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ORIGINAL RESEARCH

The prognostic value of neutrophil-to-lymphocyte ratio combined with multiple indicators in patients with severe pneumonia

Qing Hu[1,2], Pan Pan[3], Bing Xiang[1,2,*]

[1]Department of hematology, West China Hospital, Sichuan University, 610000 Chengdu, Sichuan, China
[2]Chengdu Shangjin Nanfu Hospital of West China Hospital, Sichuan University, 610000 Chengdu, Sichuan, China
[3]Emergency Department, West China Hospital, Sichuan University, 610000 Chengdu, Sichuan, China

***Correspondence**
study@hhu.edu.cn
(Bing Xiang)

Abstract

This study aims to evaluate the prognostic significance of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), creatinine, and lactic acid in patients diagnosed with severe pneumonia (SP). We conducted a retrospective analysis of patient data from our hospital who were diagnosed with severe pneumonia between June 2020 and June 2023. The patients were divided into two groups: survivors (363 cases) and non-survivors (346 cases). We collected demographic, clinical and laboratory data and used multifactorial logistic regression to identify prognostic risk factors. We also evaluated the predictive accuracy of each parameter using Receiver Operating Characteristic (ROC) curve analysis. Statistical analysis was performed using SPSS 26.0. In the study, it was found that patients who died had higher levels of certain markers in their blood, including NLR, PLR, procalcitonin (PCT), C-reactionprotein (CRP), Brain natriuretic peptide (BNP), blood creatinine, lactic acid and age Shock Index (SI) ($p < 0.001$). They also had lower levels of partial pressure of oxygen (PO_2) and partial pressure carbon dioxide (PCO_2) ($p < 0.05$). On the other hand, patients who survived had lower levels of these markers and higher levels of PO_2 and PCO_2. After analyzing the data, it was determined that NLR, PLR, creatinine and lactic acid were significant risk factors for poor prognosis in patients with SP. The Area Under ROC Curve (AUCs) for these factors ranged from 0.577 to 0.725, and they had sensitivities ranging from 67.9% to 77.7% and specificities ranging from 61.2% to 80.7%. When these factors were combined, they provided a more accurate evaluation of prognosis, with an AUC of 0.789 and a sensitivity of 67.1% and specificity of 77.4% at the optimal threshold. NLR, PLR, creatinine and lactic acid are significant prognostic indicators in SP patients. A combined assessment of these parameters enhances prognostic accuracy, aiding in better management.

Keywords

Severe pneumonia; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Prognostic value

1. Background

Severe Pneumonia (SP) is a serious of lung infection that causes significant inflammation in the lung tissues such as bronchioles, alveoli and interstitium. This condition can worsen over time and lead to organ dysfunction and even life-threatening complications. The progression and severity of pneumonia are influenced by two key factors: immune response and tissue resilience [1]. It is worth noting that around 20% of hospitalized pneumonia patients require intensive care, and one-third of these patients need mechanical ventilation [2]. SP is a leading cause of death from infectious diseases and can rapidly develop into a severe condition [3]. Recent studies have shown that a single inflammatory marker may not provide sufficient insight into the severity and prognosis of SP. However, the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) have been found to be useful in diagnosis. In particular, NLR is an effective serum biomarker for community-acquired pneumonia and can help identify SP patients and assess the risk of complications [4]. Elevated NLR and PLR levels have also been linked with stroke-associated pneumonia, suggesting their potential as blood-based biomarkers for this condition [5]. While current research on NLR combined with other factors for SP prognosis is limited, this study aims to explore the relationship between NLR and multiple factors, and to assess its predictive efficacy for SP patients' prognosis.

2. Materials and methods

2.1 Study subjects

A retrospective analysis was conducted on patients with severe pneumonia (SP) who were admitted to our hospital between June 2020 and June 2023. The inclusion criteria for this study were modified based on the recommendations of international scholars, which aimed to simplify the traditionally complex diagnostic criteria for severe pneumonia [6]. Our study adopted China's 2015 guidelines for adult Community-Acquired Pneumonia (CAP), which utilizes these simplified criteria. Diagnosis of severe pneumonia is established if patients meet either one major criterion or at least three minor ones: Major Criteria: Necessity for mechanical ventilation via tracheal intubation. Requirement of vasoactive drugs after active fluid resuscitation in cases of infectious shock. Minor Criteria: Respiratory rate exceeding 30 breaths per minute. Ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2 ratio). Presence of multiple lobar infiltrates. Impaired consciousness or disorientation. Blood urea nitrogen levels $\geq$7 mmol/L. Hypotension necessitating active fluid resuscitation. Criteria for Exclusion: Patients were excluded if they had: Severe hepatic or renal insufficiency, immunocompromise or immunosuppression, hematologic diseases, incomplete clinical data, recent use of medications affecting peripheral blood cell counts, and non-pulmonary infections.

