Case-Control Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Association of follow-up neutrophil-to-lymphocyte ratio and systemic inflammation response index with stroke-associated pneumonia and functional outcomes in cerebral hemorrhage patients: a case-controlled study

Mengmeng Xu, MD[a], Jingru Wang, MD[a], Chenyi Zhan, MD[a], Ying Zhou, MD[a], Zhixian Luo, MD[a], Yunjun Yang, MD, PhD[b,*], Dongqin Zhu, MD[b,*]

Background: The neutrophil-to-lymphocyte ratio (NLR) and systemic inflammation response index (SIRI) at admission are independent diagnostic biomarkers in stroke-associated pneumonia (SAP). Our study aimed to investigate the association between NLR, SIRI, specifically follow-up NLR and SIRI, and SAP, as well as their relationship with functional outcomes.

Patients and methods: We retrospectively included 451 consecutive intracerebral hemorrhage patients from May 2017 to May 2019. We conducted univariate and multivariable analyses to identify the factors independently associated with SAP and poor functional outcomes.

Results: Compared to 127 (28.16%) patients diagnosed with SAP, those without SAP had both lower baseline and follow-up NLR and SIRI values ($P < 0.001$). After adjustments, we found that baseline NLR [OR, 1.039 (95% CI, 1.003–1.077); $P = 0.036$] and follow-up NLR [OR, 1.054 (95% CI, 1.011–1.098); $P = 0.012$] were independently associated with SAP. The follow-up NLR was also associated with a higher mRS [OR, 1.124 (95% CI, 1.025–1.233); $P = 0.013$] and lower ADL-MBI score [OR, 1.167 (95% CI, 1.057–1.289); $P = 0.002$] at discharge. Multivariable analysis indicated that advanced age and nasogastric tube feeding were independently associated with SAP ($P < 0.05$). We constructed a dynamic nomogram to identify SAP risk. Further subgroup analysis revealed that baseline NLR [OR, 1.062 (95% CI, 1.007–1.120); $P = 0.026$] is independently associated with SAP in the nasogastric feeding group, while follow-up NLR [OR, 1.080 (95% CI, 1.024–1.139); $P = 0.005$] was associated with the occurrence of SAP in non-nasogastric feeding patients.

Conclusions: We found elevated baseline and follow-up NLR values were associated with SAP occurrence, and increasing follow-up NLR indicated poor functional outcomes. Inflammatory markers at different stages may offer individualized guidance for patients receiving various treatments.

Keywords: Association, cerebral hemorrhage, neutrophil to lymphocyte ratio, outcome; stroke-associated pneumonia, systemic inflammation response index

Introduction

Globally, the mortality and disability of intracerebral hemorrhage (ICH) remain significantly high[1,2]. Among survivors of ICH, stroke-associated pneumonia (SAP) is the most common devastating complication, with an incidence rate of 34.6%[3]. SAP exacerbates cerebral tissue hypoxia, resulting in secondary impairments, considerable disability or functional outcome burdens, along with increased medical expenses and prolonged hospitalization of patients[3–6].

A three-year study of 20,677 patients in 14 stroke centers reveals that about one-third of stroke deaths and poor functional

[a]Department of Radiology, The First Affiliated Hospital of Wenzhou Medical University and [b]Department of Nuclear Medicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, People's Republic of China

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding authors. Address: Department of Nuclear Medicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, People's Republic of China. Tel.: +86 0577 55579667; fax: +86 55578999+664070. E-mail: zhudongqin@wmu.edu.cn (D. Zhu), and fax: +86 55578999+663972. E-mail: yyjunjim@163.com (Y. Yang).

International Journal of Surgery (2024) 110:4014–4022

Received 19 December 2023; Accepted 3 March 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 18 March 2024

http://dx.doi.org/10.1097/JS9.0000000000001329

outcomes could be intervened, such as intracranial hypertension, stroke-associated pneumonia, or other complications[7]. A cohort study of 5521 ICH patients demonstrates that SAP significantly increases the risk of complications, such as epileptic seizure, atrial fibrillation, gastrointestinal bleeding, deep vein thrombosis, decubitus ulcer, recurrent stroke, and urinary system infection, leading to poor outcomes[5]. Currently, the incidence of SAP remains high. There have been multicentre, randomized trials using antibiotics to prevent pneumonia. However, studies have not yielded satisfactory results. Neither the preventive antibiotics in stroke study (PASS)[8] nor the prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF) study[9] provides evidence to support the use of prophylactic antibiotics for reducing the incidence of pneumonia. The possible cause could be the failure to identify patients at high risk of SAP appropriately. Therefore, the imperative lies in discovering effective indicators for early recognition and prevention of SAP to improve acute stroke outcomes.

The evidence suggests that inflammation is indispensable in the pathophysiology of stroke and integral in the occurrence and progression of SAP[10]. In emergency settings, neutrophil-to-lymphocyte ratio (NLR) is a cost-effective parameter that can better predict bacteremia than conventional parameters such as CRP levels and neutrophil counts[11]. NLR is associated with COVID-19 disease progression[12]. Furthermore, studies have reported that NLR showed a better predictive ability for pneumonia after stroke than the systemic inflammation response index (SIRI)[4,13]. Inflammation is a dynamic process, and in clinical practice, clinicians sometimes repeat examine inflammatory markers to monitor patients' disease conditions. However, the association between follow-up inflammatory markers and SAP was unclear. This study aimed to explore whether the follow-up inflammatory composite markers NLR and SIRI are independently associated with SAP and poor functional outcomes in ICH patients.

HIGHLIGHTS

- Follow-up NLR was associated with SAP and poor functional outcomes of intracerebral hemorrhage patients.
- Baseline NLR was independently associated with SAP in the nasogastric feeding group.
- Follow-up NLR was independently associated with SAP in non-nasogastric feeding group.

Methods

Standard protocol approvals, registrations, and patient consents

This study was authorized by our hospital's Ethics Committee. Due to the anonymity and retrospective nature of the data, the written form of informed consent was waived. Moreover, the work conformed to the STROCSS criteria[14], Supplemental Digital Content 1, http://links.lww.com/JS9/C154 and the STROBE case-control reporting guidelines[15]. Supplemental Digital Content 2, http://links.lww.com/JS9/C155.

Study population

We retrospectively collected the data of patients diagnosed with spontaneous ICH in our hospital from May 2017 to May 2019. Patients underwent baseline and follow-up computed tomography scans within 6 and 72 hours after symptoms onset were included in this study. Exclusion criteria were as follows: (1) secondary ICH caused by traumatic brain injury, aneurysm, tumor, or arteriovenous malformation; (2) with severe hepatic or renal dysfunction, hematological or metabolic diseases; (3) use of immunosuppressants for more than three months; (4) diagnosed with pneumonia or active infection or pyrexia within two weeks before admission; (5) lack of determined primary endpoint. The study was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn). The workflow process of our study is shown in Supplemental Figure 3, Supplemental Digital Content 3, http://links.lww.com/JS9/C156. The details of the sample size calculation are shown in Supplemental Digital Content 1, http://links.lww.com/JS9/C156.

Data collection

The whole blood counts (including neutrophils, monocytes, and lymphocytes) were collected at admission, and follow-up blood counts were recorded within seven days after admission (the vast majority within 2-4 d). Previous studies have shown that the peak of inflammation markers occurs in three days after ICH[16,17]. The detailed data collected from the electronic medical record system were as follows: (1) demographic data (sex and age); (2) medical history (hypertension, diabetes, and previous history of stroke); (3) initial clinical data (nasogastric tube feeding, mechanical ventilation, neurosurgery, GCS scores, Braden scores, and ADL-MBI scores[18]. We gathered nasogastric tube feeding information to evaluate dysphagia since individuals with dysphagia generally require such interventions[19]); (4) imaging features (baseline and follow-up hematoma volume, hematoma expansion, and the presence of IVH. We used the 'level tracing' and 'draw' functions of three dimensional Slicer software to measure the baseline and follow-up volume of the hematoma[20]); and (5) other laboratory examination variables (blood glucose, albumin, PT, and APTT). Composite indices NLR and SIRI were calculated using the formula NLR = neutrophil count/lymphocyte count and SIRI = (neutrophil count × monocyte count)/lymphocyte count.

Study outcomes

The primary endpoint was stroke-associated pneumonia. SAP was the recommended term for lower respiratory tract infections within 7 days after stroke. According to the 2015 consensus[21], SAP diagnoses were based on intracerebral hemorrhage in combination with the clinical manifestations of pneumonia (fever, cough, and dyspnea), positive chest computed tomography scans, and positive laboratory examinations. They were confirmed through records of antibiotic use during hospitalization. The secondary outcomes were the length of hospitalization and functional outcomes. We used the mRS score and ADL-MBI score to assess the functional outcomes of the ICH patients. Patients with an mRS score of 0–2 or an ADL-MBI score of more than 61 were classified as having good functional outcomes, whereas those with an mRS score of 3–6 or an ADL-MBI score of 0-60 were considered to have poor functional outcomes[22,23].

Statistical analysis

We classified patients into the SAP group and the non-SAP group. Continuous variables were demonstrated as means ± standard deviation (SD) or medians (interquartile range, [IQR]). Categorical variables were presented as counts (with percentages). Global burden of disease data reveals that a quarter of the disease burden is shouldered by people aged 60 and above[24]. Furthermore, considering binary values were more accessible to implement in clinical practice than continuous values, we dichotomized the specific ages into advanced and non-advanced ages. In addition, the Chi-square test was used to assess correlations and differences between categorical variables. For continuous variables, we compared intergroup differences using the Mann-Whitney U test or Student t-test as appropriate. The method of missing values handling is shown in Supplemental Digital Content 2, http://links.lww.com/JS9/C156.

Regarding whether inflammatory indicators were genuinely related to SAP, we divided the variables into three categories in chronological order[25]. Then, we gradually introduced one, two, and three sets of variables to correct for the association between inflammatory indicators and SAP[26]. Afterward, inflammatory and clinical variables with P values less than 0.05 were further analyzed in multicollinearity analysis. We detected the multicollinearity through variance inflation factor (VIF) less than 5 or tolerance greater than 0.1[27]. After excluding multicollinearity between variables, all factors were included in a multivariable logistic regression model to identify independent predictors of SAP. We plotted the receiver operating characteristic (ROC) curves to evaluate the predictive performance of models. The DeLong test was used to compare the AUC differences between different models. We constructed the dynamic nomogram to visualize the final predictive model.

Statistical analyses were performed with SPSS (version 27), R (version 4.2.2), and MedCalc (version 20.0). A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Comparison of clinical characteristics

A total of 451 patients were included in this study. Table 1 shows that 127 (28.16%) ICH patients developed SAP, of which 90 (70.90%) were male. In the SAP group, the number of patients with advanced age (aged ≥60) was 76 (59.80%), while in the non-SAP group, the number of patients with advanced age was 126 (38.90%) ($P<0.001$). The number of patients who underwent nasogastric tube feeding was 78 (61.90%) and 81 (25.00%) in the SAP and non-SAP group, respectively ($P<0.001$). The median of Braden and ADL-MBI scores at admission in the SAP group were 14.00 (13.00–16.00) and 10.00 (0.00–20.00), respectively. Patients with SAP showed significantly lower admission Braden scores and ADL-MBI scores (all $P<0.001$), and a higher percentage with a history of stroke ($P=0.047$) than those without SAP. In terms of imaging features, the patients with SAP had a larger median baseline hematoma volume [17.84 (9.18, 28.06) vs. 12.80 (6.94, 24.38), $P=0.003$] and a higher proportion of IVH [58 (45.70%) vs. 104 (32.10%), $P=0.007$]. Compared to the non-SAP group, the SAP group had a more extended hospital stay [18.00 (14.00, 28.00) days vs. 15.00 (12.00, 21.75) days; $P<0.001$]. There was no significant

Table 1

Comparisons of clinical characteristics between stroke-associated pneumonia (SAP) and non-SAP groups.

