

Neutrophil to lymphocyte ratio is a prognosis factor for post-operative pneumonia in aneurysmal subarachnoid hemorrhage patients

Yue Chen¹, Bao-Qiang Lian², Lei Peng³, Chen-Yu Ding², Yuan-Xiang Lin², Liang-Hong Yu², Deng-Liang Wang², De-Zhi Kang²

¹The Graduate School of Fujian Medical University, Fuzhou, Fujian 350001, China;

²Department of Neurosurgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350001, China;

³Department of Neurosurgery, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang, Hubei 443000, China.

Abstract

Background: Although a variety of risk factors of pneumonia after clipping or coiling of the aneurysm (post-operative pneumonia [POP]) in patients with aneurysmal subarachnoid hemorrhage (aSAH) have been studied, the predictive model of POP after aSAH has still not been well established. Thus, the aim of this study was to assess the feasibility of using admission neutrophil to lymphocyte ratio (NLR) to predict the occurrence of POP in aSAH patients.

Methods: We evaluated 711 aSAH patients who were enrolled in a prospective observational study and collected admission blood cell counts data. We analyzed available demographics and baseline variables for these patients and analyzed the correlation of these factors with POP using Cox regression. After screening out the prognosis-related factors, the predictive value of these factors for POP was further assessed.

Results: POP occurred in 219 patients (30.4%) in this cohort. Patients with POP had significantly higher NLR than those without (14.11 ± 8.90 vs. 8.80 ± 5.82 , $P < 0.001$). Multivariate analysis revealed that NLR remained a significant factor independently associated with POP following aSAH after adjusting for possible confounding factors, including the age, World Federation of Neurosurgical Societies (WFNS) grade, endovascular treatment, and ventilator use. And the predictive value of NLR was significantly increased after WFNS grade was combined with NLR (NLR vs. WFNS grade \times NLR, $P = 0.011$).

Conclusions: Regardless of good or poor WFNS grade, patients having NLR >10 had significantly worse POP survival rate than patients having NLR ≤ 10 . NLR at admission might be helpful as a predictor of POP in aSAH patients.

Keywords: Aneurysm; Subarachnoid hemorrhage; Infection; Inflammation; Pneumonia; Neutrophil; Lymphocyte

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) continues to be life-threatening as it is associated with high morbidity and mortality.^[1] aSAH patients are often associated with non-neurologic complications, including post-operative pneumonia (POP). Despite extensive studies and improvements in critical care, the occurrence rate of POP in aSAH continue to be high, and may affect up to 13% to 37% of patients after surgical treatment, and is still difficult to predict.^[2-5]

The aSAH patients with POP had worse outcomes than those without, both during hospitalization and after discharge.^[6] Many risk factors for POP have been studied (eg, age, the severity of aSAH, ventilator use, congestive

heart failure, etc),^[4,7-9] but the clinical predictive model has still not been well established. The severity of aSAH is well known to be associated with POP. However, early prediction of the risk of POP may facilitate optimized care; therefore, finding a readily measurable marker for POP in patients with aSAH would be helpful for early prognostication and risk stratification, and may provide clues for further studies about preventive antibiotic therapy.^[10]

The neutrophil to leukocyte ratio (NLR), is a well-known marker for inflammation condition of patients, has been shown to be a predictor of clinical prognosis in patients with ischemic stroke and hemorrhagic stroke, and a predictor for poor prognosis of aSAH, stroke-associated pneumonia in acute ischemic stroke patients and community-acquired

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Yue Chen, Bao-Qiang Lian, and Lei Peng contributed equally to this work.

Correspondence to: Dr. De-Zhi Kang, Department of Neurosurgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350001, China
E-Mail: kdz99999@sina.com.

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pneumonia.^[11-14] However, the connection between NLR and POP following aSAH is still unclear. Therefore, the aim of this study was to assess the feasibility of using NLR to predict pneumonia after clipping or coiling of the aneurysm in patients with aSAH.

Methods

Ethics approval

This study was designed in accordance with the guidelines outlined in the *Declaration of Helsinki* and approved by the local Ethics Committee of the First Affiliated Hospital of Fujian Medical University. Informed consent for each patient was obtained from the patients or their authorized legal representative if patients cannot sign the form by themselves.