The investigation followed the principles of medical ethics, was sanctioned by the hospital's Ethics Committee, and procured informed consent from patients or their kin for all interventions and therapies.

2.2 Research methods

2.2.1 Data collection

We documented patient characteristics, including age, gender, duration of hospitalization, past medical history encompassing hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic renal insufficiency and sepsis. In addition to this information, we also recorded systolic and diastolic blood pressure readings as well as heart rate, respiratory rate and oxygen saturation of blood (SPO_2) levels.

2.2.2 Clinical laboratory indicator collection

The early morning fasting venous blood samples of SP patients were taken and analyzed at our hospital's central laboratory. Blood neutrophil counts and percentages, lymphocyte counts, neutrophil-to-lymphocyte ratios, platelet-to-lymphocyte ratios, platelets, hemoglobin, procalcitonin (PCT), C-reactive protein (CRP), recombinant human brain natriuretic peptide (BNP), blood creatinine, serum albumin, blood glucose, potential of hydrogen (PH), partial pressure of oxygen (PO_2), partial pressure carbon dioxide (PCO_2), Carbonic acid hydrogen radical (HCO_3^-), potassium, sodium and lactate levels were all measured.

2.2.3 Grouping method

Patients were divided into two groups according to their survival status: the survival group (363 cases) and the death group (346 instances).

2.2.4 Statistical methods

The management and analysis of data were executed through the utilization of Statistical Package for the Social Science (SPSS) 26.0 (IBM, Chicago, IL, USA). The assessment of quantitative data normality was conducted by means of the Shapiro-Wilk (SW) test. Data that displayed a normal distribution were presented as mean $\pm$ standard deviation ($\bar{x} \pm s$) and then compared between groups using the two independent samples t-test. On the other hand, non-normally distributed data were expressed as median (M) with an Interquartile Range (IQR 25%, 75%), and group comparisons were carried out utilizing the Kruskal-Wallis test. The categorical data were presented as case numbers and percentages, which were then compared using the χ^2 test. Prognostic risk factors were identified through logistic regression analysis, while assessing the effectiveness of potential risk factors in prognosis assessment was done via Receiver Operating Characteristic (ROC) curve evaluation. All tests conducted were two-tailed and statistical significance was determined at a level of 0.05.

3. Results

3.1 General characteristics

The study included 709 eligible SP patients, separated into two groups: 363 (51.20% survival) and 346 (48.80% mortality). There were no significant differences between the groups in terms of gender, age, length of hospital stay, or comorbidities ($p > 0.05$), as shown in Table 1.

3.2 Laboratory indicator comparison

Laboratory results showed significant differences between the survival and death groups in lymphocyte counts (LYM), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), platelet-to-lymphocyte ratio (PLR), procalcitonin (PCT), creatinine, and lactic acid levels between the survival and death groups ($p < 0.05$). Table 2 shows that the death group had significantly higher values for NLR, PLR, PCT, CRP, BNP, blood creatinine, lactic acid, and age severity index (age SI) ($p < 0.001$), but lower PO_2 and PCO_2 levels compared to the survival group ($p < 0.05$).

3.3 Multivariate logistic regression analysis

In the multivariate logistic regression analysis, a stepwise backward selection strategy was used. Initially, the model incorporated all potential risk factors for both groups. The variables with p-values greater than 0.05 were then excluded sequentially, leaving just the significant variables in the final model. NLR, PLR, creatinine, and lactic acid were found to be significant risk factors for poor outcomes in SP patients ($p < 0.001$), as shown in Table 3.

3.4 Prognostic predictive value of each risk factor

NLR, PLR, creatinine, and lactate showed significant prognostic value for SP patient prognosis. The areas under the curve

TABLE 1. Comparative analysis of clinical characteristics between the survival group and the mortality group (n, %, $\bar{x} \pm s$).

Variable	Survival group (n = 363)	Mortality group (n = 346)	χ^2/t value	p value
Gender				
Male	227 (62.53%)	223 (64.45%)	0.281	0.596
Female	136 (37.47%)	123 (35.55%)		
Age	64.66 ± 17.95	65.96 ± 17.56	−0.973	0.331
Hospitalization days	23.59 ± 17.42	23.62 ± 13.48	−0.034	0.973
Hypertension	140 (38.57%)	129 (37.28%)	0.124	0.752
Diabetes	86 (23.69%)	76 (21.97%)	0.299	0.584
Chronic obstructive pulmonary disease	103 (28.37%)	104 (30.06%)	0.243	0.622
Chronic renal failure	87 (23.97%)	89 (25.72%)	0.293	0.589
Sepsis	126 (34.71%)	133 (38.44%)	1.062	0.303

(AUCs) were 0.725, 0.719, 0.577 and 0.679, respectively, with sensitivity of 77.70%, 71.10%, 67.90% and 72.50%, and specificity of 67.80%, 80.70%, 75.80% and 61.20%, respectively. The combined prognostic evaluation of these factors resulted an AUC of 0.789, with an optimal threshold sensitivity of 67.10% and specificity of 77.40%, as shown in Table 4 and Fig. 1.

4. Discussion

Critical pneumonia frequently requires admission to the Intensive Care Unit (ICU) due to its rapid progression and severity, making it a prevalent critical condition in clinical settings. Patients may rapidly exhibit symptoms such as disturbances in consciousness, hypovolemic shock, hepatic and renal insufficiency, and impairment of the circulatory system. Distinguished by its sudden onset, limited treatment timeframe, and elevated morbidity and mortality rates, precise prognosis prediction and evaluation for critical pneumonia is of paramount significance. Standard infection markers such as C-reactive protein (CRP) [7] and white blood cell (WBC) counts demonstrate inadequate sensitivity and specificity, highlighting the necessity for more succinct and conveniently accessible indicators to assess SP prognosis. Despite the abundance of clinical signs available, determining illness severity and prognosis with a single signal is difficult. As a result, there is a crucial need to explore the combined use of biomarkers for more precise clinical evaluation.

Our research has revealed that a model amalgamating NLR, PLR, creatinine and lactate exhibits remarkable sensitivity and specificity in forecasting SP prognosis. This model can act as an adjunct to existing infection markers and furnish invaluable guidance in clinical settings.

NLR and PLR can reflect the inflammatory and immune status of the host. The inflammatory response is a pivotal element in the advancement and progression of Community-Acquired Pneumonia (CAP). NLR functions as an uncomplicated and conveniently accessible marker of inflammation, and it reflects alterations in neutrophil and lymphocyte counts during infections and has been identified as an autonomous predictor of mortality in immunocompetent CAP patients across various age groups, including children and seniors [8]. Typically, neutrophilia and/or lymphopenia, common immune responses during infections, contribute to increased NLR levels. The root causes for these alterations may involve demarginalization of neutrophils coupled with delayed apoptosis, alongside marginalization of lymphocytes complemented by accelerated apoptosis [9]. Numerous investigations have illuminated the correlation between Platelet-to-Lymphocyte Ratio (PLR) and unfavorable prognosis in diverse ailments, including but not limited to rheumatic diseases, glomerulonephritis and cancer [10–12].

Our study reveals that the NLR outperforms PLR in predicting in-hospital mortality as evidenced by a higher Area Under the Curve (AUC) value. This may be because NLR, as an indicator of immune homeostasis imbalance and inflammation intensity, reflects both aspects of innate and acquired immunity. As such, it represents the physiological response of the immune system to systemic inflammation. Furthermore, lymphopenia and neutrophilia are physiological immune responses to trauma, stress, and systemic inflammatory diseases. In the realm of infectious diseases, particularly those caused by bacterial pathogens, the mobilization and stimulation of neutrophils play a critical role in mounting an efficacious immune response [13]. Moreover, numerous investigations have demonstrated an association between NLR and unfavorable prognosis or elevated mortality in stroke-associated pneumonia [14]. Consistent with previous literature, NLR surpasses existing scoring systems such as CURB-65 and Pneumonia Severity Index (PSI), along with commonly used biomarkers including procalcitonin, adrenomedullin, CRP levels, and white blood cell counts for prognosis prediction. Furthermore, elevated NLR levels were connected to higher mortality rates among renal transplant recipients suffering from severe pneumonia. Remarkably enough, NLR was superior to PLR along with PSI and CURB-65 scores in forecasting mortality among these patients [15].

In addition, the sensitivity of NLR was higher (77.70%), while the specificity of PLR was higher (80.7%). This may be due to comparable platelet levels observed among both

TABLE 2. Comparison of laboratory parameters between the survival and mortality groups.

Variable	Survival group (n = 363)	Mortality group (n = 346)	*Z* value	*p* value
Systolic blood pressure (mmHg)	128.00 (113.00, 148.00)	127.00 (115.00, 146.00)	0.991	0.362
Diastolic blood pressure (mmHg)	76.00 (67.00, 89.00)	75.00 (65.00, 88.00)	0.863	0.425
Heart rate (beats/min)	116.00 (100.00, 136.00)	121.00 (105.00, 138.00)	−1.953	0.051
Respiratory rate (beats/min)	33.00 (26.00, 40.00)	32.00 (26.00, 40.00)	0.524	0.604
SPO_2 (%)	88.00 (81.00, 94.00)	84.00 (77.00, 92.00)	1.332	0.216
WBC ($\times 10^9$/L)	10.80 (7.93, 14.71)	10.80 (8.29, 14.78)	−0.713	0.484
Neutrophils ($\times 10^9$/L)	9.41 (6.82, 12.22)	9.41 (6.90, 12.73)	−0.912	0.362
Granulocyte (%)	87.60 (83.40, 91.30)	87.50 (82.80, 91.50)	0.930	0.352
Hct (L/L)	0.34 (0.28, 0.40)	0.33 (0.26, 0.38)	2.124	0.034
LYM ($\times 10^9$/L)	0.61 (0.42, 0.91)	0.53 (0.31, 0.63)	5.412	<0.001
NLR	11.65 (5.67, 17.25)	17.75 (13.29, 23.64)	−10.374	<0.001
PLT ($\times 10^9$/L)	122.00 (85.00, 187.00)	122.00 (76.00, 150.00)	2.352	0.019
PLR	177.18 (98.38, 188.19)	221.61 (184.85, 230.19)	−10.100	<0.001
Procalcitonin (μg/L)	2.95 (1.08, 2.95)	3.54 (1.68, 3.54)	−6.344	<0.001
C-Reactive Protein (mg/L)	121.38 (87.30, 141.00)	125.42 (125.42, 125.42)	−5.142	<0.001
BNP (pg/mL)	1771.00 (506.00, 5045.50)	2731.50 (1216.00, 8719.50)	−4.162	<0.001
Hemoglobin (g/L)	109.00 (88.00, 135.00)	107.00 (82.00, 126.00)	1.824	0.069
Creatinine (μmol/L)	80.00 (53.00, 109.00)	85.00 (63.90, 139.00)	−3.533	<0.001
Albumin (g/L)	29.80 (26.50, 33.20)	28.70 (25.40, 33.30)	1.965	0.050
Blood potassium (mmol/L)	3.70 (3.30, 4.36)	3.90 (3.42, 4.51)	−2.686	0.007
Blood sodium (mmol/L)	135.40 (132.00, 140.40)	135.05 (130.50, 139.60)	1.823	0.068
Blood glucose (mmol/L)	8.48 (6.80, 11.70)	8.20 (6.10, 11.80)	1.202	0.236
PH	7.33 (7.31, 7.43)	7.36 (7.30, 7.44)	−1.467	0.143
PO_2 (mmHg)	75.90 (59.80, 83.68)	72.30 (58.00, 72.90)	4.725	<0.001
PCO_2 (mmHg)	45.40 (33.90, 51.00)	44.35 (31.50, 47.00)	2.955	0.003
Lactate (mmol/L)	2.10 (1.80, 2.70)	2.90 (2.20, 3.80)	−8.291	<0.001
HCO_3^-	24.60 (21.60, 27.90)	19.80 (18.10, 22.20)	10.118	<0.001
Age shock index	55.09 (44.00, 69.71)	64.37 (48.76, 82.72)	−5.122	<0.001

Note: SPO_2: Pulse Oxygen Saturation; WBC: White blood cell; Hct: Hematocrit; LYM: lymphocyte; NLR: neutrophil-to-lymphocyte ratio; PLT: Platelet; PLR: platelet-to-lymphocyte ratio; BNP: Brain natriuretic peptide; PH: hydrogen ion concentration; PO_2: Oxygen partial pressure; PCO_2: Partial pressure of carbon dioxide; HCO_3^-: Bicarbonate radical.

TABLE 3. Multivariate logistic regression analysis of prognostic factors in patients with severe pneumonia.

Variable	B	SE	Wald	OR	95% CI	*p* value
NLR	0.064	0.009	46.881	1.067	(1.047, 1.086)	<0.001
PLR	0.007	0.001	48.191	1.007	(1.005, 1.010)	<0.001
Creatinine	0.002	0.001	3.724	1.002	(1.000, 1.005)	0.047
Lactate	0.215	0.039	30.886	1.240	(1.149, 1.338)	<0.001

Note: NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; B: coefficient of regression; SE: Standard Error; OR: odd ratio; CI: confidence interval.

TABLE 4. Prognostic value of various parameters in patients with severe pneumonia.

Variable	AUC	95% CI	*p* value	Sensitivity (%)	Specificity (%)
NLR	0.725	(0.687, 0.763)	<0.001	77.70	67.80
PLR	0.719	(0.679, 0.758)	<0.001	71.10	80.70
Creatinine	0.577	(0.535, 0.618)	<0.001	67.90	75.80
Lactate	0.679	(0.638, 0.720)	<0.001	72.50	61.20
NLR + PLR + Creatinine + Lactate	0.789	(0.756, 0.822)	<0.001	67.10	77.40

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; AUC: Area Under the Curve; CI: confidence interval.

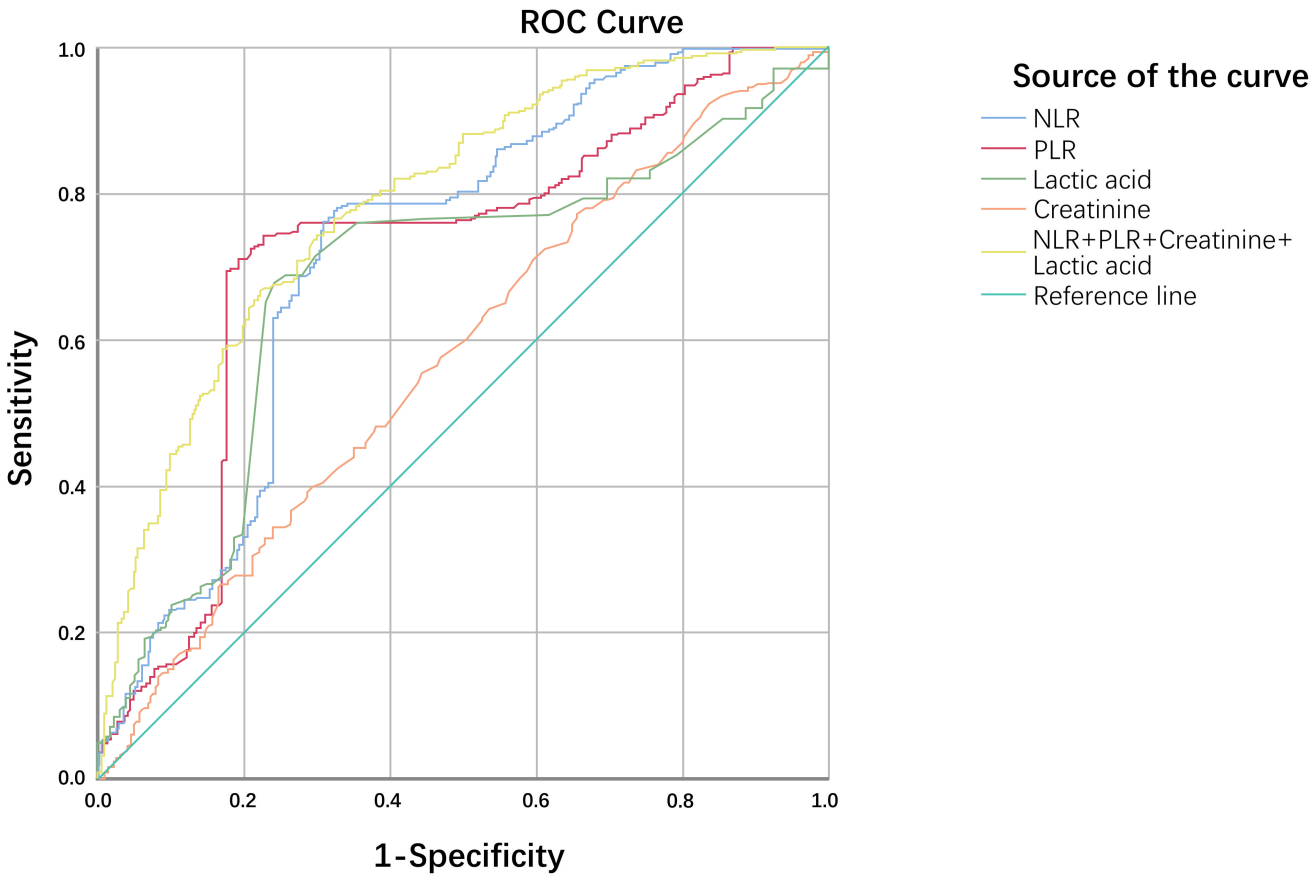

FIGURE 1. ROC curve of various indexes in patients with severe pneumonia. ROC: Receiver Operating Characteristic; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

survivors and non-survivors. Platelets are essential in regulating inflammatory and immune responses by modulating platelet surface adhesion, immune receptor expression, and the release of inflammatory mediators and cytokines that facilitate leukocyte interactions and recruitment [16].

Creatinine is a metabolite of creatine and phosphocreatine in muscles, and it is commonly used to assess kidney function [17]. When renal function declines, creatinine accumulates in the blood, leading to an elevated level [18]. In our study, creatinine was found to be elevated in the non-survival group and was identified as an independent risk factor for SP. Prior research has indicated an association between renal impairment and adverse outcomes in pneumonia [19]. In a study evaluating the predictive ability of estimated glomerular filtration rate (eGFR) for pneumonia prognosis, the receiver operating characteristic (ROC) curve using the Youden index demonstrated an AUC of 0.64. Patients hospitalized with pneumonia and an eGFR <56 mL/min/1.73 m^2 were at a higher risk of in-hospital mortality. This may be attributed to the increased risk of various infectious diseases associated with renal dysfunction. Furthermore, the decline in kidney function may lead to immune dysfunction, contributing to the poor prognosis of SP patients [20]. However, in our findings, the AUC area was only 0.577, with relatively low specificity and sensitivity. This suggests that the impact of creatinine on severe pneumonia is minimal (OR: odd ratio = 1.002), and its association with adverse outcomes in SP may still be mediated by inflammation.

In the human body, lactate can be produced through the glycolytic pathway, especially during exercise or in hypoxic conditions [21]. Clinically, elevated lactate levels are typically considered an indicator of tissue hypoxia or poor perfusion

[22]. High lactate levels are closely associated with inflammatory responses, shock states, and tissue hypoxia, all of which may worsen the prognosis of conditions such as pneumonia. A characteristic feature of severe pneumonia is low oxygen saturation, and tissue hypoxia can lead to increased lactate levels. Previous studies have indicated that elevated lactate can further exacerbate infections. Additionally, it can lead to the occurrence and progression of multiple organ dysfunction, thereby further increasing the risk of patient mortality [23]. In our study, the AUC value was 0.679, with good sensitivity, which may be related to the systemic inflammation and multi-organ dysfunction caused by changes in lactate levels. These findings emphasize the importance of timely monitoring and managing lactate levels to improve patient prognosis and reduce mortality rates.

Some studies have incorporated PLR, erythrocyte distribution width, and NLR to evaluate the prognostic value in pediatric severe pneumonia. Other researchers have combined chest CT scores with NLR to predict pneumonia prognosis [23], while there are investigations into the clinical utility of NLR, PLR and the Systemic Inflammatory Response Index in forecasting the occurrence and severity of pneumonia following intracerebral hemorrhage [24]. Although there is variation in the prediction models and their respective predictive values among studies, they all play a significant role in directing clinical treatment. The findings of this investigation unveil novel prospects for delving into the collective utilization of diverse indicators, such as the NLR, to evaluate the prognosis of SP patients. