

Prediction of Antibiotic Efficacy in Cerebral Hemorrhage-Associated Pneumonia Using Inflammatory Hematological Indices: A Retrospective Study

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Purpose: The role of inflammatory response in secondary infections following cerebral hemorrhage has attracted considerable attention. We aimed to explore the associations between inflammatory markers and antibiotic efficacy on the cerebral hemorrhage-associated pneumonia.

Methods: We conducted a retrospective study including 200 patients with cerebral hemorrhage-associated pneumonia. In the retrospective study, baseline data, blood cell counts, and C-reactive protein (CRP) were collected. The inflammatory markers including neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), monocyte–lymphocyte ratio (MLR), systemic immune-inflammatory index (SII) were calculated. The difference between the values at admission and at the time of initial efficacy evaluation was denoted by “ Δ ”. These inflammatory markers were examined as potential biomarkers to predict the efficacy of initial antibiotic treatment in finally included patients by univariate analysis and multivariate logistic regression models.

Results: In the final analysis, there were 105 cases with effective antibiotic treatment and 95 cases with ineffective antibiotic treatment. At the time of initial efficacy evaluation, there were significant differences in the values of NLR, MLR, PLR, SII, and CRP, $P < 0.05$. Significant differences were also showed in the values of Δ NLR, Δ MLR, and Δ SII, $P < 0.05$. The results of multivariate logistic regression model showed that Δ NLR (OR: 1.260, $P = 0.016$), Δ PLR (OR: 0.985, $P = 0.008$), and CRP (OR: 0.975, $P = 0.043$) at the time of efficacy evaluation were possibly associated with the antibiotic efficacy.

Conclusion: Δ NLR, Δ PLR, and CRP at the time of efficacy evaluation appear the promising parameters in guiding antibiotic treatment in patients with cerebral hemorrhage-associated pneumonia. However, large-sample, multicenter external validation studies are still needed.

Keywords: cerebral hemorrhage, pneumonia, platelet–lymphocyte ratio, neutrophil–lymphocyte ratio, systemic immune-inflammatory index

Introduction

Cerebral hemorrhage is an acute cerebrovascular disease with high lethality and disability.¹ Surgical interventions including craniotomy hematoma removal and minimally invasive puncture are important to improve the prognosis for patients with moderate to massive bleeding or with severe intracranial pressure increase.² However, postoperative complications, especially pneumonia, remain a major obstacle to the clinical recovery of patients.

Studies on cerebral hemorrhage have shown that the incidence of cerebral hemorrhage-associated pneumonia is about 20% and is especially higher in critically ill patients.^{3,4} Pneumonia not only prolongs the ICU hospitalization but also increases the mortality of patients,⁵ and significantly increases the medical economic burden.⁶ The pathogenesis involves stroke-induced immunosuppression and activation of the inflammatory response,⁷ swallowing dysfunction due to medullary lesion or impaired consciousness,⁸ disruption of the airway barrier due to mechanical ventilation, and chronic lung disease.⁹

Inflammatory markers from blood neutrophil, lymphocyte, monocyte, and platelet counts such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been widely used to aid in the diagnosis of infectious diseases. In recent years, other novel marker such as systemic inflammatory index (SII) has further enriched the diagnosis of infectious diseases.^{10,11} With the advantages of easy detection, low cost, and dynamic reproducibility, these markers can comprehensively reflect the systemic inflammatory response and immune status, which are especially valuable in primary medical institution and intensive care unit.

These inflammatory markers exhibit significant value in the early diagnosis, severity assessment, and prognosis prediction of pneumonia.^{12–16} However, the significance of these inflammatory markers for assessment of the effectiveness of antibiotic treatment in patients with cerebral hemorrhage-associated pneumonia has not been reported in any study, which became the purpose of this study.

Methods

Study Design

The retrospective study was conducted at the Neurosurgery Department and Neurocritical care unit of the First Affiliated Hospital of Yangtze University. This study included consecutive hospitalized patients at the study center from January 2020 to December 2024. The study has been approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University, in compliance with STROBE guidelines and the Helsinki Declaration.

The patients with cerebral hemorrhage and imaging changes consistent with pneumonia were included in the study. The patients included also underwent surgeries related to cerebral hemorrhage after admission. The patients with death within 72 hours of admission, with imaging changes consistent with pneumonia within one week prior to admission, and with hematological diseases resulting in abnormal blood cell counts were excluded from the study.