Characteristics	SAP ($N=127$) [n (%)]	Non-SAP ($N=324$) [n (%)]	P
Demographic			
Age (years)			**<0.001**
<60	51 (40.20)	198 (61.10)	
≥60	76 (59.80)	126 (38.90)	
Male	90 (70.90)	208 (64.20)	0.179
Medical history			
Smoking[a]	47 (37.30)	96 (29.60)	0.117
Alcohol consumption[a]	48 (38.10)	100 (30.90)	0.143
Hypertension[a]	90 (71.40)	243 (75.00)	0.438
Diabetes mellitus[a]	17 (13.50)	51 (15.70)	0.550
Previous stroke	17 (13.40)	24 (7.40)	**0.047**
Admission clinical status			
Nasogastric tube feeding[a]	78 (61.90)	81 (25.00)	**<0.001**
Mechanical ventilation[a]	25 (19.80)	54 (16.70)	0.427
Neurosurgery[a]	14 (11.10)	42 (13.00)	0.593
Admission measurements			
SBP, mmHg[b]	159.40 ± 23.49	156.84 ± 23.92	0.309
DBP, mmHg[b]	90.00 (79.25,101.00)	89.00 (80.00,100.00)	0.664
Admission GCS score[c]			**<0.001**
3–4	7 (5.60)	11 (3.40)	
5–12	62 (49.20)	72 (22.50)	
13–15	57 (45.20)	237 (74.10)	
Admission Braden score[a]	14.00 (13.00,16.00)	16.00 (14.00,17.00)	**<0.001**
Admission ADL-MBI score[d]	10.00 (0.00,20.00)	25.00 (10.00,40.00)	**<0.001**
Imaging features			
Location of ICH			0.775
Deep	101 (79.50)	253 (78.10)	
Lobe	11 (8.70)	25 (7.70)	
Infratentorial	15 (11.80)	46 (14.20)	
Baseline hematoma volume, ml	17.84 (9.18,28.06)	12.80 (6.94,24.38)	**0.003**
Follow-up hematoma volume, ml	20.39 (9.26,34.32)	13.69 (7.19,25.84)	**<0.001**
Hematoma expansion	31 (24.40)	54 (16.70)	0.059
Presence of IVH	58 (45.70)	104 (32.10)	**0.007**
Time from onset to initial CT, h	3.50 (2.00,4.50)	3.00 (2.00,4.00)	**0.035**
Time from onset to follow-up CT[a], h	20.00 (12.88,28.00)	21.00 (12.50,29.00)	0.537
Laboratory testing, median [IQR]			
Leucocyte count, ×109/L	9.92 (7.97,12.31)	8.52 (6.65,10.82)	**<0.001**
Platelet count[e], ×109/L	196.50 (172.75,230.25)	206.00 (167.00,249.75)	0.223
Neutrophil count[f], ×109/L	7.97 (5.92,10.30)	6.50 (4.39,9.30)	**<0.001**
Monocyte count[f], ×109/L	0.47 (0.35,0.61)	0.45 (0.33,0.60)	0.354
Lymphocyte count[f], ×109/L	1.01 (0.74,1.47)	1.29 (0.92,1.81)	**<0.001**
Follow-up neutrophil count[g], ×109/L	7.96 (6.40,10.88)	6.27 (4.95,8.76)	**<0.001**
Follow-up monocyte count[g], ×109/L	0.64 (0.46,0.84)	0.58 (0.46,0.80)	0.332
Follow-up lymphocyte count[g], ×109/L	0.98 (0.71,1.37)	1.23 (0.94,1.58)	**<0.001**
Baseline NLR[f]	7.62 (4.19,12.89)	5.03 (2.76,9.21)	**<0.001**
Baseline SIRI[f]	3.33 (1.84,5.82)	2.18 (1.11,4.24)	**<0.001**
Follow-up NLR[g]	8.21 (5.83,12.29)	5.23 (3.30,8.49)	**<0.001**
Follow-up SIRI[g]	5.05 (3.04,9.00)	3.03 (1.73,5.50)	**<0.001**

Table 1

(*Continued*)

Characteristics	SAP (*N* = 127) [n (%)]	Non-SAP (*N* = 324) [n (%)]	*P*
Glucose level[h], mmol/ml	7.20 (6.10,9.30)	7.15 (6.10,8.60)	0.509
Albumin[i], g/L	39.75 (35.65,43.10)	40.10 (37.00,42.90)	0.372
PT[a], s	13.10 (12.50,13.90)	12.90 (12.50,13.50)	0.077
APTT[a], s	34.25 (31.18,37.83)	33.50 (31.13,36.50)	0.147
Outcome, median [IQR]			
Hospitalization time, day	18.00 (14.00,28.00)	15.00 (12.00,21.75)	**< 0.001**
mRS score at discharge[g]			**< 0.001**
0–2	18 (14.80)	99 (30.90)	
3–6	104 (85.20)	221 (69.10)	
ADL-MBI score at discharge[j]	15.00 (0.00,35.00)	35.00 (21.00,50.00)	**< 0.001**

Bold text values represent *P* values less than 0.05.
[a]1/451(0.22%) missing values.
[b]8/451(1.77%) missing values.
[c]5/451(1.11%) missing values.
[d]4/451(0.89%) missing values.
[e]25/451(5.54%) missing values.
[f]30/451(6.65%) missing values.
[g]9/451(2.00%) missing values.
[h]3/451(0.67%) missing values.
[i]16/451(3.55%) missing values.
[j]2/451(0.44%) missing values.
Abbreviations: ADL, activities of daily living; APTT, activated partial thromboplastin time and mRS, modified Rankin Scale; CT, computed tomography; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MBI, modified Barthel index; NLR, neutrophil to lymphocyte ratio; PT, prothrombin time; SAP, stroke-associated pneumonia; SBP, systolic blood pressure; SIRI, systemic inflammation response index.

difference in the history of hypertension and diabetes mellitus between the SAP and non-SAP groups.

