	4.47(4.13–4.80)	4.46(4.13–4.80)	4.47(4.13–4.80)	0.998
MONO, median (IQR), 10^9/L	0.42(0.29–0.56)	0.50(0.32–0.66)	0.39(0.29–0.53)	< 0.001
CRP, median (IQR)	4.68(1.57–15.14)	8.13(2.30–25.36)	4.19(1.42–12.28)	< 0.001
SII, median (IQR)	2080.02(1153.63–3384.03)	2941.94(1732.85–4270.80)	1854.80(942.43–2873.32)	< 0.001
NLR, median (IQR)	9.86(5.49–14.92)	12.24(8.76–18.49)	8.75(4.52–13.74)	< 0.001
SIRI, median (IQR)	3.71(1.93–6.29)	5.58(3.32–10.20)	3.19(1.64–5.49)	< 0.001
PLR, median (IQR)	200.40(149.23–288.52)	244.89(156.29–327.81)	192.25(146.15–273.05)	0.001

IQR interquartile range, *BMI* body mass index, *SAP* systolic pressure, *DAP* diastolic pressure, *MAP* mean arterial pressure, *AR* aneurysm maximum height to neck diameter ratio, *SR* aneurysm maximum diameter to the parent vessel diameter(s) ratio, *ICA* internal carotid artery, *AComA* anterior communicating artery, *PComA* posterior communicating artery, *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *PC* posterior circulation, *LY* lymphocyte, *PLT* platelet, *NEUT* neutrophil, *EO* eosinophil, *LEUC* leucocyte, *RBC* red blood cell, *MONO* monocyte, *SIRI* systemic inflammatory response index, *SII* systemic immune inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio. SIRI = monocyte count×neutrophil count / lymphocyte count; SII = platelet count×neutrophil count / lymphocyte count; NLR = neutrophil count / lymphocyte count; PLR = platelet count / lymphocyte count

of aSAH-associated pneumonia. The absolute neutrophil, lymphocyte, and monocyte counts were calculated from blood samples collected from all patients on admission. Blood samples was analyzed in the hospital within 6 h using an autoanalyzer (Mindray Hematology Analyzer BC-6900 series; Mindray Corporation, Shenzhen, China).

Definition of variables

We endorsed the diagnostic criteria for aSAH-associated pneumonia based on the modified Centers for Disease Control and Prevention criteria, excluding patients diagnosed with pneumonia before admission [16]. The IA morphological features, including aneurysm size, neck width, maximum height, maximum width, aspect ratio, size ratio, parent vessel diameter, shape, the Hunt-Hess scale, and the modified Fisher grades that were obtained by two readers with 5 years of experience in vascular neuroimaging, respectively. Assuming a large deviation in the morphologic parameters of IA, the final norm was determined by a third reader with 10 years of experience in vascular neuroimaging. The definition of deviations were as follows: (1) inconsonant interpretation of the aneurysmal shape, location, and the modified Fisher grades for categorical variables; and (2) the difference of data measurement is greater than 1 mm, for the continuous variables, such as aneurysm size, neck width, maximum height, maximum width, and parent vessel diameter.

SIRI is calculated as monocyte count×neutrophil count / lymphocyte count[17]; Systemic immune- inflammation index (SII) is calculated as platelet count×neutrophil count / lymphocyte count[18]; neutrophil-to-lymphocyte ratio (NLR) is calculated as neutrophil count / lymphocyte count[19]; platelet-lymphocyte ratio (PLR) is calculated as platelet count / lymphocyte count[20].

Statistical analysis

Continuous variables were presented as medians with interquartile range or means ± standard deviations, whereas categorical data were expressed as proportions. Baseline variables were compared between the χ^2 test or Fisher`s exact test for categorical variables and the Mann–Whitney U test for continuous variables with a normal or skewed distribution. We used two models, no variable adjustment was performed in the first model, and all potential confounders were included in the multivariate logistic regression analysis in the two model. A nomogram was developed based on the results of the multivariable logistic analysis to predict the occurrence of pneumonia. The predictive performance of the nomogram was evaluated using receiver operating characteristic (ROC) analysis, C-index, and calibration curve. To assess the ability of SIRI, SII, NLR, and PLR to predict aSAH-associated pneumonia, we evaluated and calculated the area under the curve (AUC) and receiver operating characteristic (ROC) curves, which were also used to determine the optimal cut-off point using Youden index. Differences were evaluated for statistical significance using the DeLong test. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. In addition, the dose–response relationship between SIRI, SII, NLR, PLR, and

aSAH-associated pneumonia was evaluated using Restricted cubic spline (RCS) combined with a logistic regression model, with four knots (at the 25th,50th,75th, and 95th percentiles) and the OR of all potential covariates was adjusted (Model 2).

All statistical analyses were performed using the R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value < 0.05 was measured statistically significant.

Results

In total, 562 consecutive patients (median age: 58 years (range 49–66), women: 362 [64.4%]) were ultimately enrolled in this study (Fig. 1). The median with interquartile ranges [Median(IQR)] for each biomarker sample collected are as follows: SIRI,3.71 (1.93–6.29); SII, 2080.02 (1153.63–3384.03); NLR, 9.86 (5.49–14.92); PLR, 200.40 (149.23–288.52), respectively. Of those, 158 (28.11%) patients developed aSAH-associated pneumonia.

The patients were divided into two groups based on the occurrence of aSAH-associated pneumonia are shown in Table 1. The pneumonia group presented with higher modified fisher scale ($p < 0.001$) and higher Hunt-Hess scale ($p < 0.001$), higher rates of hypertension ($p < 0.001$), diabetes ($p = 0.008$), hyperlipidemia ($p = 0.004$), previous stroke ($p < 0.001$), previous or current smoking ($p = 0.022$), previous or current drinking ($p = 0.035$), SR ($p = 0.038$) in Table 1. We observed that the meaningfully association between posterior circulation aneurysms and the development of pneumonia

Table 2 The quartile of blood-based biomarkers in patients with aSAH who received endovascular treatment and the risk of aSAH-associated pneumonia