Data Collection

The following data were collected from the hospital information system: demographic characteristics (including gender and age), disease data (including symptoms, signs, imaging results, blood test results, Glasgow Coma Scale scores, and surgery duration), combined diseases (including baseline pulmonary diseases, diabetes, and hypertension).

We collected the results of blood cell counts (including neutrophil, lymphocyte, monocyte, platelet) and blood C-reactive protein (CRP) at admission and at the time of initial efficacy evaluation. If the antibiotic was effective and without change, the results of blood cell counts and CRP after 72 hours of antibiotic treatment would be used as the results at the time of efficacy evaluation. If the antibiotic was ineffective, the results of blood cell counts and CRP at the time of antibiotic change would be used as the results at the time of efficacy evaluation. We calculated NLR, MLR, PLR, and SII as follows: $NLR = \text{neutrophil count} / \text{lymphocyte count}$; $MLR = \text{monocyte count} / \text{lymphocyte count}$; $PLR = \text{platelet count} / \text{lymphocyte count}$; $SII = (\text{neutrophil count} \times \text{platelet count}) / \text{lymphocyte count}$. The difference between values at the two times was denoted by “ Δ ”.

The diagnosis and efficacy evaluation of patients with pneumonia should refer to the diagnostic and treatment guidelines for acquired pneumonia in adults in China.¹⁷ Respiratory symptoms, signs, chest CT or chest X-ray results, and blood test results needed to be taken into account. The assessment of pneumonia required the joint judgment of two experienced physicians. Patients with a disputed diagnosis needed a third physician to discuss together.

The diagnosis of pneumonia was determined based on the following criteria: new or progressive infiltrative shadows or ground glass shadows displayed on chest CT or X-rays, combined with two or more of the following three clinical conditions: (1) fever, body temperature greater than 38 degree Celsius; (2) purulent airway secretions; (3) leukocytes greater than $10 \times 10^9/L$ or less than $4 \times 10^9/L$. The flowchart of the study was shown in [Figure 1](#).

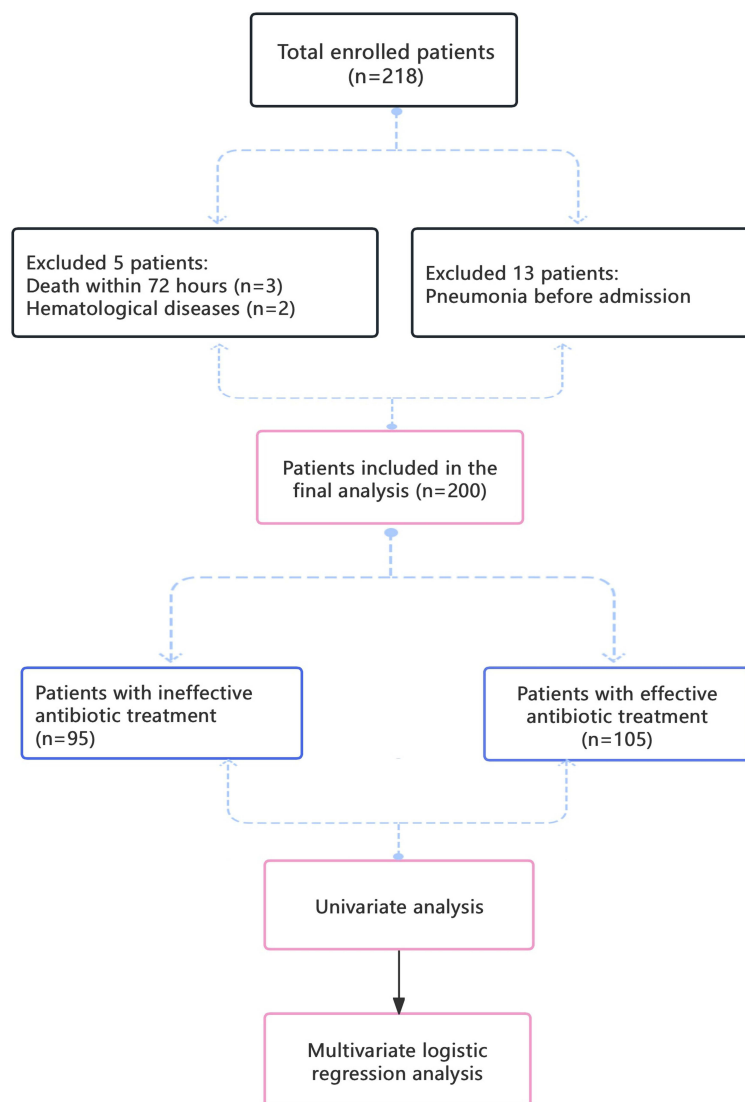


Figure 1 Flowchart of the study.