Study population

Patients with aSAH administrated between January 2013 and June 2018 to the Department of Neurosurgery of the First Affiliated Hospital of Fujian Medical University were prospectively enrolled into a prospective, observational cohort, aSAH outcomes project study. In the current study, data of patients in this prospective cohort were retrospectively analyzed.

The inclusion criteria were: (1) the SAH caused by intracranial aneurysm was confirmed via computed tomography angiography (CTA) or digital subtraction angiography (DSA); (2) had admission blood cell counts data; (3) admitted to our hospital within seven days of symptom onset; (4) clipping or coiling of the aneurysm was performed. The exclusion criteria were: (1) <18 years old; (2) diagnosed with pneumonia before admission; (3) previous use of steroids or immunosuppressants; (4) prior history of other neurological diseases such as intracranial tumors, stroke, or severe head trauma; (5) other systemic diseases, such as autoimmune disease, uremia, cirrhosis, cancer, and chronic lung or heart diseases; (6) patients refuse to sign informed consent.^[15] The included patients had no history of antibiotic use and no history of drug use other than chronic diseases such as diabetes, hypertension, and so on, requiring long-term medication, in hospital and during the week before surgery.

Patient management

Clinical management followed the guideline from the American Heart Association and American Stroke Association.^[16] Critical care management followed the guideline from the Neurocritical Care Society.^[17] Following the local antibiotic stewardship committee recommendation for pre-operative prophylactic antibiotic use with 1 g of cefazolin sodium half an hour before surgery and one dose of the same sodium cefazolin over 3 h of surgery.

Clinical variables

Comprehensive data of each patient, including medical information history, history of present illness, clinical admission status, imaging, treatment received, and all

other data related to their hospitalization were collected. The location and size of the aneurysm was determined via CTA or DSA. The modified Fisher scale was used to classify the amount of subarachnoid blood presented on the admission computed tomography (CT) scan.^[18] The severity of aSAH was assessed based on the initial World Federation of Neurosurgical Societies (WFNS) grade. Medical data of each patient were assessed by two doctors to obtain the initial WFNS grade. If a large deviation in the modified Fisher scale or WFNS grade was seen, the final score would be given by a third doctor. The above assessment is completed within 24 h of admission.

As part of the routine patient care procedure, white blood cell (WBC) differential count at admission was obtained for each patient. The NLR was calculated as neutrophil count divided by lymphocyte count. Researchers who collected blood cell counts data were blinded to patient details. The laboratory examination of admission is completed within 48 h after admission.

The diagnosis of POP was re-conducted by two researchers (a neurosurgeon and a neuro critical care physician, both with extensive clinical experience) who were blinded to other clinical and laboratory findings. Patients were diagnosed with POP if they developed lower respiratory tract infections within 30 days after surgical treatment according to the modified Centers for Disease Control and Prevention criteria.^[19] The modified CDC criteria: possible POP meet the CDC diagnosis criteria, but could not be diagnosed based on the admission or follow-up chest X-ray, without other possible diagnosis or explanation; for confirmed POP is: meet all CDC diagnosis criteria and had a confirmed diagnostic change on at least one of the chest X-ray images. In the current study, both possible and confirmed pneumonia as determined by the modified CDC criteria were considered as pneumonia.^[12,20] Any patients who were overtly diagnosed with pneumonia before admission were excluded.

Clinical grade

In this study, good-grade was defined as admission WFNS Grade <3, whereas poor-grade was defined as WFNS Grade ≥ 3 .^[21]

Follow-up protocols

Patients began recording their lungs immediately after surgery. During the patient's post-operative hospitalization, the patient's lung condition was recorded during daily room visits by asking for a medical history and physical examination assessment. If symptoms of suspected lung infection are present, further refine the appropriate laboratory tests for the lung CT scan. For patients who have been discharged within 30 days, they are asked to return to the hospital again for a review at 30 days post-operatively, asking about their lung condition from the time of discharge to the time of the review, and about their lung condition at the time of the review. The endpoint of follow-up was the presence of POP or 30 days post-operatively.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 (SPSS Inc, Chicago, IL, USA) and R statistical software (R, version 3.6.3, R Project, www.r-project.org). Continuous variables were shown as mean \pm standard deviation and analyzed by 2-sample *t* test. Categorical variables were expressed as counts (percentage) and analyzed with the Pearson χ^2 test or Fisher exact test. The candidate pool of multivariate predictors included all available demographics and baseline variables that had univariate association $P < 0.10$ with the occurrence of POP. Cox regression was used to calculate hazard ratios and 95% confidence intervals (CIs) of risk factors. Use multivariate survival analysis to generate multivariate models. Candidate predictors include all the single factor variables selected above. The backward stepwise regression method was used to generate the final model, thereby removing the least important variables from Model 1 at a time until $P < 0.05$ for all remaining variables. The percentage of patients surviving POP for 30 days after surgical treatment was calculated using Kaplan-Meier method, the survival curves were drawn and compared using the log-rank test. $P \leq 0.05$ was considered significant. Interaction tests were conducted between all important variables retained in the multivariable model.

Results

Patient characteristics

A total of 711 patients were included in this study and categorized into POP group ($n = 219$) and non-POP group ($n = 492$), the average age of patients was 55.13 ± 11.30 years, with 61.32% (436/711) being female. Patient demographics and baseline medical characteristics were compared between the two groups and the results are shown in Table 1. Patients with POP had significantly higher NLR than those without [Table 1]. The included numerical variables were tested and conformed to normal distribution, and the Homogeneity Variance Test showed that the variances are homogeneous.

The median of NLR in this study is 8.50, so consider using 8.50 as the cutoff value of NLR in the “normal population” and convert NLR into a binary variable. In univariate analysis, the use of the ventilator is converted into orderly multi-classification data according to the mechanical ventilation time (0–24, 24–48, 48–72, more than 72 h) for analysis. In a sub-group analysis at the NLR level, whether the mechanical ventilation time is greater than 24 h will convert the ventilator usage into a binary variable.

Moreover, patients in the high NLR group had higher WFNS grade, modified Fisher scale, rate of ventilator use, WBC count, neutrophil count, and lower lymphocyte count than those in the low NLR group [Table 2].

For those 219 patients who experienced POP, when tested for bacterial and fungal infection, 48.9% (107/219) had positive sputum culture results. The majority had bacterial infection ($n = 94$), with *Streptococcus pneumoniae* (27.7%, 26/94) being the most common cause, followed by *Acinetobacter baumannii* (18.8%, 18/94), *Staphylococcus aureus* (18.1%, 17/94), and *Pseudomonas aeruginosa* (13.8%, 13/86); of the 13 fungal infection cases, the most commonly seen fungi was *Candida albicans* (46.2%, 6/13).

NLR and POP

219 patients (30.80%) experienced POP within one month after clipping or endovascular treatment of aneurysm. Eleven variables, including the age, WFNS grade, modified Fisher scale, hypertension, endovascular treatment, mechanical ventilator use >24 h, WBC count, neutrophil count, lymphocyte count, NLR, and WFNS grade \times NLR had univariate associations $P < 0.10$ with the occurrence of POP [Table 1] and were put into multivariate model analyses.

Multivariate survival analysis models showed that the risk of POP was significantly associated with age (hazard ratio [HR]: 1.042, 95% CI: 1.029–1.056, $P < 0.001$), WFNS grade (HR: 2.166, 95% CI: 1.496–3.137, $P < 0.001$), modified Fisher scale (HR: 1.320, 95% CI: 1.133–1.539, $P < 0.001$), endovascular treatment (HR: 0.500, 95% CI: 0.338–0.739, $P = 0.001$), NLR (HR: 1.045, 95% CI: 1.026–1.064, $P < 0.001$) [Table 3].

In addition, although the mechanical ventilation index was eliminated from the multivariate survival analysis model, in view of its clinical significance, we still conducted a sub-group analysis. When the patients were groups into mechanical ventilator used >24 and 0 to 24 h groups, sub-group analysis reveal that NLR was still related to POP. In the mechanical ventilator used >24 h group ($n = 130$), POP occurred in 110 patients (84.62%), and the average NLR of these patients was significantly higher than that of the 20 patients without POP (14.20 ± 7.42 vs. 10.05 ± 6.68 , $P = 0.021$); For non-mechanical ventilation or mechanical ventilator used 0 to 24 h patients ($n = 581$), POP occurred in 109 patients (18.76%), and the average NLR of these patients was also significantly higher than those without POP (12.48 ± 7.36 vs. 8.44 ± 5.51 , $P < 0.001$).