Pneumonia	Quartile of SIRI	No	Events, n (%)	Model 1* Adjusted OR (95% CI)	P value	Model 2† Adjusted OR (95% CI)	P value
	Q1, ≤1.933	140	15(9.5)	Ref		Ref	
	Q2,1.934–3.712	141	34(21.5)	2.648(1.368–5.124)	0.004	2.229(1.064–4.670)	0.034
	Q3,3.713–6.289	141	41(26)	3.417(1.789–6.527)	<0.001	2.383(1.145–4.956)	0.020
	Q4,≥6.289	140	68(43)	7.870(4.192–14.775)	<0.001	6.759(3.280–13.930)	<0.001
	P for trend				<0.001		<0.001
	Quartile of SII	No	Events, n (%)	Model 1* Adjusted OR (95% CI)	P value	Model 2† Adjusted OR (95% CI)	P value
Pneumonia	Q1, ≤1153.633	141	19(12)	Ref		Ref	
	Q2,1153.634–2080.020	140	34(21.5)	2.060(1.109–3.824)	0.022	2.016(0.99–4.102)	0.053
	Q3,2080.021–3384.033	143	41(26)	2.581(1.411–4.723)	0.002	2.132(1.062–4.281)	0.033
	Q4,≥3384.034	138	64(40.5)	5.553(3.085–9.997)	<0.001	5.910(2.964–11.786)	<0.001
	P for trend				<0.001		<0.001
	Quartile of NLR	No	Events, n (%)	Model 1* Adjusted OR (95% CI)	P value	Model 2† Adjusted OR (95% CI)	P value
Pneumonia	Q1, ≤5.492	140	22(13.9)	Ref		Ref	
	Q2,5.493–9.863	140	27(17.1)	1.282(0.690–2.381)	0.432	0.873(0.428–1.781)	0.709
	Q3,9.864–14.917	142	44(27.9)	2.408(1.352–4.291)	0.003	1.934(0.989–3.785)	0.054
	Q4,≥14.918	140	65(41.1)	4.648(2.646–8.166)	<0.001	3.733(1.938–7.191)	<0.001
P for trend					<0.001		<0.001
	Quartile of PLR	No	Events, n (%)	Model 1* Adjusted OR (95% CI)	P value	Model 2† Adjusted OR (95% CI)	P value
Pneumonia	Q1, ≤149.233	141	34(21.5)	Ref		Ref	
	Q2,149.234–200.400	140	29(18.4)	0.822(0.469–1.442)	0.495	1.191(0.619–2.288)	0.601
	Q3,200.401–288.524	140	45(28.5)	1.491(0.883–2.518)	0.135	2.366(1.255–4.462)	0.008
	Q4,≥288.525	141	50(31.6)	1.729(1.030–2.902)	0.038	2.141(1.162–3.943)	0.015
	P for trend				<0.001		<0.001

aSAH aneurysmal subarachnoid hemorrhage, *SIRI* systemic inflammatory response index, *SII* systemic immune inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *CI* confidence interval, *OR* odds ratio, *Ref* reference, *Q* quartile

*Model 1: No variable adjustment

†Model 2: Adjusted for age, modified Fisher score, hypertension, diabetes, hyperlipidemia, previous stroke, heart disease, previous or current smoking, previous or current drinking, location, SR

($p = 0.001$), while there was no significant correlation between aneurysms in other locations and pneumonia. Patients in the pneumonia group also had higher C-reactive protein (CRP) ($p < 0.001$), lymphocytes ($p = 0.008$), neutrophils ($p < 0.001$), monocytes ($p < 0.001$), and leukocytes ($p < 0.001$) in Table 1. SIRI, SII, NLR, and PLR of the pneumonia group are higher than that of the non-pneumonia group, respectively (5.58, 3.32–10.20 vs 3.19, 1.64–5.49, $p < 0.001$; 2941.94, 1732.85–4270.80 vs 1854.80, 942.43–2873.32, $p < 0.001$; 12.24, 8.76–18.49 vs 8.75, 4.52–13.74, $p < 0.001$; 244.89, 156.29–327.81 vs 192.25, 146.15–273.05, $p = 0.001$; Table 1).

The relationship between SIRI, SII, NLR, PLR, and aSAH-associated pneumonia compared to CRP, leucocyte, and neutrophil

Table 2 shows the association between SIRI, SII, NLR, and PLR quartiles and aSAH-associated pneumonia. Compared with the lowest quartile, patients in the second, third, and fourth SIRI, SII, NLR, and PLR quartiles were associated with an increased risk of the developing aSAH-associated pneumonia ($p < 0.001$). SIRI (adjusted OR:2.229, 95%CI: 1.064–4.670; 2.383,95% CI: 1.145–4.956; 6.759, 95% CI: 3.280–13.930, respectively), SII (adjusted OR: 2.016, 95% CI: 0.99–4.102; 2.132, 95% CI: 1.062–4.281; 5.910, 95% CI: 2.964–11.786; respectively), NLR (adjusted OR: 0.873, 95% CI: 0.428–1.781; 1.934, 95% CI: 0.989–3.785; 3.733, 95% CI: 1.938–7.191; respectively),PLR (adjusted OR: 1.191, 95% CI: 0.619–2.288; 2.366, 95% CI: 1.255–4.462; 2.141, 95% CI: 1.162–3.943; respectively) factors increase the risk of developing aSAH-associated pneumonia.

Figure 2 shows the non-linear association between the SIRI, SII, NLR, and PLR and the risk of high aSAH-associated pneumonia with restricted cubic splines (RCS). We found that the elevated SIRI was connected with a higher risk of aSAH-associated pneumonia.

When comparing SIRI with PLR, SII, NLR CRP, leucocyte, and neutrophil of the predictive power, the SIRI (0.701, 95% CI: 0.653–0.749) presented a higher (AUC) than SII (0.669, 95% CI: 0.620–0.718), NLR (0.665, 95% CI: 0.616–0.714), PLR (0.587, 95% CI: 0.534–0.641), CRP (0.617, 95% CI: 0.576–0.658), leucocyte (0.691,95% CI:0.651–0.729), neutrophil(0.695, 95% CI: 0.655–0.733) (Figs. 3, 4; Table 3). The optimal cut-off value for SIRI of aSAH-associated pneumonia
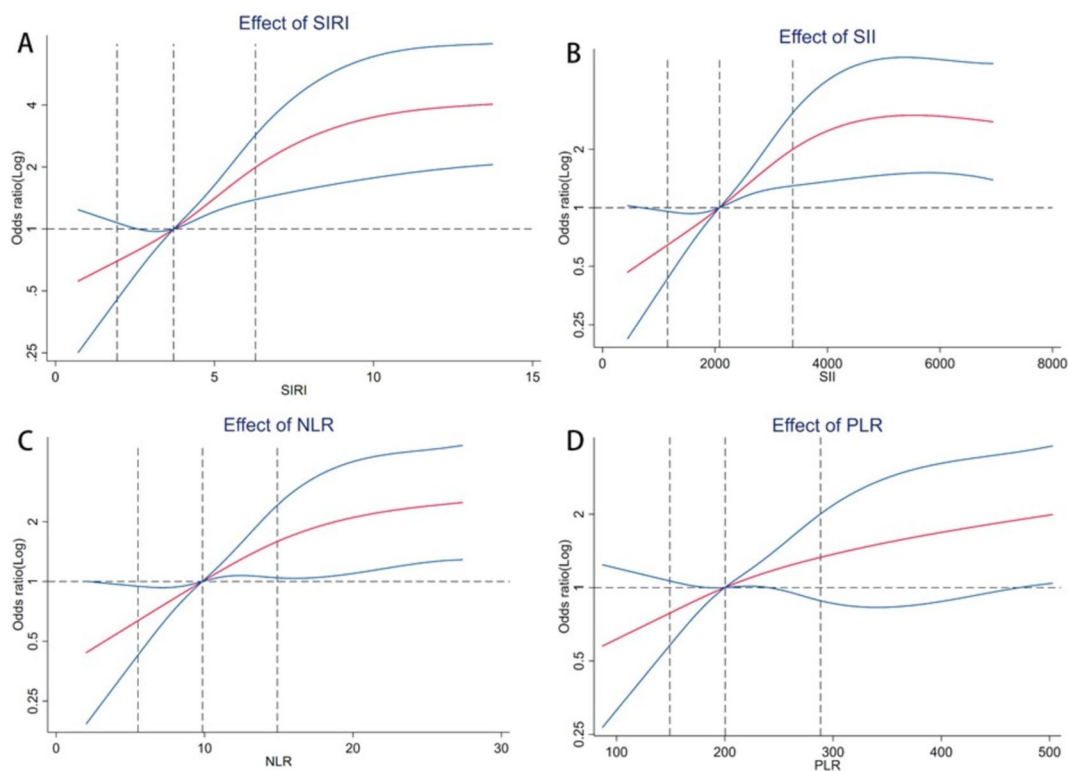
Fig. 2 Adjusted odds ratios of blood-based biomarkers of SIRI (**A**), SII (**B**), NLR (**C**), and PLR (**D**) with aSAH-associated pneumonia. SIRI = systemic inflammatory response index; SII = systemic immune inflammation index; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio. Red line indicates adjusted odds ratio, and blue lines indicate the 95% confidence interval bands. The other vertical dashed lines indicate the first, second, and third quartiles of SIRI, SII, NLR, and PLR. The data were fitted using a logistic regression model of restricted cubic splines with 4 knots (25th, 50th, 75th, and 95th percentiles) for SIRI, SII, NLR, PLR, adjusting for potential covariates as model 2. The lowest 5% and highest 5% of patients are not shown in the figures because of small sample sizes
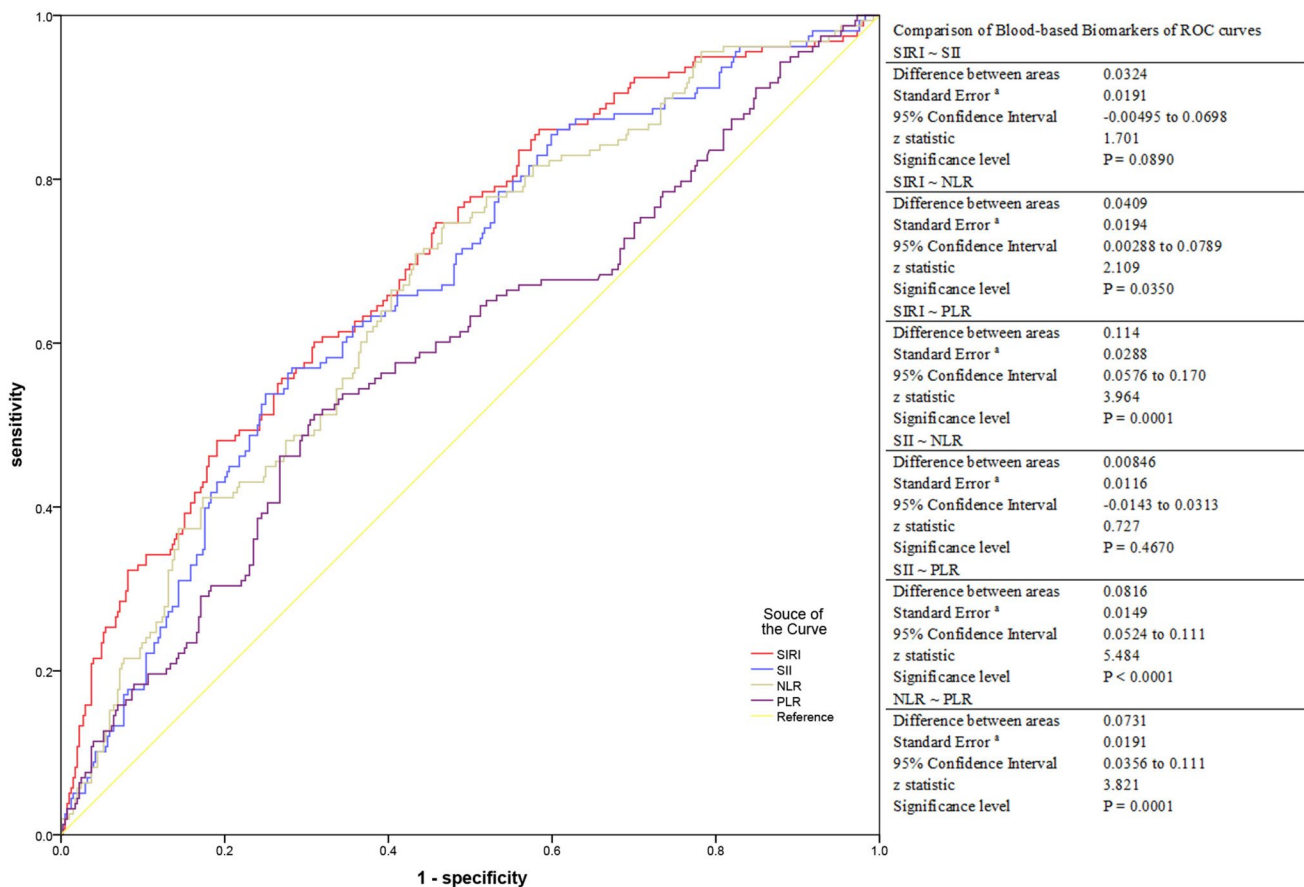
was 4.703, which predicted aSAH-associated pneumonia with a sensitivity of 70.8, a specificity of 60.1 (Table 3). The SIRI improve the predictive ability of CRP, leucocyte, and neutrophil, (CRP + SIRI) (0.722, 95% CI: 0.683–0.759), (leucocyte + SIRI) (0.709, 95% CI: 0.670–0.746), (neutrophil + SIRI) (0.710, 95% CI: 0.671–0.747) (Fig. 4). Delong's test showed that compared with SII ($p = 0.089$), leukocyte ($p = 0.538$), and neutrophil counts ($p = 0.657$), SIRI exhibited similar predictive abilities without statistically significant differences (Figs. 3, 4). Moreover, SIRI demonstrated superior predictive ability compared to NLR ($p = 0.035$), PLR ($p < 0.001$), and CRP ($p = 0.019$) individually (Figs. 3, 4). In the combined predictive models, the predictive abilities of SIRI + CRP ($p = 0.171$), SIRI + leukocyte count ($p = 0.373$), and SIRI + neutrophil count ($p = 0.295$) were comparable to that of SIRI alone, without statistically significant differences (Fig. 4). All potential significant factors associated with pneumonia occurrence were incorporated into the nomogram (Fig. 5A) to predict the probability of developing pneumonia. The calibration curves (Fig. 5B) revealed a strong agreement between the predicted and observed probabilities.