Univariate analysis of inflammatory indexes and SAP

The comparison of combined inflammatory indicators between SAP and non-SAP groups is listed in Table 1 and Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/JS9/C156. The baseline NLR and SIRI of the SAP group were significantly higher than those of the non-SAP group [7.62 (4.19,12.89) vs. 5.03 (2.76,9.21), $P < 0.001$; 3.33 (1.84, 5.82) vs. 2.18 (1.11, 4.24), $P < 0.001$]. Moreover, the follow-up NLR and SIRI of the SAP group were also higher than those of the non-SAP group [8.21 (5.83,12.29) vs. 5.23 (3.30, 8.49), $P < 0.001$; 5.05 (3.04, 9.00) vs. 3.03 (1.73, 5.50), $P < 0.001$]. As shown in Tables 2 and 3, we gradually introduced three sets of variables and developed four models. The three sets of variables were categorized according to different collection orders, including the first set (demographics and medical conditions), the second set (admission clinical status and admission measurements), and the third set (imaging features and blood results).

Table 2

The variables were divided into three groups based on the acquisition time.

First	Second	Third
Demographic	Admission clinical status	Imaging features
Age	Nasogastric tube feeding	Baseline hematoma volume
Male	Mechanical ventilation	Follow-up ICH volume
	Neurosurgery	Hematoma expansion
Medical conditions		Presence of IVH
Smoking	Admission measurements	
Alcohol consumption	SBP	Blood results
Hypertension	DBP	Glucose
Diabetes	GCS score	Albumin
Previous stroke	Braden score	
	ADL-MBI score	

Multivariate logistic regression of risk factors for SAP

Regarding whether inflammatory indicators were genuinely related to SAP, we gradually introduced one, two, and three sets of variables in chronological order (Table 3). After adjusting for confounders, logistic regression analysis revealed that elevated baseline NLR [OR, 1.038 (95% CI, 1.000–1.077); $P = 0.049$] and follow-up NLR [OR, 1.051 (95% CI, 1.008–1.097); $P = 0.020$] during the hospitalization were still associated with SAP. As shown in Table 3, there was no significant difference in baseline SIRI and follow-up SIRI between the SAP and non-SAP groups after introducing the second and third sets of variables. Multicollinearity was not observed between the independent predictors and SAP (VIF for all < 5). Subsequently, the clinical predictors with univariate analysis *P* less than 0.05, such as advanced age (≥ 60), previous stroke, nasogastric tube feeding, baseline ADL-MBI score, the presence of IVH, and potential inflammatory indicators related to SAP, were separately included with 'backward: LR' method to perform logistic regression. After collinearity analysis, statistically significant clinical and inflammatory indicators were subjected to multivariate logistic regression. Eventually, the results showed that independent risk factors of SAP were baseline NLR [OR, 1.039 (95% CI, 1.003–1.077); $P = 0.036$], follow-up NLR [OR, 1.054 (95% CI, 1.011–1.098); $P = 0.012$]. Notably, after adjustments, the independent association between advanced age [OR, 2.223 (95% CI, 1.364–3.622); $P = 0.001$], nasogastric tube feeding [OR, 3.441 (95% CI: 2.106–5.623); $P < 0.001$] and SAP still existed (Table 4).

To evaluate the additional predictive value of follow-up NLR, we constructed two models named model 1 and model 2. Model 1 contained baseline NLR, nasogastric tube feeding, and advanced age. Model 2 contained baseline NLR, follow-up NLR, nasogastric tube feeding, and advanced age.

The ROC curves and dynamic nomogram of SAP

The ROC curves of the models are shown in Fig. 1. The AUC, sensitivity, and specificity of the follow-up NLR were 0.702 (95% CI, 0.657–0.744), 67.5%, and 67.4%, respectively, indicating good SAP predictive power. As for baseline NLR, the optimal cut-off value of baseline NLR for identifying SAP was 5.55, which yielded a sensitivity of 64.9%, a specificity of 56.7%, and an AUC of 0.628 (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/C156). Model 2 showed better SAP predictive power than Model 1 (AUC, 0.769 vs. 0.740; $P = 0.020$). Model 2 yielded a sensitivity of 77.1% and a specificity of 67.6%. As model 2 presented the best predictive performance, we used it as the final predictive model and constructed an online dynamic nomogram to visualize it (Fig. 2 and https://pneumonia.shinyapps.io/SAPapp/).

Table 3

The association of baseline and follow-up neutrophil to lymphocyte ratio (NLR), systemic inflammation response index (SIRI) with stroke-associated pneumonia (SAP).

The Association of Baseline and follow-up NLR, SIRI with SAP; Odds Ratio (95% CI)				
Groups of variables in model	**Baseline NLR**	**Baseline SIRI**	**Follow-up NLR**	**Follow-up SIRI**
Univariate	**1.067 (1.034–1.102)**	**1.110 (1.049–1.175)**	**1.086 (1.049–1.124)**	**1.036 (1.004–1.069)**
First[a]	**1.058 (1.024–1.094)**	**1.081 (1.018–1.148)**	**1.089 (1.050–1.130)**	**1.032 (1.000–1.064)**
First and second[b]	**1.037 (1.001–1.074)**	1.047 (0.982–1.117)	**1.058 (1.016–1.102)**	1.005 (0.976–1.036)
First, second and third[c]	**1.038 (1.000–1.077)**	1.048 (0.980–1.119)	**1.051 (1.008–1.097)**	1.001 (0.969–1.035)

Bold text values represent *P* values less than 0.05.
[a]Adjusted for age, sex, smoking, drinking, hypertension, diabetes, and stroke history;
[b]Additionally adjusted for nasogastric tube feeding, mechanical ventilation, neurosurgery, SBP, DBP, GCS score, Braden score, ADL-MBI score;
[c]Additionally adjusted for baseline and follow-up hematoma volume, hematoma expansion, IVH, glucose, and albumin.

The relationship between NLR and SAP in patients with and without nasogastric tube feeding

After stratifying the patients according to the exposure to nasogastric tube feeding, we found that in the nasogastric tube feeding group, elevated baseline NLR [OR, 1.062 (95% CI, 1.007–1.120); $P = 0.026$] was a significant risk factor for SAP, while follow-up NLR ($P = 0.523$) was not significantly associated with SAP (Supplementary Table 2, Supplemental Digital Content 3, http://links.lww.com/JS9/C156). In contrast, in the non-nasogastric tube feeding group, elevated follow-up NLR [OR; 1.080 (95% CI, 1.024–1.139); $P = 0.005$] was associated with an increased risk of SAP, while baseline NLR ($P = 0.495$) did not remain significantly associated with SAP.

Association between inflammatory indexes and functional outcomes

Based on mRS and ADL-MBI scores at discharge, we divided patients into subgroups with good or poor functional outcomes and compared the inflammatory index between the two groups. As shown in Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/JS9/C156, patients in the poor functional outcomes group had a significantly higher follow-up NLR than those in the good functional group [6.35 (4.04,10.05) vs. 4.05 (2.74, 7.22), $P < 0.001$]. Univariate analysis clinical predictors with $P < 0.05$ were subjected to multivariate logistic regression using the "backward: LR" method. Subsequently, as shown in Supplementary Table 4, Supplemental Digital Content 3, http://links.lww.com/JS9/C156, no statistically significant association was identified between follow-up SIRI ($P = 0.110$) and baseline NLR ($P = 0.085$) for the functional outcomes.

Follow-up NLR was an independent risk factor for poor functional outcomes (no matter using mRS or ADL-MBI criteria). As presented in Supplementary Figure 2, Supplemental Digital Content 3, http://links.lww.com/JS9/C156, the AUC of follow-up NLR for SAP prediction was 0.683 in mRS criterion and 0.665 in the ADL-MBI criterion, respectively. Of note, no matter which prognostic measurement was used, there was an independent association between follow-up NLR and functional outcomes.

Table 4

Univariate and multivariate analyses of the potential inflammatory and clinical predictors related to stroke-associated pneumonia (SAP) in cerebral hemorrhage patients.

	Univariate analysis	**Multivariate logistics regression[a] (Stepwise)**		**Multivariate logistics regression[b] (Stepwise)**	
Variable	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Inflammatory indicators					
Baseline NLR	**< 0.001**	1.054 (1.018,1.092)	**0.003**	1.039 (1.003,1.077)	**0.036**
Baseline SIRI	**< 0.001**	—	0.327	—	—
Follow-up NLR	**< 0.001**	1.067 (1.028,1.108)	**< 0.001**	1.054 (1.011,1.098)	**0.012**
Follow-up SIRI	**< 0.001**	—	0.732	—	—
Clinical characteristics					
Age(years) < 60 vs. ≥ 60	**< 0.001**	2.012 (1.275,3.176)	**0.003**	2.223 (1.364,3.622)	**0.001**
Previous stroke	**0.047**	—	0.265	—	—
Nasogastric tube feeding	**< 0.001**	3.344 (1.977,5.657)	**< 0.001**	3.441 (2.106,5.623)	**< 0.001**
Admission GCS score	**< 0.001**	—	0.211	—	—
Admission Braden score	**< 0.001**	—	0.410	—	—
Admission ADL-MBI score	**< 0.001**	0.982 (0.967,0.998)	**0.031**	—	0.248
Time from onset to initial CT, h	**0.035**	—	0.168	—	—
Baseline hematoma volume, ml	**0.003**	—	0.616	—	—
Follow-up hematoma volume, ml	**< 0.001**	—	0.359	—	—
Presence of IVH	**0.007**	1.486 (0.929,2.375)	0.098	—	—

Bold text values represent *P* values less than 0.05.
[a]Multivariable logistic regression (backward) was performed separately for inflammatory factors and clinical indicators.
[b]Inflammatory and clinical indicators with *P* less than 0.05 were combined for multivariate logistic regression.

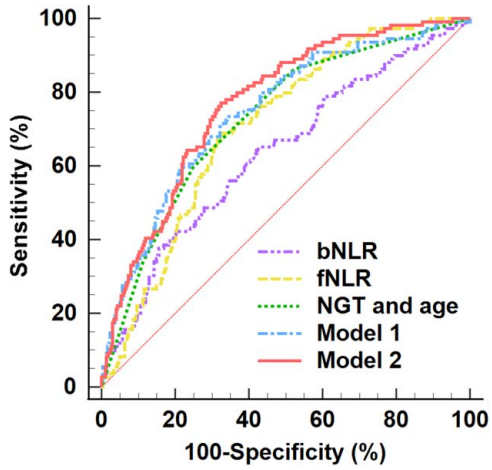

Figure 1. Receiver operator curves of baseline NLR, follow-up NLR, and clinical indicators for predicting SAP.

Discussion

In this study, we examined the association between NLR, SIRI (baseline and follow-up), and SAP and also explored the relationship between inflammatory indicators and poor functional outcomes. Baseline NLR and follow-up NLR levels were significantly higher in patients with SAP. Moreover, it was presented that in the non-nasogastric feeding group, follow-up NLR was significantly associated with SAP, while a significant association was observed between baseline NLR and SAP in the nasogastric feeding group. In addition, patients with elevated follow-up NLR were inclined to experience poor functional outcomes at discharge. Finally, we developed a dynamic nomogram to identify the individual risk of SAP.

Our research results were in keeping with the previous analysis of stroke-associated pneumonia. The incidence of SAP was about 28.2%[28]. ICH patients with advanced age, more severe neurological impairment at admission, underwent nasogastric tube feeding, and higher NLR values were more likely to encounter SAP[29–31]. Several easy-to-use scales, such as the A2DS2[32], AIS-APS[33], PANTHERIS[34], and the ISAN scores[35], have been previously recognized as promising tools for predicting SAP in routine clinical practice. There was also a prediction model based on deep learning[36]. Nevertheless, antibiotics are not recommended to prevent poststroke pneumonia in patients with dysphagia[9]. Preventive use of antibiotics does not affect functional outcomes or mortality, and no preventive effect on pneumonia has been found in either hemorrhagic or ischemic stroke patients[37]. This phenomenon may be explained by the fact that patients with varying risks of pneumonia received the same preventive antibiotics without finding suitable indicators to screen ICH patients prone to developing SAP.

To our knowledge, similar studies concerning follow-up inflammatory indicators are scarce, and our study examined the relationship between follow-up NLR, SIRI, and SAP. After adjusting for confounders, we found that both baseline NLR and

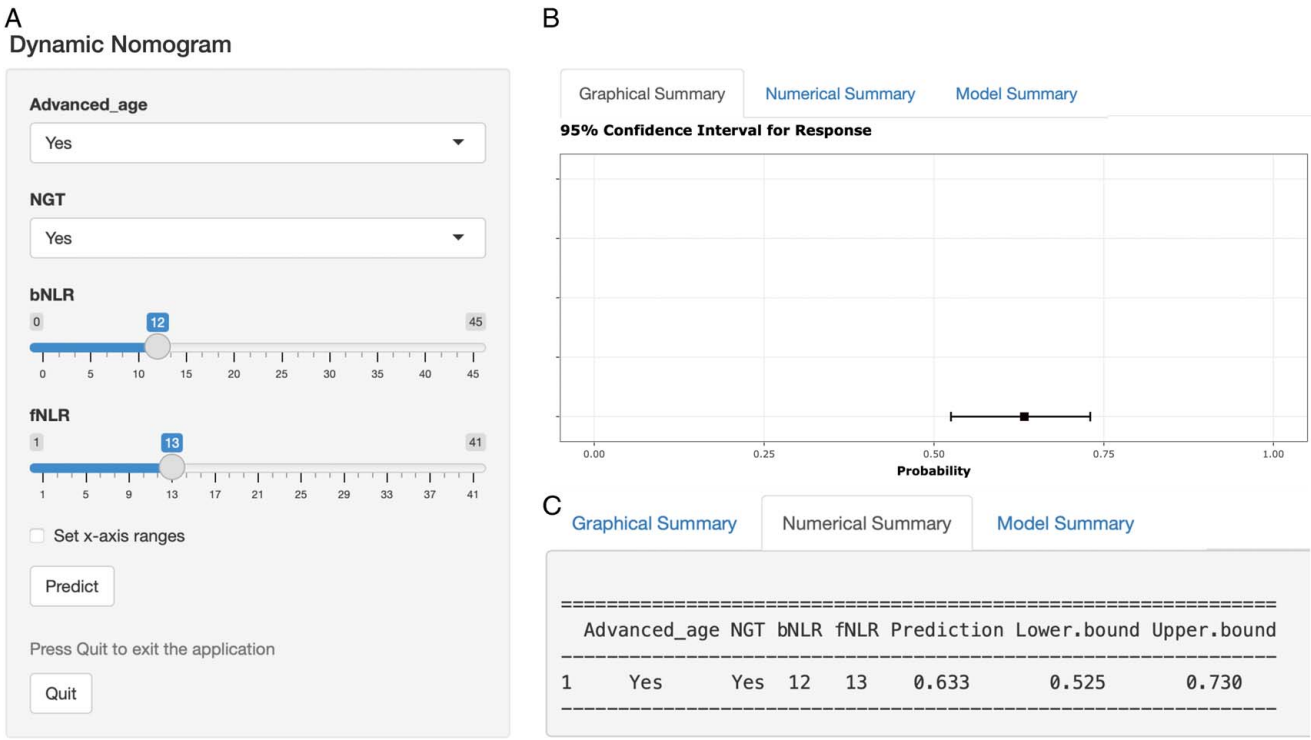

Figure 2. Online dynamic nomogram accessible at https://pneumonia.shinyapps.io/SAPapp/. A. Established nomogram for the prediction of SAP. The user can input patient information like advanced age (age ≥ 60), NGT (nasogastric tube feeding), bNLR (baseline NLR), and fNLR (follow-up NLR) in this interface. B. Depicting an example of an 81-year-old (advanced age) male who underwent nasogastric tube feeding with a baseline NLR of 12 and a follow-up NLR of 13. The patient yielded a risk of SAP 0.633 with a 95% CI: 0.525–0.730, and on the sixth day from ICH onset, he was diagnosed with SAP. C. Numerical summary shows the actual values of SAP probability and 95% confidence intervals.

follow-up NLR were independently associated with SAP. Interestingly, the follow-up NLR was also associated with a higher mRS score and lower ADL-MBI score at discharge.

Stroke activates the autonomic nervous system and the stress axis, disrupting the balance between the immune and the central nervous systems, leading to secondary immunodeficiency, significantly increasing the chance of infections, and stroke-associated pneumonia (SAP)[38,39]. The inflammatory response after stroke is a defense mechanism against infection. However, it may also lead to neurological sequelae, as infections occurring after stroke complicate up to one-third of conditions and are strongly associated with the poor outcomes of stroke patients[40,41]. NLR integrates information from the innate and adaptive immune systems and is a rapid and straightforward parameter reflecting systemic inflammation and stress response in critically ill patients. Previous studies[42,43], including a meta-analysis of 6302 stroke patients, have shown that elevated NLR, SIRI, MLR, and PLR are associated with SAP and may be valuable and valid biomarkers to help predict SAP. The NLR can not only predict pneumonia and delirium after stroke[44] but also the poor functional outcomes of aneurysmal subarachnoid hemorrhage[45]. According to the above reasons, it is not difficult to understand that elevated NLR is highly associated with SAP and poor functional outcomes.

Furthermore, this study confirmed that Model 2, which incorporated baseline NLR, follow-up NLR, advanced age, and nasogastric tube feeding, exhibited a higher AUC and possessed better predictive power for SAP than Model 1. Why is the elevated follow-up NLR associated with SAP and poor functional outcomes? One possible explanation is that inflammation is a dynamic process[46], and monitoring the follow-up level of inflammatory indicators may accurately reflect the body's inflammatory and immunologic status[47]. Another possible reason could be that follow-up NLR reflects the effectiveness of treatment during hospitalization[48]. Based on the level of follow-up results, clinicians might consider the presence of infection-related complications associated with ICH and select suitable treatment measures timely.

Moreover, we categorized the patients into two groups based on whether they received nasogastric feeding. In the nasogastric tube feeding group, the significant association between elevated baseline NLR and SAP may be due to mechanical irritation, which could trigger inflammatory responses that affect the patient's immune system and weaken resistance to infection. However, in the non-nasogastric feeding group, inflammation response may be primarily caused by the ICH. Elevated NLR levels during the follow-up period may indicate that patients with impaired immune systems failed to respond effectively to inflammation[47], thereby increasing the risk of SAP. These results might suggest that inflammatory markers at different stages may be suitable for patients with different treatments, potentially providing them with tailored guidance.

We selected patients in the pre-COVID-19 pandemic years (2017–2019) to exclude viral pneumonia as much as possible because of the similarity and difficulty in differentiating the clinical presentation of COVID-19 from SAP. Last but not least, the elevated follow-up NLR had good performance in identifying SAP, and compared to other indicators, the measurement method was more straightforward, cheaper, and easier to accept, such as the ability to collect blood even when the patient is unconscious. We established a model to predict SAP and turned it into a user-friendly online dynamic nomogram accessible at https://pneumonia.shinyapps.io/SAPapp/. It might help evaluate the risk of SAP.

The current study has some limitations. Firstly, it is essential to acknowledge that this study is limited by its observational and retrospective design nature. We cannot guarantee that the laboratory examination results were observed before the initial onset of the SAP, which is a source of bias. However, this reflects real-world practice and could also be taken as evidence for the generalizability of our findings. Most of the follow-up blood samples were collected within 2–4 days, and the peak incidence of pneumonia was the third day after stroke, with a median onset time of the fourth day, making the first four days after stroke the optimal time to evaluate pneumonia prevention strategies[49]. Secondly, this was a single-center study conducted at a large tertiary hospital in Southern Zhejiang, and the findings might have limited generalizability in all hospitals in China that care for ICH patients, including smaller community hospitals. Thirdly, we have explored the short-term functional outcomes between baseline and follow-up NLR and SIRI. The association between follow-up NLR and the medium- or long-term functional outcomes remains unknown. Hence, we urge caution in interpreting our findings, and future prospective and multicenter research is needed to explore the association between inflammatory indicators and medium- or long-term functional outcomes.

Conclusion

We found that elevated baseline and follow-up NLR were significantly associated with SAP and poor functional outcomes in ICH patients. Moreover, we established a dynamic nomogram to identify the individual risk of SAP. Subgroup analysis of the non-nasogastric feeding group demonstrated a significant association between follow-up NLR and SAP, while in the nasogastric feeding group, baseline NLR exhibited a significant association with SAP. Follow-up NLR is a readily available and cost-effective serum biomarker that may assist in discovering SAP or monitoring short-term functional outcomes in ICH patients. This finding may serve as a reminder that patients receiving different treatments may require monitoring of inflammatory biomarkers at different stages to evaluate disease progression. Thus, it is crucial for clinicians to regularly monitor the trends of inflammatory indicators in patients to determine the direction of the disease progression and make timely decisions.

Ethical approval

This study was approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (No. Y2019-027-01).

Consent

Due to the anonymity and retrospective nature of the data, the written form of informed consent was waived.

Sources of funding

This study was supported by the Wenzhou Major Program of Science and Technology Innovation (Grant No. ZY2020012) and Key Laboratory of Novel Nuclide Technologies on Precision

Diagnosis and Treatment and clinical Transformation of Wenzhou City (2023HZSY0012).

Author contribution

Conception and design of the study: Y-J.Y and D-Q.Z.; acquisition and analysis of data: M-M.X., C-Y.Z., J-R.W., Y.Z., Z-X.L., and D-Q.Z.; drafting a significant portion of the manuscript or figures: M-M.X and J-R.W., and manuscript review: all.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

The study was registered at Chinese Clinical Trial Registry (www.chictr.org.cn), number ChiCTR2200064360.

Guarantor

Dongqin Zhu and Yunjun Yang.

Data availability statement

Data are available from the corresponding author upon reasonable request.

Provenance and peer review

None.

Acknowledgements

None.