Through the analysis of receiver operating curve [Figure 1], the comparison between NLR and classic forecast indicators can be found that the NLR's POP prediction effect is better than WBC ($Z = 2.636$, $P = 0.008$), which is equivalent to WFNS ($Z = 1.052$, $P = 0.293$). Additionally, we found a significant interaction between the WFNS level and NLR. The area under curve (AUC) of NLR was significantly increased after the WFNS grade was combined with the NLR ($Z = 2.552$, $P = 0.011$).

POP survival analysis of aSAH patients with and without elevated admission NLR

Based on the receiver operating characteristic (ROC) curve analysis, the best threshold for NLR in predicting POP was 10.04. Patients with admission NLR >10 ($n = 285$) had significantly higher incidence of POP than patients with admission NLR ≤ 10 ($n = 426$) (40.00% [114/285] vs. 24.65% [105/426], $P < 0.001$).

Kaplan-Meier analysis showed that among good-grade patients (WFNS Grade <3 , $n = 564$), 176 patients (31.21%) had admission NLR >10 . *Post-hoc* log-rank testing revealed good-grade patients with admission NLR >10 had significantly worse POP survival rate than good-grade patients with NLR ≤ 10 (85.05% [330/388] vs. 69.32% [122/176], $P < 0.001$). Among poor-grade

Table 1: Aneurysmal subarachnoid hemorrhage patients' demographics and baseline characteristics according to the occurrence of POP.

| Characteristics | POP group (n = 219) | non-POP group (n = 492) | Statistical values | P value | HR |
|---------------------------------------|----------------------|-------------------------|---------------------|---------|-------|
| Demographics | | | | | |
| Age (years) | 60.12 ± 10.94 | 52.91 ± 10.75 | 8.22* | <0.001 | 1.042 |
| Female | 133 | 303 | 0.05 [†] | 0.829 | 0.800 |
| Admission clinical grade | | | | | |
| WFNS grade | 2 (1–4) | 1 (1–1) | 11.91* | <0.001 | 1.726 |
| I | 88 | 413 | | | |
| II | 24 | 39 | | | |
| III | 15 | 8 | | | |
| IV | 45 | 26 | | | |
| V | 47 | 6 | | | |
| Modified Fisher scale | 3 (1–4) | 1 (1–2) | 11.37* | <0.001 | 1.287 |
| Medical history | | | | | |
| Hypertension | 119 | 175 | 22.01 [†] | <0.001 | 1.132 |
| Diabetes | 24 | 38 | 14.14 [†] | 0.158 | 1.524 |
| Smoking history | 32 | 88 | 0.53 [†] | 0.282 | 1.121 |
| Aneurysm characteristics | | | | | |
| Multiple aneurysms | 54 | 111 | 0.37 [†] | 0.541 | 1.186 |
| Ruptured aneurysm size (mm) | 5.70 ± 2.67 | 5.61 ± 3.00 | 0.39* | 0.694 | 0.982 |
| Treatment | | | | | |
| Time to admission >24 h | 102 | 260 | 9.04 [†] | 0.123 | 1.013 |
| Admission to surgical treatment >48 h | 114 | 281 | 5.75 [†] | 0.210 | 0.834 |
| Surgical treatment method | | | 12.19 [†] | <0.001 | 0.672 |
| Clipping | 189 | 367 | | | |
| Coiling | 30 | 125 | | | |
| Mechanical ventilator used | | | 219.44 [†] | <0.001 | 5.187 |
| 0–23 h | 109 | 472 | | | |
| 24–47 h | 16 | 7 | | | |
| 48–71 h | 26 | 5 | | | |
| ≥72 h | 68 | 8 | | | |
| Admission laboratory results | | | | | |
| RBC (10 ¹² /L) | 4.40 ± 0.51 | 4.41 ± 0.57 | 0.10* | 0.920 | 1.104 |
| WBC (10 ⁹ /L) | 13.58 ± 5.19 | 10.92 ± 3.92 | 6.70* | <0.001 | 0.990 |
| Neutrophil (10 ⁹ /L) | 11.75 ± 4.91 | 8.91 ± 3.72 | 7.63* | <0.001 | 1.053 |
| Lymphocyte (10 ⁹ /L) | 1.02 ± 0.47 | 1.29 ± 0.61 | -4.81* | <0.001 | 0.829 |
| NLR | 14.11 ± 8.90 | 8.80 ± 5.82 | 8.64* | <0.001 | 1.049 |
| Platelet (10 ⁹ /L) | 219.54 ± 68.17 | 220.17 ± 60.03 | -0.12* | 0.902 | 1.001 |
| Interactions | | | | | |
| WFNS grade × NLR | 29.67 (10.42, 57.80) | 7.96 (4.40, 13.42) | 10.97* | <0.001 | 1.006 |