Additionally, the C-index was 0.827, and the ROC curve (Fig. 5C) demonstrated excellent discrimination with an AUC of 0.827 (95% CI 0.789–0.865) ($p < 0.001$) for the nomogram in predicting pneumonia.
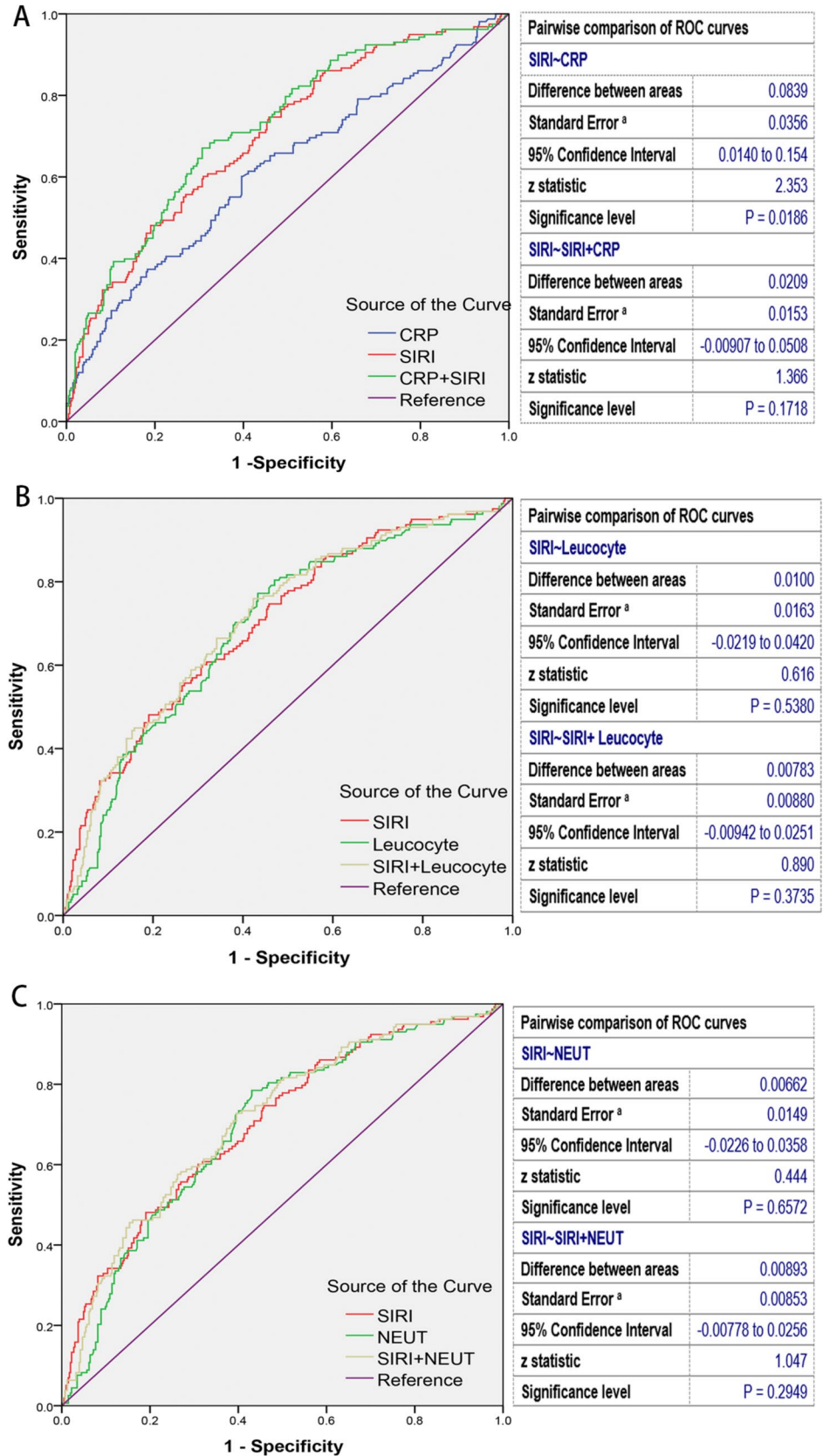
Discussions

Here, we show that a higher SIRI is associated with aSAH-associated pneumonia. Pneumonia is a common and frequent complication in patients with stroke in the first 90 days, with a peak incidence on the third day [21]. Poor functional outcome even death was correlated with aSAH-associated pneumonia [22], so the prevention of pneumonia is very important. Previous studies have shown that higher SIRI is closely associated with the severity and prognosis of stroke [23]. We investigated whether SIRI can predict aSAH-associated pneumonia and evaluated its predictive power compared with SII, NLR, and PLR. Our study demonstrated that SIRI, SII, NLR, and PLR on admission were independently

Comparison of Blood-based Biomarkers of ROC curves	
SIRI ~ SII	
Difference between areas	0.0324
Standard Error [a]	0.0191
95% Confidence Interval	-0.00495 to 0.0698
z statistic	1.701
Significance level	P = 0.0890
SIRI ~ NLR	
Difference between areas	0.0409
Standard Error [a]	0.0194
95% Confidence Interval	0.00288 to 0.0789
z statistic	2.109
Significance level	P = 0.0350
SIRI ~ PLR	
Difference between areas	0.114
Standard Error [a]	0.0288
95% Confidence Interval	0.0576 to 0.170
z statistic	3.964
Significance level	P = 0.0001
SII ~ NLR	
Difference between areas	0.00846
Standard Error [a]	0.0116
95% Confidence Interval	-0.0143 to 0.0313
z statistic	0.727
Significance level	P = 0.4670
SII ~ PLR	
Difference between areas	0.0816
Standard Error [a]	0.0149
95% Confidence Interval	0.0524 to 0.111
z statistic	5.484
Significance level	P < 0.0001
NLR ~ PLR	
Difference between areas	0.0731
Standard Error [a]	0.0191
95% Confidence Interval	0.0356 to 0.111
z statistic	3.821
Significance level	P = 0.0001

Souce of the Curve: SIRI, SII, NLR, PLR, Reference

Fig. 3 Comparison for the Predictive Ability of Blood-based Biomarkers for aSAH-associated Pneumonia. [a]DeLong et al.; ROC = receiver operating characteristic. SIRI (0.701 [0.653–0.749]); SII (0.669 [0.620–0.718]); NLR (0.665 [0.616–0.714]); PLR (0.587 [0.534–0.641]). Furthermore, the difference between SIRI and NLR ($P = 0.035$); SIRI and PLR ($P < 0.001$); SII and PLR ($P < 0.001$); NLR and PLR ($P < 0.001$) have statistical significance

Fig. 4 The Predictive Ability of SIRI, CRP, leucocyte, and neutrophil for aSAH-associated pneumonia

A

Source of the Curve
- CRP
- SIRI
- CRP+SIRI
- Reference

Pairwise comparison of ROC curves	
SIRI~CRP	
Difference between areas	0.0839
Standard Error [a]	0.0356
95% Confidence Interval	0.0140 to 0.154
z statistic	2.353
Significance level	P = 0.0186
SIRI~SIRI+CRP	
Difference between areas	0.0209
Standard Error [a]	0.0153
95% Confidence Interval	-0.00907 to 0.0508
z statistic	1.366
Significance level	P = 0.1718

B

Source of the Curve
- SIRI
- Leucocyte
- SIRI+Leucocyte
- Reference

Pairwise comparison of ROC curves	
SIRI~Leucocyte	
Difference between areas	0.0100
Standard Error [a]	0.0163
95% Confidence Interval	-0.0219 to 0.0420
z statistic	0.616
Significance level	P = 0.5380
SIRI~SIRI+ Leucocyte	
Difference between areas	0.00783
Standard Error [a]	0.00880
95% Confidence Interval	-0.00942 to 0.0251
z statistic	0.890
Significance level	P = 0.3735

C

Source of the Curve
- SIRI
- NEUT
- SIRI+NEUT
- Reference

Pairwise comparison of ROC curves	
SIRI~NEUT	
Difference between areas	0.00662
Standard Error [a]	0.0149
95% Confidence Interval	-0.0226 to 0.0358
z statistic	0.444
Significance level	P = 0.6572
SIRI~SIRI+NEUT	
Difference between areas	0.00893
Standard Error [a]	0.00853
95% Confidence Interval	-0.00778 to 0.0256
z statistic	1.047
Significance level	P = 0.2949

correlated with aSAH-associated pneumonia. ROC curve analysis and nomogram elucidated that SIRI on admission have a well predictive ability.

In several studies, an association between inflammation and the development of pneumonia has been reported. And SIRI, as an inflammatory biomarker, we found for the first time that it can be used to predict the occurrence of pneumonia. There are several convincing reasons for the close relationship between the SIRI and aSAH-associated pneumonia. The first explanation might be immunodepression after aneurysmal subarachnoid hemorrhage [9].The initial ruptured aneurysm deposits blood in the subarachnoid space [24]. Over time, the breakdown and degradation of red blood cells leads to the deposition of hemoglobin. Methemoglobin, heme, and chlorinated heme produced by the breakdown of red blood cells may lead to the activation of TLR4, an inflammatory cascade signal that damages neurons [24–29]. Due to immunosuppression, neutrophils are demarginated and stimulated by Inflammatory factors; however, lymphocytes undergo apoptosis, with a shift from pro-inflammatory Th-1–type response to an anti-inflammatory Th-2–type response; this outcome increases the susceptibility [30, 31], which may increases the probability of pneumonia following subarachnoid hemorrhage [32, 33]. Moreover, it has been reported that monocytes could be target cells in immunosuppression; monocyte deactivation, with decreased antigen presentation capacity and depressed secretion of pro-inflammatory cytokines, increased the risk for pneumonia. The second explanation might be brain injury on hospital admission. In the relationship between the acute brain injury and the occurrence of pneumonia, inflammation potentially assumes a significant role. Studies have shown that [34] following acute brain injury, there is a subsequent activation of the body's inflammatory response, triggering the activation of immune cells and the release of inflammatory factors. This cascading process has the potential to exert a notable influence on the inflammatory response within the pulmonary system, subsequently impacting the susceptibility to infection. For example, within several hours after brain injury, T cell inactivation is seen. These variations could play important roles in acute brain injury and precede pneumonia. In addition, alterations in immune system after brain injury that could develop infectious complications as follows: decrease of monocyte function; decrease of T cell functions (decreased response to mitogenic activation and decreased IL-2 production); and decrease of B cell function. However, further studies are required to confirm these hypotheses.

Our study also suggests a relation between older age ($p < 0.001$) and aSAH-associated pneumonia. Moreover, the proportion of hypertension, diabetes, hyperlipidemia, previous stroke, heart disease, previous or current smoking, previous or current drinking were significantly higher in the pneumonia group. Interestingly, we also found that the SIRI was higher when the patients were older. Previous studies have shown that patients with underlying diseases have a high inflammatory load [35] this suggested that SIRI may be a mediating effect between advanced age and pneumonia. However, further research is needed to confirm. As in previous studies, patients with aSAH-associated pneumonia had poorer outcomes during hospitalization and discharge than patients without aSAH-associated pneumonia [22, 35]. Although studies have shown that prophylactic use of antibiotics in stroke patients cannot improve their functional outcome [36] and antibiotics are not recommended for patients with elevated SIRI, enhanced respiratory management can be performed. During the patient's hospitalization, we observed a total of eight deaths. Of these, two patients did not develop pneumonia during hospitalization, as previously reported [37], which reminds us of the importance of early detection of pneumonia.

Table 3 The predictive ability of blood-based biomarkers for aSAH-associated pneumonia

| Variables	AUC	95% CI	Sensitivity	Specificity	Youden Index
SII	0.669	0.620–0.718	53.8	75	0.288
NLR	0.665	0.616–0.714	74.7	53.2	0.279
SIRI	0.701	0.653–0.749	60.1	70.8	0.292
PLR	0.587	0.534–0.641	51.3	69.1	0.204
CRP	0.617	0.576–0.658	60.1	60.4	0.205
LEUC	0.691	0.651–0.729	77.2	56.7	0.339
NEUT	0.695	0.655–0.733	78.48	56.93	0.354
SIRI + CRP	0.722	0.683–0.759	67.1	69.3	0.364
SIRI + LEUC	0.709	0.670–0.746	75.95	57.67	0.336
SIRI + NEUT	0.710	0.671–0.747	72.78	60.4	0.332

aSAH aneurysmal subarachnoid hemorrhage, *CI* confidence interval, *AUC* area under the curve, *SIRI* systemic inflammatory response index, *SII* systemic immune inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio

Strength and limitations

This study firstly showed that the SIRI on admission can predict aSAH-associated pneumonia. The strengths of this study are as follows. First, patients with aneurysmal subarachnoid hemorrhage all were treated with endovascular treatment, the mainstream treatment now, avoided the bias caused by the clipping of treatment Second, several necessary parameters for SIRI required on admission, could be obtained quickly.

Our study had several limitations. The reasons for the limited predictive ability of inflammatory biomarkers may include the following: (1) The occurrence of pneumonia is a complex process influenced by various factors, including
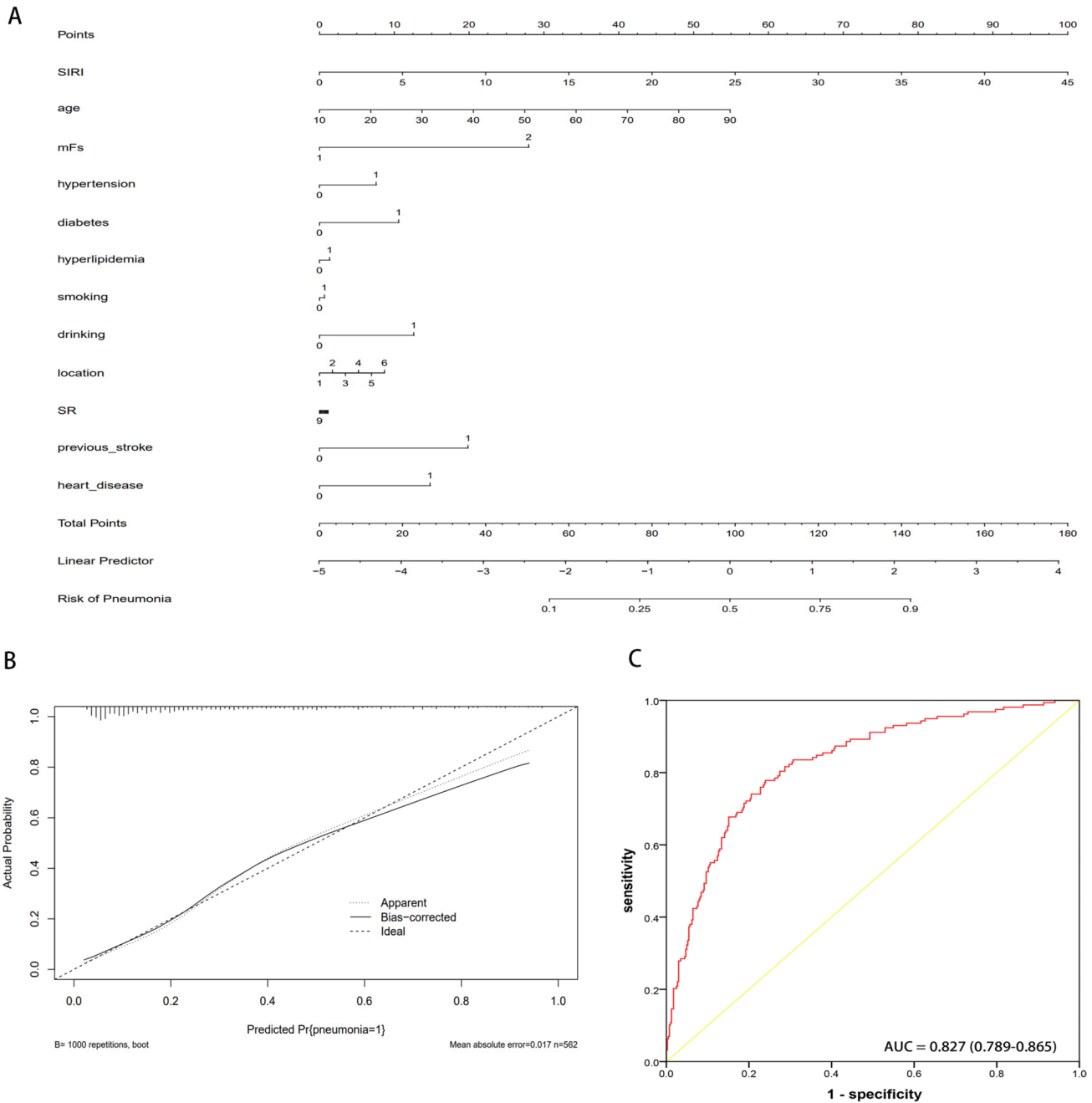
Fig. 5 Utility of nomogram for predicting pneumonia after aneurysmal subarachnoid hemorrhage by endovascular treatment. Points were age, modified Fisher score, hypertension, diabetes, hyperlipidemia, previous stroke, heart disease, previous or current smoking, previous or current drinking, location, SR and SIRI, MFS = modified Fisher score

pathogen infection, immune status, and the body's resistance. While inflammatory markers can reflect the body's inflammatory state, they may not encompass all possible factors comprehensively. (2) Sufficient sample size is required for the establishment of predictive models, and our sample size may be relatively small. (3) The lack of external validation studies on the predictive ability of inflammatory biomarkers may limit the assessment of their accuracy and stability. This is a retrospective study that restricts the generalization of the findings to some extent. Prospective multicenter studies should be considered in the future. The peak incidence of stroke-associated pneumonia usually occurred three to seven days after admission [21], and our study showed that the peak incidence of the occurrence time of pneumonia was mainly concentrated between 2–4 days after admission, with a maximum value of 16 days and a minimum value of 2 days, the SIRI on admission could not dynamically reveal the patient's inflammatory state at that time. Furthermore, our database was insufficient for collecting the specific distribution of lymphocyte subtypes (such as T cells or B cells).

Conclusions

In conclusion, SIRI is a reliable predictor for pneumonia after aneurysmal subarachnoid hemorrhage by endovascular treatment, which may provide insights into further clinical-practices of prophylactic antibiotic therapy. Nevertheless, further prospective multicenter studies are needed to verify the association between SIRI and pneumonia after aneurysmal subarachnoid hemorrhage by endovascular treatment.

Data availability We enrolled patients at three centers (Beijing Tiantan Hospital, Capital Medical University; Beijing Tongren Hospital, Capital Medical University; The Third Xiangya Hospital, Central South University) from January 2019 to September 2021. If necessary, we can provide the data set to the editor.

Declarations

Ethical approval Informed consent was obtained for all participants. This study was approved by the centers review board (Beijing Tiantan Hospital, Capital Medical University; Beijing Tongren Hospital, Capital Medical University; The Third Xiangya Hospital, Central South University) and was in accordance with the principles of the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

References

1. Zheng S, Wang H, Chen G, Shangguan H, Yu L, Lin Z et al (2021) Higher serum levels of lactate dehydrogenase before microsurgery predict poor outcome of aneurysmal subarachnoid hemorrhage. Front Neurol 12:720574. https://doi.org/10.3389/fneur.2021.720574

2. Ding C, Peng L, Lin Y, Yu L, Wang D, Kang D (2019) Elevated lactate dehydrogenase level predicts postoperative pneumonia in patients with aneurysmal subarachnoid hemorrhage. World neurosurgery 129:e821–e830. https://doi.org/10.1016/j.wneu.2019.06.041

3. Alaraj A, Hussein A, Esfahani D, Amin-Hanjani S, Aletich V, Charbel F (2017) Reducing length of stay in aneurysmal subarachnoid hemorrhage: A three year institutional experience. J Clin Neurosci: Off J Neurosurg Soc Australasia 42:66–70. https://doi.org/10.1016/j.jocn.2017.03.049

4. Levine J, Kofke A, Cen L, Chen Z, Faerber J, Elliott J et al (2010) Red blood cell transfusion is associated with infection and extracerebral complications after subarachnoid hemorrhage. Neurosurgery 66:312–8; discussion 8. https://doi.org/10.1227/01.Neu.0000363747.47587.6c

5. Frontera J, Fernandez A, Schmidt J, Claassen J, Wartenberg K, Badjatia N et al (2008) Impact of nosocomial infectious complications after subarachnoid hemorrhage. Neurosurgery 62:80–7; discussion 7. https://doi.org/10.1227/01.Neu.0000311064.18368.Ea

6. Giede-Jeppe A, Reichl J, Sprügel M, Lücking H, Hoelter P, Eyüpoglu I et al (2019) Neutrophil-to-lymphocyte ratio as an independent predictor for unfavorable functional outcome in aneurysmal subarachnoid hemorrhage. J Neurosurg 132:400–407. https://doi.org/10.3171/2018.9.Jns181975

7. Li R, Lin F, Chen Y, Lu J, Han H, Yan D et al (2021) In-hospital complication-related risk factors for discharge and 90-day outcomes in patients with aneurysmal subarachnoid hemorrhage after surgical clipping and endovascular coiling: a propensity score-matched analysis. J Neurosurg 1–12. https://doi.org/10.3171/2021.10.Jns211484

8. Chaudhry S, Kahlert U, Kinfe T, Lamprecht A, Niemelä M, Hänggi D et al (2020) Elevated systemic IL-10 Levels indicate immunodepression leading to nosocomial infections after aneurysmal subarachnoid hemorrhage (SAH) in patients. Int J Mol Sci 21. https://doi.org/10.3390/ijms21051569

9. Sarrafzadeh A, Schlenk F, Meisel A, Dreier J, Vajkoczy P, Meisel C (2011) Immunodepression after aneurysmal subarachnoid

hemorrhage. Stroke 42:53–58. https://doi.org/10.1161/strokeaha.110.594705

10. Gibson P, Cuthbertson B, Croal B, Rae D, El-Shafei H, Gibson G et al (2010) Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 105:186–191. https://doi.org/10.1016/j.amjcard.2009.09.007

11. Tao C, Wang J, Hu X, Ma J, Li H, You C (2017) Clinical value of neutrophil to lymphocyte and platelet to lymphocyte ratio after aneurysmal subarachnoid hemorrhage. Neurocrit Care 26:393–401. https://doi.org/10.1007/s12028-016-0332-0

12. Chaudhry S, Stoffel-Wagner B, Kinfe T, Güresir E, Vatter H, Dietrich D et al (2017) Elevated systemic IL-6 Levels in patients with aneurysmal subarachnoid hemorrhage is an unspecific marker for Post-SAH complications. Int J Mol Sci 18. https://doi.org/10.3390/ijms18122580

13. Warusevitane A, Karunatilake D, Sim J, Smith C, Roffe C (2016) Early Diagnosis of pneumonia in severe stroke: clinical features and the diagnostic role of C-Reactive protein. PloS one 11:e0150269. https://doi.org/10.1371/journal.pone.0150269