Statistical Analysis

Continuous variables were exhibited as “mean \pm standard deviation (SD)” or “median (interquartile range, IQR)”. *T*-tests or Mann–Whitney *U*-tests were considered for comparison based on the normal distribution. Categorical variables were exhibited in percentage, and compared using Chi-Square, Continuity-Correction, or Fisher’s Exact Test as appropriate. A bilateral *P*-value <0.05 was considered statistically significant. The predictive ability was determined based on Receiver Operating Characteristic (ROC) analysis and the area under the characteristic curve (AUC). The optimal cut-off value was defined as the value with the maximized Youden index. Variables with *P*-value <0.1 in the univariate analysis were included in a multivariate logistic regression model to identify potential influencing factors associated with the antibiotic efficacy. The statistical analyses were performed using IBM SPSS Statistics software (version 23) and GraphPad Prism software (version 10).

Results

Differences of Characteristics Between Patients with Effective and Ineffective Antibiotic Treatment

A total of 200 patients were included in the final analysis. There were 98 males and 102 females. The median age was 62 years. There were 54 cases with Glasgow Coma Scale (GCS) scores less than 11. The median surgery duration was

180 minutes. There were 45 cases with baseline lung diseases, 111 cases with intraventricular hemorrhage, 135 cases with hypertension, 23 cases with diabetes and 21 cases with hypertension and diabetes. The proportion of females in patients with effective antibiotic treatment was 60.0%, significantly higher than that in patients with ineffective antibiotic treatment (41.1%), $P=0.007$. The proportion of cases with GCS less than 11 in patients with effective antibiotic treatment was 9.5%, significantly lower than that in patients with ineffective antibiotic treatment (46.3%), $P<0.001$. There were no significant differences between patients with effective and ineffective antibiotic treatment in age, surgery duration, and proportions of combined diseases, $P>0.05$ (Table 1).

Inflammatory Markers Associated with the Antibiotic Efficacy for Cerebral Hemorrhage-Associated Pneumonia (Univariate Analysis)

The median values of NLR, MLR, and PLR at admission were 10.41, 0.68, and 186.86, respectively. The median SII at admission was $1851.36 \times 10^9/L$. The median CRP at admission was 7.36mg/L. There were no significant differences in these inflammatory markers between patients with effective and ineffective antibiotic treatment, $P>0.05$ (Table 2).

The median values of NLR, MLR, PLR, and SII at the time of initial efficacy evaluation in all included patients were 8.24, 0.69, 182.01, and $1448.22 \times 10^9/L$ respectively. The median CRP was 29.01mg/L. At the time of initial efficacy evaluation, the levels of NLR (6.42 vs 11.18, $P<0.001$), MLR (0.59 vs 0.89, $P<0.001$), and PLR (166.30 vs 197.65, $P=0.024$) in patients with effective treatment were all significantly lower than those in patients with ineffective treatment. The SII level ($1189.36 \times 10^9/L$ vs $1801.35 \times 10^9/L$, $P<0.001$) in patients with effective treatment was also significantly lower. The CRP level in patients with effective treatment was 14.16mg/L, significantly lower than that in patients with ineffective treatment (52.14mg/L), $P<0.001$ (Table 2).

Among all included patients, the median values of Δ NLR, Δ MLR, and Δ PLR were 1.70, 0.00, and 11.73, respectively. The median Δ SII was $243.78 \times 10^9/L$. The median value of Δ CRP was 0.00mg/L. The values of Δ NLR (2.60 vs -0.68 , $P=0.003$) and Δ MLR (0.10 vs -0.17 , $P<0.001$) were all significantly higher in patients with effective treatment. The value of Δ SII in patients with effective treatment was $451.89 \times 10^9/L$, significantly higher than that in patients with ineffective treatment ($37.98 \times 10^9/L$), $P=0.001$. There were no significant differences in Δ PLR (18.47 vs -2.26 , $P=0.087$) and Δ CRP (0.00 vs 0.00, $P=0.075$) between patients with effective and ineffective antibiotic treatment (Table 2).