Values are expressed as n, mean ± standard deviation, or median (interquartile range). *F value for normally distributed numeral variables. [†]χ² value for categorical variables. POP: Post-operative pneumonia; NLR: Neutrophil to lymphocyte ratio; RBC: Red blood cell; WBC: White blood cell; WFNS: World Federation of Neurosurgical Societies.

patients (WFNS Grade ≥3, n = 147), 108 of them (73.47%) had admission NLR >10. *Post-hoc* log-rank testing revealed that poor-grade patients having admission NLR >10 had significantly worse POP survival rate than poor-grade patients having NLR ≤10 (43.59% [17/39] vs. 21.30% [23/108], P = 0.014). Moreover, the POP survival rate of good-grade patients with admission NLR >10 was still better than that of poor-grade patients with NLR ≤10 (P = 0.002) [Figure 2].

Discussion

In this study, we found that higher NLR was associated with POP in aSAH patients. After adjusting for confounders, multivariate analysis revealed that NLR remained a significant factor associated with the POP.

NLR, which could be easily obtained from blood cell counts, might be a strong complete blood count panel predictor of POP and outperform many classic predictors of POP, including WBC, hypertension, and smoking.

POP is a common and severe complication usually occurs within 30 days after surgical treatment of aSAH patients.^[2,22] Based on the study investigating the relationship between severity of SAH and POP, assessing the WFNS grade could be helpful in the prediction of POP.^[5] However, finding a readily measurable marker for predicting POP would still be helpful for early prognosis and risk stratification.^[10] Current data demonstrated that the predictive performances of NLR and WFNS grade were comparable (Z = 1.194, P = 0.233). The WBC differential count is routinely collected for aSAH patients. Therefore

Table 2: Aneurysmal subarachnoid hemorrhage patients' demographics and baseline characteristics by the NLR value.

| Characteristics | Lower NLR (NLR ≤8.50) | Higher NLR (NLR >8.50) | Statistical values | P value |
|---------------------------------------|-----------------------|------------------------|---------------------|---------|
| Patients | 356 | 355 | | — |
| POP events | 67 (18.82) | 152 (42.82) | 48.02 [†] | <0.001 |
| Demographics | | | | |
| Age (years) | 54.89 ± 11.27 | 55.37 ± 11.34 | -0.57 [*] | 0.571 |
| Female | 214 (60.11) | 222 (62.54) | 0.44 [†] | 0.507 |
| Admission clinical grade | | | | |
| WFNS grade | 1 (1-1) | 1 (1-4) | -8.86 [*] | <0.001 |
| I | 298 (83.71) | 203 (57.18) | | |
| II | 29 (8.15) | 34 (9.58) | | |
| III | 4 (1.12) | 19 (5.35) | | |
| IV | 18 (5.06) | 53 (14.93) | | |
| V | 7 (1.97) | 46 (12.96) | | |
| Modified Fisher scale | 1 (1-2) | 2 (1-4) | -8.77 [*] | <0.001 |
| Medical history | | | | |
| Hypertension | 139 (39.04) | 155 (43.66) | 1.56 [†] | 0.522 |
| Diabetes | 30 (8.43) | 32 (9.01) | 2.71 [†] | 0.781 |
| Smoking history | 66 (18.54) | 64 (18.03) | 3.52 [†] | 0.860 |
| Aneurysm characteristics | | | | |
| Multiple aneurysms | 86 (24.16) | 79 (22.25) | 0.36 [†] | 0.548 |
| Ruptured aneurysm size (mm) | 5.44 ± 2.86 | 5.84 ± 2.93 | -1.84 [*] | 0.066 |
| Treatment | | | | |
| Time to admission >24 h | 190 (53.37) | 172 (48.45) | 55.71 [†] | 0.189 |
| Admission to surgical treatment >48 h | 206 (57.87) | 189 (53.24) | 11.25 [†] | 0.215 |
| Surgical treatment method | | | 0.19 [†] | 0.664 |
| Clipping | 276 (77.53) | 280 (78.87) | | |
| Coiling | 80 (22.47) | 75 (21.13) | | |
| Mechanical ventilator used >24 h | 35 (9.83) | 95 (26.76) | 0.04 [†] | <0.001 |
| Admission Laboratory | | | | |
| RBC (10 ¹² /L) | 4.40 ± 0.52 | 4.41 ± 0.54 | -0.03 [*] | 0.977 |
| WBC (10 ⁹ /L) | 9.77 ± 3.64 | 13.71 ± 4.47 | -12.92 [*] | <0.001 |
| Neutrophil (10 ⁹ /L) | 7.41 ± 3.10 | 12.17 ± 4.07 | -17.52 [*] | <0.001 |
| Lymphocyte (10 ⁹ /L) | 1.61 ± 0.64 | 0.86 ± 0.30 | 19.93 [*] | <0.001 |
| Platelet (10 ⁹ /L) | 220.58 ± 63.77 | 219.38 ± 61.49 | 0.26 [*] | 0.799 |

Values are expressed as *n*, *n* (%), mean ± standard deviation, or median (interquartile range). ^{*}F value for normally distributed numeral variables. [†]χ² value for categorical variables. POP: Post-operative pneumonia; NLR: Neutrophil to lymphocyte ratio; RBC: Red blood cell; WBC: White blood cell; WFNS: World Federation of Neurosurgical Societies.

Table 3: Multivariate model analysis of possible predictors of POP.

| Factors | Final model (Model 6) [†] | | | | |
|------------------------|------------------------------------|-------|--------|-------------|---------|
| | B | SE | Wald | Adjusted HR | P value |
| Age | 0.041 | 0.007 | 39.618 | 1.042 | <0.001 |
| WFNS grade | 0.773 | 0.189 | 16.745 | 2.166 | <0.001 |
| Modified Fisher scale | 0.278 | 0.078 | 12.615 | 1.320 | <0.001 |
| Endovascular treatment | -0.693 | 0.199 | 12.076 | 0.500 | 0.001 |
| NLR | 0.044 | 0.009 | 21.968 | 1.045 | <0.001 |
| WFNS × NLR | 0.009 | 0.003 | 8.357 | 1.009 | 0.004 |

Multivariate analysis: all variables in Table 1 having *P* < 0.05 were included in multivariate analysis. [†]Backward stepwise regression methods were used to produce the final model, in which process the least nonsignificant variable was removed from the model 1 at a time until all remaining variables had *P* < 0.05. POP: Post-operative pneumonia; NLR: Neutrophil to lymphocyte ratio; WFNS: World Federation of Neurosurgical Societies.

NLR, derived from the WBC differential count is easy to obtain and calculate, without adding extra cost, and is potentially a simple way for clinicians to determine the POP risk for patients. Moreover, we also found an additive interaction between WFNS grade and NLR. Multivariate analysis revealed that NLR and WFNS grade × NLR

remained the significant factors associated with POP following aSAH after adjusting for possible confounding factors, including the age, WFNS grade, endovascular treatment, and ventilator use. The AUC of NLR was significantly increased after the WFNS grade was combined with the NLR (*P* < 0.05).

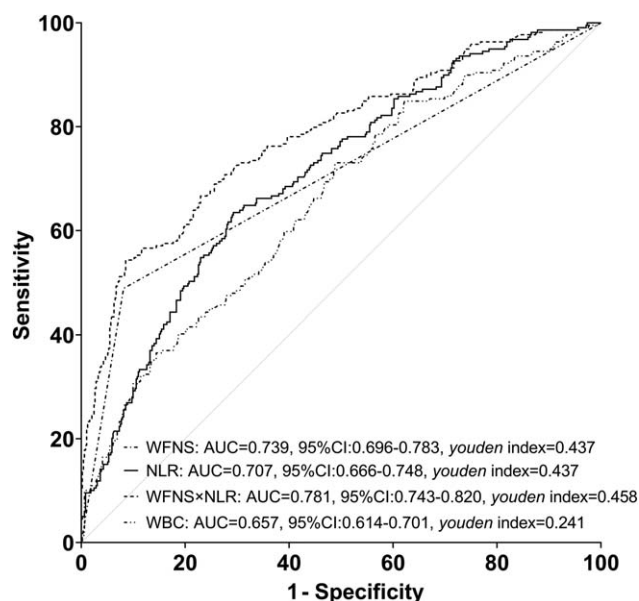


Figure 1: ROC curve analyses comparing NLR, WFNS grade, WBC count, and WFNS × NLR at admission for identifying POP in aSAH patients. The AUCs of NLR, WFNS grade, WBC count and WFNS × NLR were 0.707 (95% CI: 0.666–0.748), 0.739 (95% CI: 0.696–0.783), 0.657 (95% CI: 0.614–0.701), and 0.781 (95% CI: 0.743–0.820), respectively. Z test revealed that the AUCs of NLR and WFNS grade were comparable ($Z = 1.052, P = 0.293$); but the AUC of WBC count was significantly lower than that of WFNS grade ($Z = 2.636, P = 0.008$). The AUC of NLR was significantly increased after the WFNS grade was combined with the NLR ($Z = 2.552, P = 0.011$). aSAH: Aneurysmal subarachnoid hemorrhage; AUC: Area under curve; CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio; POP: Post-operative pneumonia; ROC: Receiver operating characteristic; WBC: White blood cell; WFNS: World Federation of Neurosurgical Societies.

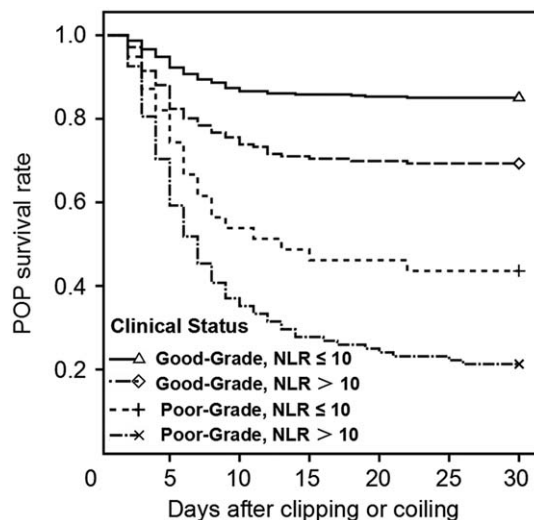


Figure 2: The Kaplan-Meier curve of the 30-day POP survival rate of patients with NLR >10 and NLR ≤10. The Kaplan-Meier curve shows a 30-day POP survival rate of 85.05% (330/388) for good-grade patients having NLR ≤10, of 69.32% (122/176) for good-grade patients having NLR >10, of 43.59% (17/39) for poor-grade patients having NLR ≤10, and of 21.30% (23/108) for poor-grade patients having NLR >10. The log-rank test showed that $P < 0.001$. Post-hoc log-rank testing revealed that the good-grade patients having NLR ≤10 had significantly worse POP survival rate than good-grade patients having NLR >10 ($P < 0.001$), and the poor-grade patients having NLR ≤10 had significantly worse POP survival rate than poor-grade patients having NLR >10 ($P = 0.014$). Moreover, the POP survival rate of good-grade patients with admission NLR >10 was still better than that of poor-grade patients with NLR ≤10 ($P = 0.002$). NLR: Neutrophil to lymphocyte ratio; POP: Post-operative pneumonia.

In this study of 711 aSAH patients, approximately 40% of all patients, 30% of good-grade patients, and 70% of poor-grade patients had admission NLR >10. Patients having admission NLR >10 had significantly worse POP survival rate than patients having NLR ≤10. However, this effect was limited to patients with the same admission clinical grade. POP survival rate of good-grade patients having admission NLR >10 was still significantly worse than that of poor-grade patients having NLR ≤10.

The aSAH patients with POP might have a prolonged clinical course, early prognosis of this cohort will enable physicians to discuss expected clinical course of disease with the family members and make informed decisions on treatment options. In the current study, ROC curve analysis revealed that the best threshold of NLR for predicting POP of aSAH patients was 10.04, and the corresponding sensitivity and specificity was 63.5% and 70.7%, respectively. For the patients with elevated NLR, pre-operative education and strengthen respiratory tract management is suggested. For example: pre-operative education (smoking cessation, deep breathing exercise to improve respiratory function, clean the mouth), adjustment of the diet structure to strengthen nutrition, atomization to alleviate bronchospasm. However, this approach needs to be confirmed with further research.

There may be several possible explanations for the potential connection between the NLR and POP. One may be the immunologic changes after aSAH. It has been reported that between 63% to 88% of aSAH patients

could develop early systemic inflammatory response,^[23-25] which is altered through the sympathetic pathway and the hypothalamus-pituitary-adrenal axis.^[26,27] As a result, neutrophils are demarginated and stimulated by growth factors^[12,13,28]; however, lymphocytes undergo apoptosis, which may increase the susceptibility to infection. Second, the severity of aSAH could also be related to NLR and POP. In our cohort, the higher NLR group had a higher initial WFNS grade. Previous studies have also shown that POP has a close relationship with severe aSAH.^[4,5] Thus, the NLR might act as a marker for severe aSAH patients who are vulnerable to POP. Third, the NLR may be a simple marker of sub-clinical infection. Although we excluded pneumonia events detected before admission, an elevated NLR may indicate an underlying inflammatory process associated with POP.

We transformed NLR variables into bicategorical information and divided them into a high NLR level group and a low NLR level group and performed a confounding factor analysis, which showed that patients in the high NLR group may have worse baseline information than those in the low NLR group (this may be due to the fact that elevated NLR corresponds to an active phase of inflammatory response in this group), but there was no significant difference in clinical management between the two groups. Therefore, it is reasonable to assume that the information of the two groups of patients remains comparable. In addition, NLR levels were higher in the POP group than those in the non-POP group, regardless of whether ventilators were used or not, and it is important

for the discussion of this result that we have completed the description and added the following to the discussion section of the article: at the same time, we found an interesting phenomenon that NLR levels were higher in the POP group than those in the non-POP group, regardless of whether ventilators were used or not, and this may be because, although mechanical ventilation increases the risk of lung infection, the internal inflammatory state remains an important cause of pneumonia in patients, and NLR is an important predictor of POP.

There were several limitations of this study including its observational design. Although we assessed a relatively large sample size, there was still a possibility of selection bias and generalization of the findings to clinics should be progressed with caution. Indeed, POP occurrence rate of patients in the current study was relatively high (30.80%), although POP could occur in up to 13% to 37% of aSAH patients based on the previous studies.^[2-4,29,30] We included both possible and confirmed POP as a single variable. Because there was no radiological evidence for possible POP (accounted for only 17% of cases in this cohort), many other conditions (eg, viral infection, inflammation) can be mistakenly included as possible POP in this study. The possibility of overestimating the POP rate should be considered. However, our main results remained consistent when we included only confirmed POP cases. Another limitation of this study is that what we did was rooted in single-center data, and for the analysis of group prognosis, there is still gap to the prognosis of individual prognosis. Further research is also needed to determine whether changes in NLR over time are related to the onset of POP.

In conclusion, NLR may be helpful for predicting POP in patients with aSAH. The NLR, which is easy to obtain by calculating from the WBC differential count, may help to identify high-risk patients to begin intervention in time. In addition, there may be an additive interaction between WFNS grade and NLR. However, further large-scale studies are still needed to confirm this finding, to evaluate whether the prediction model we established can be used to screen high-risk patients with POP before surgery.

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Conflicts of interest

None.

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