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Predictive Value of Combined NLR and CRP Detection for the Efficacy of Third-Generation Cephalosporins in Post-Intracerebral Hemorrhage Pneumonia: A Retrospective Study

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Abstract: This retrospective study aimed to evaluate the predictive value of combined neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) for the efficacy of third-generation cephalosporins in treating pneumonia after intracerebral hemorrhage. A total of 162 patients were enrolled and divided into an effective group (n=89) and an ineffective group (n=73) based on treatment outcome. Baseline characteristics, NLR and CRP levels at initial treatment and at efficacy evaluation, and changes in neutrophil count were compared between groups. Multivariate logistic regression was used to identify independent predictors. Results showed that the effective group had significantly lower proportions of females and patients with GCS<11, as well as lower initial NLR (9.53 vs. 12.68), lower NLR at evaluation (6.76 vs. 11.59), and lower CRP at evaluation (13.96 vs. 45.56 mg/L) (all P<0.05). The change in neutrophil count was also significantly greater in the effective group (1.97 vs. −0.39×10⁹/L). Independent predictors included gender (OR=0.060), GCS score (OR=0.058), initial NLR (OR=0.158), evaluation NLR (OR=0.135), evaluation CRP (OR=0.171), and neutrophil count change (OR=14.323), with all P values significant. The predictive model achieved an AUC of 0.953, sensitivity of 87.3%, and specificity of 92.0%. In conclusion, comprehensive assessment of these factors offers substantial value for predicting treatment response, and future multicenter studies with larger samples are needed to confirm these findings.

1. Introduction

Intracerebral hemorrhage (ICH) is an acute cerebrovascular disease associated with high rates of

mortality and disability. For patients with moderate-to-severe hemorrhage or those complicated by elevated intracranial pressure, surgical interventions—such as craniotomy for hematoma evacuation and minimally invasive puncture drainage—are essential for improving prognosis [1]. However, postoperative complications, particularly pneumonia, remain a major obstacle to patients' clinical recovery.

According to studies on intracerebral hemorrhage (ICH), the incidence of intracerebral hemorrhage-associated pneumonia is approximately 20%, with a particularly high prevalence among critically ill patients [2-3]. Data from the China Stroke Center Alliance, which enrolled 4,877 patients with subarachnoid hemorrhage across 1,476 hospitals, revealed that 1,006 patients (20.6%) developed concomitant pneumonia [4]. In intensive care units (ICUs), this incidence can rise further to 42%. The mortality rate of ICH patients complicated with pneumonia reaches as high as 18% [5]. Pneumonia not only prolongs patients' ICU stay and increases the risk of death but also substantially raises the economic burden of medical care [6]. The pathogenesis of pneumonia complicating intracerebral hemorrhage involves multiple mechanisms, including dysphagia caused by medullary lesions or impaired consciousness, disruption of the airway barrier secondary to mechanical ventilation, as well as immunosuppression and activation of inflammatory responses [7-9].

Currently, in the clinical management of post-intracerebral hemorrhage (ICH) pneumonia, most physicians tend to prefer third-generation cephalosporins as the initial empirical antibiotic regimen. However, the common causative pathogens of hospital-acquired pneumonia (Gram-negative bacilli) exhibit relatively high resistance rates to third-generation cephalosporins [10], often leading to therapeutic failure. In assessing the efficacy of initial antimicrobial therapy, clinicians frequently rely on inflammatory biomarkers such as neutrophil count, C-reactive protein (CRP), or procalcitonin, but these indicators generally lack sufficient specificity. In recent years, novel inflammatory markers derived from routine hematological parameters (e.g., neutrophil, lymphocyte, monocyte, and platelet counts) including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), particularly NLR have been widely adopted as adjunctive diagnostic tools for infectious diseases [11-12]. These markers offer advantages such as ease of measurement, low cost, and capability for dynamic monitoring, and they provide a more comprehensive reflection of the host's inflammatory and immune status, rendering them valuable in primary care settings and intensive care units. Nevertheless, studies regarding the utility of these inflammatory markers in evaluating the effectiveness of initial third-generation cephalosporin therapy for post-ICH pneumonia remain scarce. Therefore, this study aims to explore their potential clinical significance in predicting therapeutic response.

2. Materials and Methods

2.1 Baseline Clinical Characteristics

This is a retrospective study conducted at Jingzhou First People's Hospital from January 2020 to December 2024. A total of 162 patients with pneumonia following intracerebral hemorrhage treated with third-generation cephalosporins were enrolled, including 79 males and 83 females with a mean age of 61 years. Among these patients, 35 had underlying pulmonary diseases, 110 were complicated with hypertension, and 16 had diabetes mellitus. Forty-two patients had a GCS score < 11, and 95 presented with concurrent intraventricular hemorrhage.

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Age > 18 years; (2) Computed tomography (CT) confirmation of intracranial hemorrhage, including intracerebral parenchymal hemorrhage and subarachnoid hemorrhage; (3) Admission within 48 hours of symptom onset and undergoing surgical intervention within 48 hours after admission; (4) Postoperative pulmonary infection confirmed by chest CT or chest radiograph; (5) Initial antimicrobial therapy with a third-generation cephalosporin (including ceftazidime, cefotaxime, cefoperazone-sulbactam, or ceftizoxime).

Exclusion Criteria: (1) Death within 48 hours of admission; (2) Pneumonia confirmed by chest CT or chest radiograph prior to surgery; (3) Intracranial hemorrhage resulting from ischemic stroke (i.e., hemorrhagic transformation); (4) Concomitant hematological disorders affecting blood cell counts.

2.3 Data Collection

For all enrolled patients, the following baseline data were collected: demographic characteristics, comorbid conditions (including hypertension and diabetes mellitus), underlying pulmonary diseases (such as chronic obstructive pulmonary disease, emphysema, and bronchiectasis), the Glasgow Coma Scale (GCS) score at admission, the presence or absence of intraventricular hemorrhage, and the timing of surgical intervention, along with other baseline variables.

Neutrophil count, lymphocyte count and C-reactive protein (CRP) levels of all patients were collected at the initiation of initial anti-infective therapy and at the time of efficacy evaluation. The neutrophil-to-lymphocyte ratio (NLR) was calculated based on neutrophil and lymphocyte counts, and the differences in these indicators between baseline (initial treatment) and efficacy evaluation were computed. If antimicrobial therapy was effective without regimen modification, blood cell counts and CRP results obtained after 72 hours of continuous treatment were adopted as data at the efficacy evaluation time point. If antimicrobial therapy failed to achieve efficacy, laboratory results at the time of antibiotic switching were defined as data at the efficacy evaluation time point.

2.4 Diagnosis of Pneumonia

The diagnosis of pneumonia was primarily based on the Chinese Guidelines for the Diagnosis and Treatment of Hospital-Acquired Pneumonia in Adults [13], requiring the simultaneous fulfillment of the following criteria (with a greater number of fulfilled criteria corresponding to higher diagnostic accuracy):

Imaging evidence: Chest CT or radiography demonstrating newly appearing or progressive infiltrates, consolidations, or ground-glass opacities.

Clinical evidence: At least two of the following three clinical manifestations: (1) fever (temperature > 38 ℃); (2) presence of purulent airway secretions; and (3) peripheral white blood cell count > 10 ×109/L or < 4 ×109/L.

2.5 Definition of Study Groups

Patients receiving initial third-generation cephalosporin therapy for for at least 72 hours were assigned to the effective treatment group if treatment efficacy was confirmed based on body temperature, laboratory indicators and imaging findings without escalation of antimicrobial agents. Patients who received initial third-generation cephalosporin therapy for at least 72 hours but showed an ineffective therapeutic response according to body temperature, laboratory indicators and imaging examinations and required escalation of the antimicrobial regimen were classified into

the ineffective treatment group.

2.6 Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on the distribution. Comparisons between groups were performed using the independent-samples t-test or the Mann–Whitney U test, as appropriate, based on the normality of the data. Categorical variables were presented as percentages and compared between groups using the chi-square test, continuity correction test, or Fisher's exact test, as applicable. A two-sided P-value < 0.05 was considered statistically significant. Predictive performance was assessed using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC). The optimal cutoff value was defined as the value corresponding to the maximum Youden index. Variables with a P-value < 0.05 in univariate analysis were entered into a multivariate logistic regression model to identify potential factors associated with the efficacy of third-generation cephalosporins. All statistical analyses were performed using IBM SPSS Statistics 23.0 and GraphPad Prism 10.0.

3. Results

3.1 Univariate Analysis of the Efficacy of Third-Generation Cephalosporins

Table 1 Baseline characteristics of patients in the effective and ineffective treatment groups

	Total	Ineffective group (n=73)	Effective group (n=89)	P value
Sex [n(%)]				
Female	83 (51.2%)	28 (38.4%)	55 (61.8%)	0.003
Male	79 (48.8%)	45 (61.6%)	34 (38.2%)	
Age(years)	61±10	61±10	60±9	0.580
Underlying pulmonary disease [n(%)]				
No	127 (78.4%)	55 (75.3%)	72 (80.9%)	0.393
Yes	35 (21.6%)	18 (24.7%)	17 (19.1%)	
Diabetes mellitus [n(%)]				
No	146 (90.1%)	69 (94.5%)	77 (86.5%)	0.151
Yes	16 (9.9%)	4 (5.5%)	12 (13.1%)	
Hypertension [n(%)]				
No	52 (32.1%)	23 (31.5%)	29 (32.6%)	0.884
Yes	110 (67.9%)	50 (68.5%)	60 (67.4%)	
Operation duration (min)	180 (130, 210)	180 (130, 240)	170 (130, 200)	0.409
GCS score, [n(%)]				
⩾11	120 (74.1%)	38 (52.1%)	82 (92.1%)	< 0.001
< 11	42 (25.9%)	35 (47.9%)	7 (7.9%)	
Combined intraventricular hemorrhage [n(%)]				
No	67 (41.4%)	23 (31.5%)	44 (49.4%)	0.021
Yes	95 (58.6%)	50 (68.5%)	45 (50.6%)	

There were 55 female patients (61.8%) in the effective treatment group and 28 female patients (38.4%) in the ineffective treatment group, and the difference between the two groups was statistically significant (P = 0.003). Seven patients (7.9%) in the effective treatment group had a GCS score < 11, which was significantly lower than the proportion of patients with a GCS score <

11 in the ineffective treatment group (47.9%, P < 0.001). Forty-five patients (50.6%) in the effective treatment group had concurrent intraventricular hemorrhage, this proportion was markedly lower than that in the ineffective treatment group (68.5%, P = 0.021). No statistically significant differences were observed between the effective and ineffective treatment groups with respect to age, underlying pulmonary diseases, diabetes mellitus and hypertension (all P > 0.05). See Table 1.

The median baseline NLR values upon initiation of initial third-generation cephalosporin therapy were 9.53 and 12.68 in the effective treatment group and ineffective treatment group, respectively, and the difference between the two groups was statistically significant (P = 0.008). No significant intergroup differences were found in neutrophil count, lymphocyte count and C-reactive protein (CRP) levels at the initiation of third-generation cephalosporin therapy (all P > 0.05). (See Table 2 for details.)

At the time of efficacy assessment, the median neutrophil count in the effective treatment group was 7.28×109/L, compared with 10.30×109/L in the ineffective treatment group, with a significant difference between the two groups (P < 0.001). The median lymphocyte count in the effective treatment group was 1.08×109/L, which was significantly higher than that in the ineffective treatment group (0.82×109/L, P = 0.002). At efficacy evaluation, the median NLR values in the effective and ineffective treatment groups were 6.76 and 11.59, respectively, with a statistically significant difference (P < 0.001). The median CRP levels at efficacy assessment were 13.96 mg/L in the effective treatment group and 45.56 mg/L in the ineffective treatment group, also demonstrating a statistically significant difference (P < 0.001). The change in neutrophil count from initial treatment to efficacy evaluation (Δneutrophil) was 1.97×109/L in the effective treatment group, which was significantly higher than that in the ineffective treatment group (−0.39×109/L, P < 0.001). However, no statistically significant differences were observed between the two groups in terms of changes in lymphocyte count, NLR, or CRP (all P > 0.05), as shown in Table 2.

Table 2 Comparison of inflammatory markers between the effective and ineffective treatment groups

	Treatment failure (n=73)	Treatment response (n=89)	*P* value
	At initial treatment		
Neutrophil count ($\times10^9$/L)	9.86 (7.71, 12.81)	9.14 (7.45, 11.42)	0.177
Lymphocyte count ($\times10^9$/L)	0.83 (0.58, 1.22)	0.94 (0.75, 1.38)	0.056
Neutrophil-to-lymphocyte ratio (NLR)	12.68 (7.05, 19.46)	9.53 (6.17, 13.58)	0.008
C-reactive protein (CRP, mg/L)	8.62 (2.23, 56.92)	4.96 (2.00, 14.65)	0.088
	At efficacy evaluation		
Neutrophil count ($\times10^9$/L)	10.30 (8.16, 12.76)	7.28 (5.82, 8.94)	< 0.001
Lymphocyte count ($\times10^9$/L)	0.82 (0.58, 1.23)	1.08 (0.85, 1.40)	0.002
Neutrophil-to-lymphocyte ratio (NLR)	11.59 (8.19, 17.20)	6.76 (4.26, 10.05)	< 0.001
C-reactive protein (CRP, mg/L)	45.56 (18.49, 102.69)	13.96 (5.75, 35.89)	< 0.001
	Difference value (Δ)		
Neutrophil count ($\times10^9$/L)	-0.39 (-2.22, 2.11)	1.97 (0.31, 4.07)	< 0.001
Lymphocyte count ($\times10^9$/L)	-0.06 (-0.36, 0.37)	-0.09 (-0.33, 0.26)	0.524
Neutrophil-to-lymphocyte ratio (NLR)	0.68 (-5.57, 6.92)	2.23 (-0.23, 5.93)	0.057
C-reactive protein (CRP, mg/L)	-16.83 (-78.44, 6.77)	-7.47 (-20.16, 5.11)	0.104

3.2 Multivariate Analysis of the Efficacy of Third-Generation Cephalosporins

Receiver operating characteristic (ROC) curve analysis was performed to establish the cutoff values for meaningful variables in predicting the efficacy of the initial antimicrobial regimen. The

optimal cutoff value of the initial NLR for predicting treatment efficacy was 10.78, with an area under the curve (AUC) of 0.621 (P = 0.008) (Figure 1A). At the time of efficacy assessment, the cutoff values of neutrophil count, lymphocyte count, NLR, and CRP for predicting the effectiveness of the initial regimen were 9.65×109/L, 0.88×109/L, 7.75, and 16.41mg/L, respectively, with corresponding AUCs of 0.784 (Figure 1B), 0.640 (Figure 1C), 0.787 (Figure 1D), and 0.761 (Figure 1E), all with P < 0.05. The change in neutrophil count from initial treatment to efficacy assessment (Δneutrophil) yielded a cutoff value of 0.09×109/L for predicting treatment efficacy, with an AUC of 0.736 (P < 0.001) (Figure 1F).

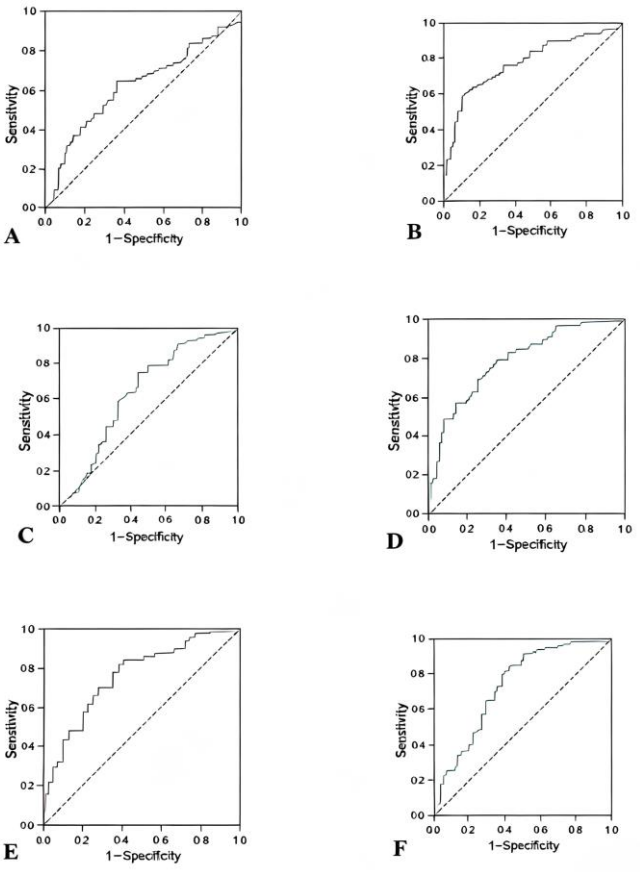

Figure 1 ROC curves of various inflammatory markers for predicting the efficacy of third-generation cephalosporins in post-ICH pneumonia

The following variables were entered into a multivariate logistic regression model to assess their association with the efficacy of the initial antimicrobial regimen, including sex, Glasgow Coma Scale (GCS) score, presence of intraventricular hemorrhage, NLR at initial treatment, neutrophil count at efficacy assessment, lymphocyte count at efficacy assessment, NLR at efficacy assessment, CRP at efficacy assessment, and the change in neutrophil count from initial treatment to efficacy assessment (Δneutrophil). The results demonstrated that sex (OR = 0.060, 95% CI: 0.007–0.484, P = 0.008), GCS score (OR = 0.058, 95% CI: 0.007–0.444, P = 0.006), NLR at initial treatment (OR = 0.158, 95% CI: 0.025–0.994, P = 0.049), NLR at efficacy assessment (OR = 0.135, 95% CI: 0.019–0.980, P = 0.048), CRP at efficacy assessment (OR = 0.171, 95% CI: 0.035–0.835, P = 0.029), and Δneutrophil (OR = 14.323, 95% CI: 1.987–103.216, P = 0.008) were identified as potential factors associated with the effectiveness of the initial antimicrobial regimen (Table 3).

The multivariate logistic regression model demonstrated a strong predictive performance, with an area under the curve (AUC) of 0.953 ($P < 0.001$), a sensitivity of 87.3%, a specificity of 92.0%, and a Youden index of 0.792 (Figure 2).

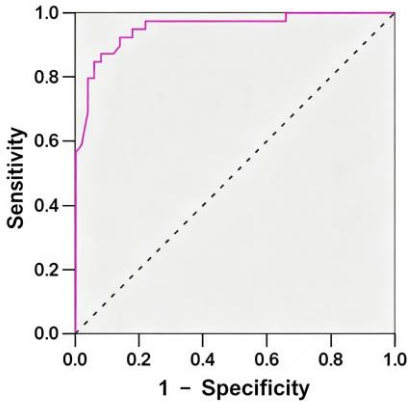

Figure 2 ROC curve of the predictive model for clinical response to third-generation cephalosporins in patients with post-intracerebral hemorrhage pneumonia

Table 3 Results of multivariate logistic regression analysis

Factor	B coefficient	S.E.	Wald χ^2	P value	OR(95%CI)
Sex	-2.815	1.065	6.980	0.008	0.060 (0.007, 0.484)
GCS	-2.855	1.042	7.508	0.006	0.058 (0.007, 0.444)
Concurrent intraventricular hemorrhage	-0.686	0.937	0.535	0.464	0.504 (0.080, 3.163)
NLR at initial treatment	-1.845	0.938	3.865	0.049	0.158 (0.025, 0.994)
Neutrophil count at efficacy evaluation	-0.844	0.942	0.804	0.370	0.430 (0.068, 2.723)
Lymphocyte count at efficacy evaluation	-1.284	0.914	1.974	0.160	0.277 (0.046, 1.660)
NLR at efficacy evaluation	-1.999	1.010	3.920	0.048	0.135 (0.019, 0.980)
Difference in neutrophil count	2.662	1.008	6.978	0.008	14.323 (1.987, 103.216)
CRP at efficacy evaluation	-1.768	0.810	4.760	0.029	0.171 (0.035, 0.835)

4. Discussion

In this study, we successfully constructed a multivariate predictive model for evaluating the efficacy of third-generation cephalosporins in the treatment of post-intracerebral hemorrhage pneumonia. The model incorporated readily available clinical indicators, including sex, Glasgow Coma Scale (GCS) score, dynamic monitoring of NLR, and CRP, and demonstrated excellent predictive performance, with an area under the curve (AUC) exceeding 0.950. The key clinical value of this model lies in its ability to identify patients at high risk of treatment failure at an early stage, thereby prompting clinicians to promptly escalate or modify antimicrobial therapy in a timely manner. This approach facilitates individualized treatment and contributes to the improvement of clinical outcomes.

The Glasgow Coma Scale (GCS) score objectively reflects the level of consciousness in patients with intracerebral hemorrhage by comprehensively assessing their eye-opening, verbal, and motor responses. The GCS score is closely correlated with the severity of neurological impairment caused by the hematoma, with lower scores indicating more severe consciousness disturbance. Numerous studies have confirmed that the GCS score is an independent risk factor for stroke-associated pneumonia [14–15]. Patients with low GCS scores often present with impaired consciousness, which compromises airway self-protective mechanisms and impairs secretion clearance, thereby significantly increasing the risk of aspiration. Moreover, these patients frequently exhibit immunosuppression, further predisposing them to respiratory tract infections. In our study, only 7.9% of patients in the treatment-effective group had a GCS score < 11, whereas this proportion reached 47.9% in the treatment-ineffective group. Zhu Y et al. also reported that ICU patients with neurological dysfunction exhibit distinct pulmonary pathogen profiles and worse clinical outcomes [16]. Therefore, we hypothesize that patients with lower GCS scores, owing to more severe neurological damage, may be more susceptible to infection with drug-resistant strains, thereby increasing the difficulty of treatment.In addition, our study revealed that sex may be associated with the therapeutic response to pneumonia following intracerebral hemorrhage. The proportion of female patients in the treatment-effective group was significantly higher than that in the treatment-ineffective group. Previous studies have shown that male patients have higher rates of pneumonia incidence and mortality compared with females. López-de-Andrés A et al. reported significantly higher pneumonia incidence in male patients [17]. Among individuals over 80 years of age, the perioperative pneumonia rate was also significantly higher in males than in females [18]. Another study indicated that among patients with community-acquired pneumonia, males presented with more severe illness and higher mortality rates [19]. Based on the above evidence, we speculate that the higher proportion of female patients in the treatment-effective group may be attributable to the relatively milder severity of pneumonia in female patients.

The most noteworthy finding of the present study is that the neutrophil-to-lymphocyte ratio (NLR) at initial treatment and efficacy evaluation, C-reactive protein (CRP) at efficacy evaluation, as well as the difference in neutrophil count between initial treatment and efficacy evaluation, are closely associated with the therapeutic response to initial treatment with third-generation cephalosporins in patients with pneumonia after intracerebral hemorrhage. As an inflammatory biomarker calculated from peripheral blood cell counts, NLR has been investigated predominantly for its value in the diagnosis and prognostic assessment of pneumonia following intracerebral hemorrhage in most recent studies [20]. Nevertheless, systematic reports regarding the role of NLR in evaluating the efficacy of anti-infective therapy with third-generation cephalosporins remain scarce. Currently, NLR is more commonly applied to predict responses to anti-tumor therapy [21], and reduced NLR levels generally indicate favorable short-term therapeutic responses. Furthermore, a small number of studies suggest that pretreatment NLR combined with other indicators can predict the therapeutic efficacy of infectious diseases. For instance, Liu et al. [22] demonstrated that the combined detection of serum procalcitonin, NLR and CRP before treatment yielded an AUC of 0.945 for predicting the risk of treatment failure in children with Mycoplasma pneumoniae pneumonia. Another study reported that the combination of procalcitonin, lactate dehydrogenase, interleukin-6 and NLR achieved an AUC as high as 0.991 in predicting treatment outcomes of bacterial bloodstream infection [23]. Mechanistically, NLR reflects not only the systemic inflammatory burden but also the degree of immune system impairment. CRP, an acute-phase response protein synthesized by the liver, rises rapidly after infection onset. Such inflammatory and immune reactions are more pronounced in patients with intracerebral hemorrhage complicated by pneumonia. Accordingly, dynamic changes in NLR and CRP levels occur during anti-infective treatment. Based on our findings, monitoring dynamic alterations in relevant inflammatory

biomarkers at baseline and 72 hours after treatment initiation helps estimate the risk of treatment failure with third-generation cephalosporins and provides evidence for subsequent adjustment of therapeutic strategies.

Nevertheless, several limitations of the present study should be acknowledged. First, the retrospective design and limited sample size may give rise to selection bias. Second, the therapeutic outcomes of patients are affected by multiple confounding factors, which may interfere with the accuracy of the analytical results. In addition, the accuracy of the dynamic changes in inflammatory indicators before and after treatment relies strictly on laboratory data obtained at fixed time points. Minor variations in the actual timing of efficacy evaluation may introduce deviations in the calculation of such changes. Furthermore, this study failed to thoroughly explore the specific molecular mechanisms and underlying signaling pathways by which inflammatory indicators modulate the therapeutic efficacy of third-generation cephalosporins. In future studies, we will expand the sample size and conduct multicenter external validation to improve the generalizability of the findings.

Despite the aforementioned limitations, our study demonstrated that the combined assessment of sex, GCS score, NLR at initial treatment and at efficacy evaluation, CRP level at efficacy evaluation, and the change in neutrophil count from baseline to efficacy assessment (Δneutrophil) exhibited high predictive value for the efficacy of third-generation cephalosporins in the treatment of post-intracerebral hemorrhage pneumonia. Dynamic monitoring of these indicators may facilitate the early identification of patients at risk of poor therapeutic response, thereby enabling timely adjustment of treatment strategies and ultimately improving patient prognosis.

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