We obtained the cut-off values for predicting antibiotic efficacy through ROC curves. The cut-off values of NLR, MLR, PLR, and SII at the time of efficacy evaluation were 7.74, 0.76, 241.87, and $1550.38 \times 10^9/L$, respectively. The

Table 1 Differences of Baseline Characteristics Between Patients with Effective and Ineffective Antibiotic Treatment

		Total (n=200)	Ineffective (n=95)	Effective (n=105)	P
Gender [n(%)]	Females	102 (51.0%)	39 (41.1%)	63 (60.0%)	0.007
	Males	98 (49.0%)	56 (58.9%)	42 (40.0%)	
Age (years)		62 (54, 67)	63 (55, 67)	58 (53, 66)	0.194
Glasgow Coma Scale score [n(%)]	≥ 11	146 (73.0%)	51 (53.7%)	95 (90.5%)	<0.001
	< 11	54 (27.0%)	44 (46.3%)	10 (9.5%)	
Lung diseases [n(%)]	No	155 (77.5%)	71 (74.7%)	84 (80.0%)	0.373
	Yes	45 (22.5%)	24 (25.3%)	21 (20.0%)	
Intraventricular hemorrhage [n(%)]	No	89 (44.5%)	36 (37.9%)	53 (50.5%)	0.074
	Yes	111 (55.5%)	59 (62.1%)	52 (49.5%)	
Hypertension [n(%)]	No	65 (32.5%)	29 (30.5%)	36 (34.3%)	0.571
	Yes	135 (67.5%)	66 (69.5%)	69 (65.7%)	
Diabetes [n(%)]	No	177 (88.5%)	84 (88.4%)	93 (88.6%)	0.973
	Yes	23 (11.5%)	11 (11.6%)	12 (11.4%)	
Hypertension and Diabetes[n(%)]	No	179 (89.5%)	84 (88.4%)	95 (90.5%)	0.636
	Yes	21 (10.5%)	11 (11.6%)	10 (9.5%)	
Surgery duration (minutes)		180 (120–210)	180 (120–240)	165 (120–200)	0.138

Table 2 Differences of Inflammatory Markers Between Patients with Effective and Ineffective Antibiotic Treatment

	Total (n=200)	Ineffective (n=95)	Effective (n=105)	P
At admission				
NLR	10.41 (6.59–14.94)	11.43 (6.75–17.86)	9.72 (6.20–14.29)	0.103
MLR	0.68 (0.47–1.03)	0.76 (0.41–1.12)	0.65 (0.48–0.94)	0.485
PLR	186.86 (127.97–277.74)	181.25 (110.08–292.78)	197.52 (136.99–272.88)	0.505
SII	1851.36 (1047.80–3228.92)	1952.12 (1094.61–3303.07)	1787.56 (1038.22–2933.78)	0.873
CRP	7.36 (2.11–29.46)	7.69 (2.22–40.61)	5.37 (1.95–15.45)	0.261
At the time of initial efficacy evaluation				
NLR	8.24 (5.16–12.38)	11.18 (7.64–16.51)	6.42 (3.98–9.33)	<0.001
MLR	0.69 (0.52–0.97)	0.89 (0.62–1.21)	0.59 (0.43–0.74)	<0.001
PLR	182.01 (139.07–251.12)	197.65 (143.97–302.83)	166.30 (138.86–231.63)	0.024
SII	1448.22 (977.53–2329.39)	1801.35 (1307.98–2813.34)	1189.36 (797.24–1781.64)	<0.001
CRP	29.01 (11.36–76.66)	52.14 (23.70–101.20)	14.16 (5.77–37.74)	<0.001
At the time of initial efficacy evaluation				
ΔNLR	1.70 (–1.02–6.30)	–0.68 (–5.36–5.72)	2.60 (–0.12–6.54)	0.003
ΔMLR	0.00 (–0.26–0.25)	–0.17 (–0.44–0.17)	0.10 (–0.13–0.31)	<0.001
ΔPLR	11.73 (–62.63–94.62)	–2.26 (–100.20–94.87)	18.47 (–31.27–89.43)	0.087
ΔSII	243.78 (–354.85–1140.28)	37.98 (–1086.34–944.42)	451.89 (–1.70–1470.83)	0.001
ΔCRP	0.00 (–13.94–1.48)	0.00 (–38.67–2.06)	0.00 (–5.08–0.45)	0.075

Notes: ^Δthe difference between values at admission and at the time of initial efficacy evaluation.

Abbreviations: CRP, C-reactive protein; NLR, neutrophil–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; SII, systemic immune-inflammatory index; PLR, platelet–lymphocyte ratio.

AUC of ROC curves were 0.766, 0.745, 0.592, and 0.719, respectively. The cut-off value of CRP at the time of efficacy evaluation was 25.75mg/L, and the AUC was 0.774 (Figure 2A). The cut-off values of ΔNLR (Figure 2B) and ΔPLR (Figure 2C) were –0.67 and –49.47, respectively. The AUC of ROC curves were 0.623 and 0.570, respectively.

Factors Associated with the Antibiotic Efficacy for Cerebral Hemorrhage Associated-Pneumonia (Multivariate Logistic Regression Analysis)

The result of multivariate logistic regression model including gender, GCS score, CRP, NLR, MLR, PLR, and SII at the time of initial efficacy evaluation showed that GCS score (OR: 0.249, 95% CI: 0.077–0.810, P=0.021) and CRP (OR: 0.981, 95% CI: 0.967–0.995, P=0.008) could be the influencing factors for the antibiotic efficacy of patients. The AUC of this model was 0.881 (95% CI: 0.818–0.944, P<0.001). The sensitivity and specificity were 76.6% and 90.0%, respectively, with a Youden index of 0.666 (Figure 3A).

The result of multivariate logistic regression model including gender, GCS score, ΔNLR, ΔMLR, ΔSII, ΔPLR, and ΔCRP showed that GCS score (OR: 0.080, 95% CI: 0.031–0.208, P<0.001) and ΔCRP (OR: 1.016, 95% CI: 1.005–1.028, P=0.004) could be the influencing factors for the antibiotic efficacy of patients. The AUC of this model was 0.845 (95% CI: 0.789–0.900, P<0.001). The sensitivity and specificity were 81.9% and 77.9%, respectively, and with a Youden index of 0.598 (Figure 3B).

The result of multivariate logistic regression model including gender, GCS score, CRP, NLR, MLR, PLR, and SII at the time of initial efficacy evaluation, as well as ΔNLR, ΔMLR, ΔSII, ΔCRP, and ΔPLR showed that GCS score (OR: 0.132, 95% CI: 0.031–0.567, P=0.006), CRP (OR: 0.975, 95% CI: 0.951–0.999, P=0.043), ΔNLR (OR: 1.260, 95% CI: 1.044–1.521, P=0.016), and ΔPLR (OR: 0.985, 95% CI: 0.975–0.996, P=0.008) could be the influencing factors for the antibiotic efficacy of patients. The AUC of this model was 0.926 (95% CI: 0.878–0.973, P<0.001). The sensitivity and specificity were 83.0% and 86.7%, respectively, and with a Youden index of 0.696 (Figure 3C).

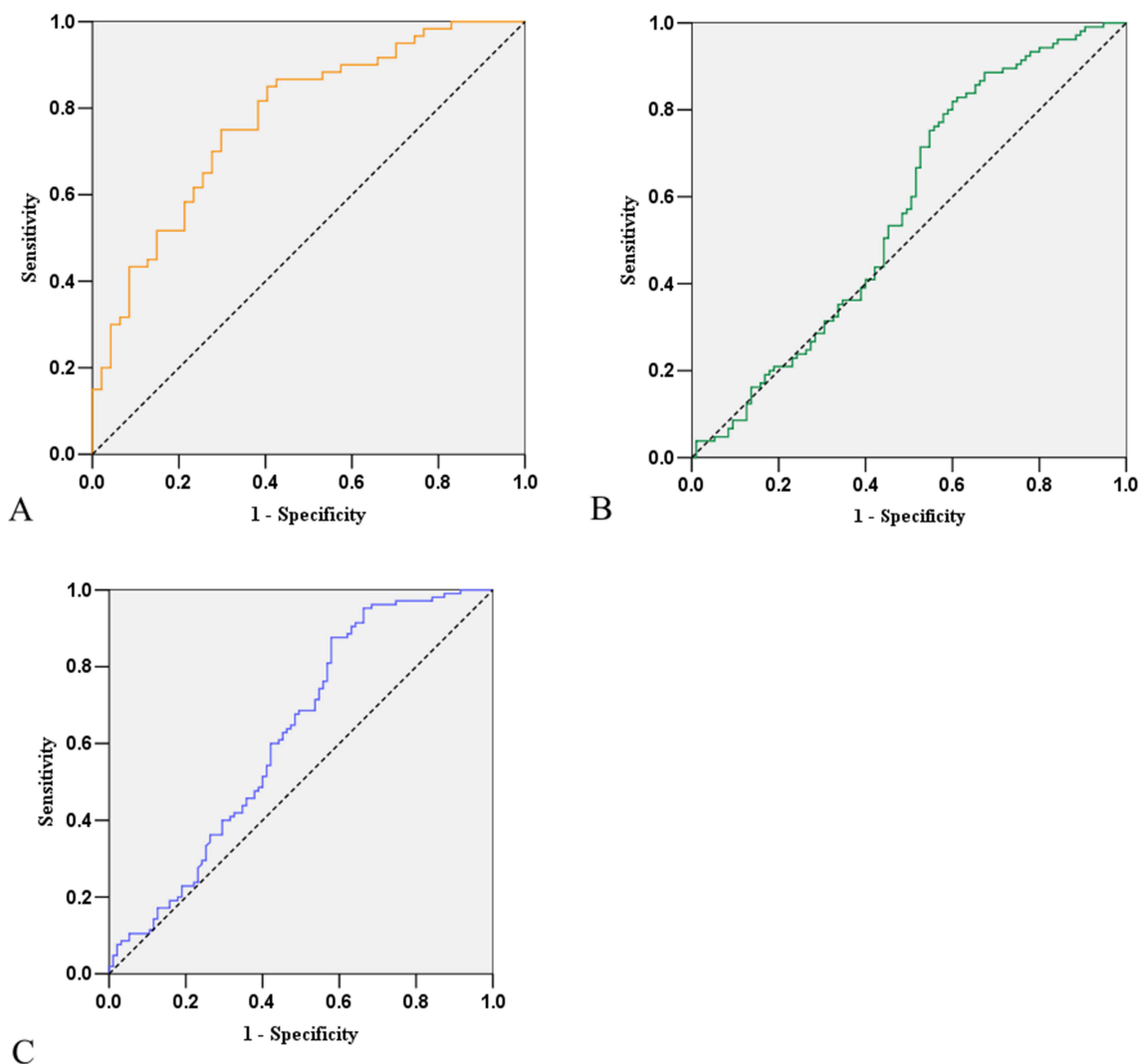


Figure 2 Receiver operating characteristic curves of CRP at the time of efficacy evaluation (A), Δ NLR (B), and Δ PLR (C) for predicting antibiotic efficacy in patients with cerebral hemorrhage-associated pneumonia.

Abbreviations: NLR, neutrophil–lymphocyte ratio; CRP, C-reactive protein; PLR, platelet–lymphocyte ratio.

Discussion

Pneumonia is a common and serious complication in patients with cerebral hemorrhage, significantly increasing mortality and the risk of poor prognosis. Inflammatory markers have important significance in the cerebral hemorrhage-associated pneumonia. They can assist in early diagnosis, severity assessment, and prognosis prediction.

Our study served as the first to evaluate the associations between CRP, inflammatory markers from peripheral blood cells, and the antibiotic efficacy of cerebral hemorrhage-associated pneumonia. CRP is a kind of reactive protein synthesized by the liver, which increases significantly in patients with bacterial infection, inflammation and tissue damage, and is widely used in the diagnosis, severity assessment and efficacy monitoring of infectious diseases.^{18–20} In patients with chronic obstructive pulmonary disease complicated with pneumonia,²¹ and patients with community-acquired pneumonia,²² CRP levels are associated with the severity of pneumonia. The highest level of CRP is also associated with the mortality of pneumococcal pneumonia.²³ Moreover, studies have shown that changes in CRP levels can serve as a reference for antibiotic efficacy. The elevated CRP level is negatively associated with the efficacy of piperacillin tazobactam in the treatment of chronic obstructive pulmonary disease complicated with pneumonia.²¹ The decreased CRP level can also be an efficacy marker of enteral nutrition support combined with antibiotic treatment in patients with severe community-acquired pneumonia in the Intensive Care Unit.²⁴ In our multivariate logistic regression

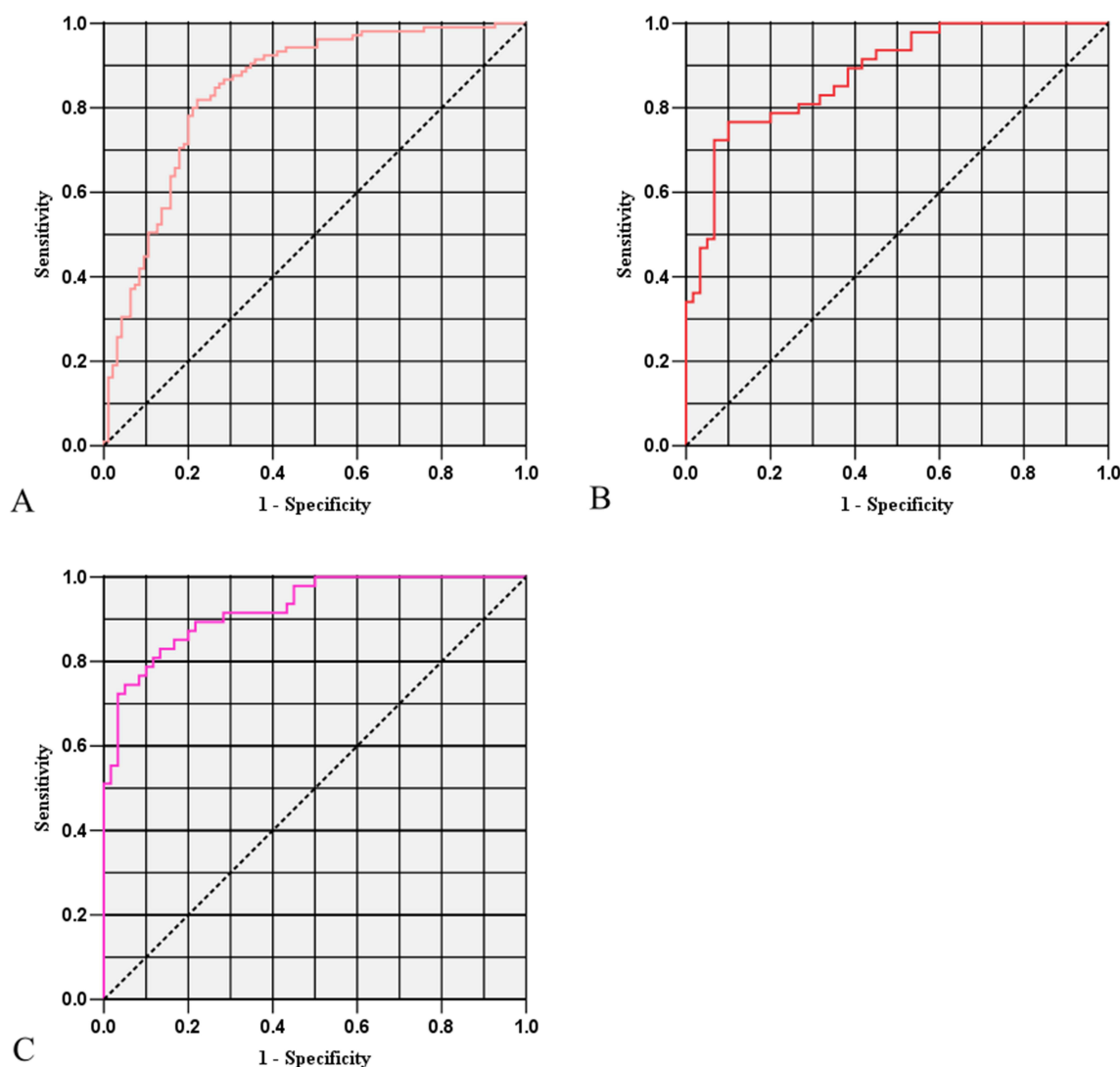


Figure 3 Receiver operating characteristic curves of the multivariate logistic regression model including inflammatory markers at the time of initial efficacy evaluation (**A**), of the model including Δ inflammatory markers (**B**), of the model including inflammatory markers at the time of initial efficacy evaluation and Δ inflammatory markers (**C**).

model, we found a higher CRP at the time of efficacy evaluation could serve as a marker for antibiotic efficacy. However, we did not find the importance of Δ CRP in the efficacy evaluation of cerebral hemorrhage-associated pneumonia.