References

[1] Cordonnier C, Demchuk A, Ziai W, *et al*. Intracerebral haemorrhage: current approaches to acute management. Lancet 2018;392:1257–68.
[2] Sheth KN. Spontaneous Intracerebral Hemorrhage. N Engl J Med 2022; 387:1589–96.
[3] Wang Y-J, Li Z-X, Gu H-Q, *et al*. China Stroke Statistics: an update on the 2019 report from the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. Stroke and Vascular Neurology 2022;7:415–50.
[4] Nam KW, Kim TJ, Lee JS, *et al*. High Neutrophil-to-Lymphocyte Ratio Predicts Stroke-Associated Pneumonia. Stroke 2018;49:1886–92.
[5] Ji R, Wang D, Shen H, *et al*. Interrelationship Among Common Medical Complications After Acute Stroke. Stroke 2013;44:3436–44.
[6] Miller CM, Behrouz R. Impact of Infection on Stroke Morbidity and Outcomes. Curr Neurol Neurosci Rep 2016;16:83.
[7] Koennecke HC, Belz W, Berfelde D, *et al*. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. Neurology 2011;77:965–72.
[8] Westendorp WF, Vermeij JD, Zock E, *et al*. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. Lancet 2015;385:1519–26.
[9] Kalra L, Irshad S, Hodsoll J, *et al*. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. The Lancet 2015;386:1835–44.
[10] Faura J, Bustamante A, Miró-Mur F, *et al*. Stroke-induced immunosuppression: implications for the prevention and prediction of post-stroke infections. J Neuroinflammation 2021;18:127.
[11] de Jager CPC, van Wijk PTL, Mathoera RB, *et al*. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Critical Care 2010;14:R192.
[12] Ponti G, Maccaferri M, Ruini C, *et al*. Biomarkers associated with COVID-19 disease progression. Critical Reviews in Clinical Laboratory Sciences 2020;57:389–99.
[13] Wang R-H, Wen W-X, Jiang Z-P, *et al*. The clinical value of neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) for predicting the occurrence and severity of pneumonia in patients with intracerebral hemorrhage. Frontiers in Immunology 2023; 14:1115031.
[14] Mathew G, Agha R, Albrecht J, *et al*. STROCSS 2021: Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021;96:106165.
[15] von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.
[16] Rendevski V, Aleksovski B, Mihajlovska Rendevska A, *et al*. Inflammatory and oxidative stress markers in intracerebral hemorrhage: Relevance as prognostic markers for quantification of the edema volume. Brain Pathol 2023;33:e13106.
[17] Ohashi SN, DeLong JH, Kozberg MG, *et al*. Role of Inflammatory Processes in Hemorrhagic Stroke. Stroke 2023;54:605–19.
[18] Legg LA, Lewis SR, Schofield-Robinson OJ, *et al*. Occupational therapy for adults with problems in activities of daily living after stroke. Cochrane Database Syst Rev 2017;7:Cd003585.
[19] Gomes CAR Jr, Andriolo RB, Bennett C, *et al*. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. Cochrane Database of Systematic Reviews 2015;2017:Cd008096.
[20] Zhu DQ, Chen Q, Xiang YL, *et al*. Predicting intraventricular hemorrhage growth with a machine learning-based, radiomics-clinical model. Aging (Albany NY) 2021;13:12833–48.
[21] Smith CJ, Kishore AK, Vail A, *et al*. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke 2015;46:2335–40.
[22] Yu H, Chen X, Guo X, *et al*. The clinical value of serum xanthine oxidase levels in patients with acute ischemic stroke. Redox Biology 2023;60: 102623.
[23] Bader ER, Pana TA, Barlas RS, *et al*. Elevated inflammatory biomarkers and poor outcomes in intracerebral hemorrhage. J Neurol 2022;269: 6330–41.
[24] Chatterji S, Byles J, Cutler D, *et al*. Health, functioning, and disability in older adults--present status and future implications. Lancet 2015;385: 563–75.
[25] Nolde JM, Schlaich MP, Sessler DI, *et al*. Machine learning to predict myocardial injury and death after non-cardiac surgery. Anaesthesia 2023;78:853–60.
[26] Mc Carthy CE, Yusuf S, Judge C, *et al*. Sleep Patterns and the Risk of Acute Stroke. Neurology 2023;100:e2191–203.
[27] Lv XN, Shen YQ, Li ZQ, *et al*. Neutrophil percentage to albumin ratio is associated with stroke-associated pneumonia and poor outcome in patients with spontaneous intracerebral hemorrhage. Front Immunol 2023;14:1173718.
[28] Yan J, Zhai W, Li Z, *et al*. ICH-LR2S2: a new risk score for predicting stroke-associated pneumonia from spontaneous intracerebral hemorrhage. J Transl Med 2022;20:193.
[29] Wang Q, Liu Y, Han L, *et al*. Risk factors for acute stroke-associated pneumonia and prediction of neutrophil-to-lymphocyte ratios. The American Journal of Emergency Medicine 2021;41:55–9.
[30] Leangpanich N, Chuphanitsakun Y, Pakaranodom K, *et al*. Scoring Of Post Stroke Pneumonia In Uttaradit Hospital. J Multidiscip Healthc 2019;12:917–23.
[31] Finlayson O, Kapral M, Hall R, *et al*. Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. Neurology 2011;77: 1338–45.

[32] Kalic M, Walter G, Meisel A, *et al*. Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke. Stroke 2012;43: 2617–23.
[33] Ji R, Shen H, Pan Y, *et al*. Novel risk score to predict pneumonia after acute ischemic stroke. Stroke 2013;44:1303–9.
[34] Harms H, Grittner U, Dröge H, *et al*. Predicting post-stroke pneumonia: the PANTHERIS score. Acta Neurologica Scandinavica 2013;128: 178–84.
[35] Ni J, Shou W, Wu X, *et al*. Prediction of stroke-associated pneumonia by the A2DS2, AIS-APS, and ISAN scores: a systematic review and meta-analysis. Expert Review of Respiratory Medicine 2021;15:1461–72.
[36] Ge Y, Wang Q, Wang L, *et al*. Predicting post-stroke pneumonia using deep neural network approaches. Int J Med Inform 2019;132:103986.
[37] Vermeij J-D, Westendorp WF, Dippel DWJ, *et al*. Antibiotic therapy for preventing infections in people with acute stroke. Cochrane Database of Systematic Reviews 2018;2018:Cd008530.
[38] Meisel C, Schwab JM, Prass K, *et al*. Central nervous system injury-induced immune deficiency syndrome. Nature Reviews Neuroscience 2005;6:775–86.
[39] Hotter B, Hoffmann S, Ulm L, *et al*. Inflammatory and stress markers predicting pneumonia, outcome, and etiology in patients with stroke. Neurology - Neuroimmunology Neuroinflammation 2020;7:e692.
[40] Liu D-D, Chu S-F, Chen C, *et al*. Research progress in stroke-induced immunodepression syndrome (SIDS) and stroke-associated pneumonia (SAP). Neurochemistry International 2018;114:42–54.
[41] Emsley HCA, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. The Lancet Neurology 2008;7:341–53.
[42] Zawiah M, Hayat Khan A, Abu Farha R, *et al*. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio, and platelet-lymphocyte ratio in stroke-associated pneumonia: a systematic review and meta-analysis. Curr Med Res Opin 2023;39:475–82.
[43] Yan D, Dai C, Xu R, *et al*. Predictive Ability of Systemic Inflammation Response Index for the Risk of Pneumonia in Patients with Acute Ischemic Stroke. Gerontology 2023;69:181–8.
[44] Guldolf K, Vandervorst F, Gens R, *et al*. Neutrophil-to-lymphocyte ratio predicts delirium after stroke. Age Ageing 2021;50:1626–32.
[45] Giede-Jeppe A, Reichl J, Sprügel MI, *et al*. Neutrophil-to-lymphocyte ratio as an independent predictor for unfavorable functional outcome in aneurysmal subarachnoid hemorrhage. J Neurosurg 2019;132: 400–7.
[46] Huang Y, Chen S, Luo Y, *et al*. Crosstalk between Inflammation and the BBB in Stroke. Curr Neuropharmacol 2020;18:1227–36.
[47] McLellan P, Henriques J, Ksontini F, *et al*. Prognostic value of the early change in neutrophil-to-lymphocyte ratio in metastatic pancreatic adenocarcinoma. Clin Res Hepatol Gastroenterol 2021;45: 101541.
[48] Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratisl Lek Listy 2021;122:474–88.
[49] de Jonge JC, van de Beek D, Lyden P, *et al*. Temporal Profile of Pneumonia After Stroke. Stroke 2022;53:53–60.