14. Chen Y, Sun J, Hu D, Zhang J, Xu Y, Feng H et al (2021) Predictive Value of pretreatment lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio in the survival of nasopharyngeal carcinoma patients. Cancer Manag Res 13:8767–8779. https://doi.org/10.2147/cmar.S338394

15. Yang H, Wang K, Li B, Li S, Li Y, Yuan L (2021) The prognostic role of blood inflammatory biomarkers and eGFR mutation status in stage iiia/n2 non-small cell lung cancer patients treated with tri-modality therapy. Front Oncol 11:707041. https://doi.org/10.3389/fonc.2021.707041

16. Smith C, Kishore A, Vail A, Chamorro A, Garau J, Hopkins S et al (2015) Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in Stroke Consensus Group. Stroke 46:2335–2340. https://doi.org/10.1161/strokeaha.115.009617

17. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H et al (2016) A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer 122:2158–2167. https://doi.org/10.1002/cncr.30057

18. Hu B, Yang X, Xu Y, Sun Y, Sun C, Guo W et al (2014) Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res: Off J Am Assoc Cancer Res 20:6212–6222. https://doi.org/10.1158/1078-0432.Ccr-14-0442

19. Peng L, Wang Y, Liu F, Qiu X, Zhang X, Fang C et al (2020) Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Immunol Immunother : CII 69:1813–1822. https://doi.org/10.1007/s00262-020-02585-w

20. Dommershuijsen L, Ruiter R, Erler N, Rizopoulos D, Ikram M, Ikram M (2022) Peripheral Immune cell numbers and C-Reactive protein in parkinson's disease: results from a population-based study. J Parkinson's Dis 12:667–678. https://doi.org/10.3233/jpd-212914

21. de Jonge J, van de Beek D, Lyden P, Brady M, Bath P, van der Worp H (2021) Temporal profile of pneumonia after stroke. Stroke STROKEAHA120032787. https://doi.org/10.1161/strokeaha.120.032787

22. Rass V, Gaasch M, Kofler M, Schiefecker A, Ianosi B, Rhomberg P et al (2018) Systemic inflammatory response syndrome as predictor of poor outcome in nontraumatic subarachnoid hemorrhage patients. Crit Care Med 46:e1152–e1159. https://doi.org/10.1097/ccm.0000000000003429

23. Zhang Y, Xing Z, Zhou K, Jiang S (2021) The predictive role of systemic inflammation response index (SIRI) in the prognosis of stroke patients. Clin Interv Aging 16:1997–2007. https://doi.org/10.2147/cia.S339221

24. Lucke-Wold B, Logsdon A, Manoranjan B, Turner R, McConnell E, Vates G et al (2016) Aneurysmal Subarachnoid hemorrhage and neuroinflammation: a comprehensive review. Int J Mol Sci 17:497. https://doi.org/10.3390/ijms17040497

25. Pradilla G, Chaichana K, Hoang S, Huang J, Tamargo R (2010) Inflammation and cerebral vasospasm after subarachnoid hemorrhage. Neurosurg Clin N Am 21:365–379. https://doi.org/10.1016/j.nec.2009.10.008

26. Muhammad S, Hänggi D (2021) Inflammation and anti-inflammatory targets after aneurysmal subarachnoid hemorrhage. Int J Mol Sci 22. https://doi.org/10.3390/ijms22147355

27. Atangana E, Schneider U, Blecharz K, Magrini S, Wagner J, Nieminen-Kelhä M et al (2017) Intravascular inflammation triggers intracerebral activated microglia and contributes to secondary brain injury after experimental subarachnoid hemorrhage (eSAH). Transl Stroke Res 8:144–156. https://doi.org/10.1007/s12975-016-0485-3

28. de Oliveira MA, Macdonald R (2018) Neuroinflammation as a target for intervention in subarachnoid hemorrhage. Front Neurol 9:292. https://doi.org/10.3389/fneur.2018.00292

29. Frontera J, Provencio J, Sehba F, McIntyre T, Nowacki A, Gordon E et al (2017) The Role of Platelet Activation and Inflammation in Early Brain Injury Following Subarachnoid Hemorrhage. Neurocrit Care 26:48–57. https://doi.org/10.1007/s12028-016-0292-4

30. Morga R, Dziedzic T, Moskala M, Slowik A, Pera J (2020) Clinical Relevance of changes in peripheral blood cells after intracranial aneurysm rupture. J Stroke Cerebrovasc Dis: Off J Natl Stroke Assoc 29:105293. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105293

31. Chamorro Á, Meisel A, Planas A, Urra X, van de Beek D, Veltkamp R (2012) The immunology of acute stroke. Nat Rev Neurol 8:401–410. https://doi.org/10.1038/nrneurol.2012.98

32. Prass K, Meisel C, Höflich C, Braun J, Halle E, Wolf T et al (2003) Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. J Exp Med 198:725–736. https://doi.org/10.1084/jem.20021098

33. Tam A, Ilodigwe D, Mocco J, Mayer S, Kassell N, Ruefenacht D et al (2010) Impact of systemic inflammatory response syndrome on vasospasm, cerebral infarction, and outcome after subarachnoid hemorrhage: exploratory analysis of CONSCIOUS-1 database. Neurocrit Care 13:182–189. https://doi.org/10.1007/s12028-010-9402-x

34. Lauzier D, Jayaraman K, Yuan J, Diwan D, Vellimana A, Osbun J et al (2023) Early Brain injury after subarachnoid hemorrhage: incidence and mechanisms. Stroke 54:1426–1440. https://doi.org/10.1161/strokeaha.122.040072

35. Finlayson O, Kapral M, Hall R, Asllani E, Selchen D, Saposnik G (2011) Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. Neurology 77:1338–1345. https://doi.org/10.1212/WNL.0b013e31823152b1

36. Westendorp W, Vermeij J, Zock E, Hooijenga I, Kruyt N, Bosboom H et al (2015) The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. Lancet (London, England) 385:1519–1526. https://doi.org/10.1016/s0140-6736(14)62456-9

37. Nam K, Kim T, Lee J, Kwon H, Lee Y, Ko S et al (2018) High neutrophil-to-lymphocyte ratio predicts stroke-associated pneumonia. Stroke 49:1886–1892. https://doi.org/10.1161/strokeaha.118.021228

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