PLR as a novel inflammation and immune marker has shown important value in the prediction, diagnosis and prognosis evaluation of infectious diseases in recent years. It is a comprehensive response to dual pathophysiological characteristics of platelet activation and lymphocyte depletion. On the one hand, platelets participate in microthrombus formation and inflammatory cascade reactions by releasing pro-inflammatory mediators such as P-selectin and platelet factor 4. On the other hand, decreased lymphocytes reflect the immune suppression due to infection or stress, especially in sepsis and severe pneumonia. Accelerated lymphocyte apoptosis is significantly associated with poor prognosis.^{25–27} PLR has shown importance in a variety of infectious diseases. The PLR level in diabetes patients combined with pneumonia was significantly higher than in patients without pneumonia.²⁸ Compared with patients without *Helicobacter pylori* infection, patients with *Helicobacter pylori* infection have significantly increased PLR. As the severity increases, the level of PLR also increases.²⁹ In patients with COVID-19, the level of PLR in mild infection patients is significantly lower than in severe infection patients. The level of PLR in survivors is also significantly lower than in dead patients.³⁰ The increased PLR level can also predict incision site infection in patients with renal cell carcinoma, with a cut-off value of 196.³¹

There were some studies about the associations of inflammatory markers from peripheral blood cells with stroke-related pneumonia. Nam et al evaluated 1317 patients with acute ischemic stroke and confirmed that a higher NLR can predict stroke-related pneumonia.³² The elevated PLR level can also predict stroke-related pneumonia.³³ The sensitivity and specificity of PLR for predicting stroke-related pneumonia are 57.5% and 70.6%, respectively, with a cut-off value of 152.22.³⁴ There were currently limited studies on the predicting performance of PLR or NLR for the antibiotic efficacy in patients with pneumonia. There are some studies mainly on the predicting performance of PLR for chemotherapy in cancer patients. In patients with locally advanced gastric cancer, PLR level is associated with the efficacy of neoadjuvant chemotherapy, and predicts overall survival and disease-free survival in patients with TNM stage 3 disease and dissected lymph node counts <28.³⁵ PLR (≥ 152.6) is also an independent risk factor (OR=4.503) for the chemotherapy response of first-line platinum in patients with non-small cell lung cancer.³⁶ In our study, compared with inflammatory markers such as NLR, MLR, and SII at the time of efficacy evaluation, Δ NLR and Δ PLR can serve as markers for antibiotic efficacy in patients with cerebral hemorrhage-associated pneumonia. Moreover, the AUC value of the prediction model established by GCS score, CRP at the time of initial efficacy evaluation, Δ NLR, and Δ PLR could reach 0.926, with sensitivity and specificity exceeding 83%.

There were several limitations in our study. First, it was a single-center and retrospective study, which may cause a selection bias. Second, the accuracy of Δ inflammatory marker (change value before and after treatment) depended on the detection results of fixed time points. There were slight differences in the time points of efficacy evaluation, which could affect the calculation of Δ inflammatory marker. Third, our study did not investigate the signal pathways through which Δ PLR and Δ NLR influenced the antibiotic efficacy. Finally, further validation of the cut-off value and external verification of the model are needed. In future studies, we will increase the sample size and conduct multicenter external validation studies.

Conclusions

Δ NLR, Δ PLR, and CRP at the time of efficacy evaluation appear the promising biomarkers in guiding antibiotic treatment in patients with cerebral hemorrhage-associated pneumonia, providing a basis for early risk stratification and individualized treatment for these patients, and providing simple and economical biomarkers for guiding early recognition of ineffective antibiotic therapy.

Ethics Approval and Informed Consent

The study was approved by and complied with the requirements of the Ethics Committee of the First Affiliated Hospital of Yangtze University (KY2025-050-01). The Ethics Committee waived the requirement for patient informed consent due to the nature of retrospective study. The confidentiality of information was protected according to the Helsinki Declaration and was used only for research purposes. The individual identifiers were removed during data collection and were replaced with serial code numbers.

Acknowledgments

We are thankful to all the medical staff in the Neurointensive Care Unit and the department of Neurosurgery, The First Affiliated Hospital of Yangtze University.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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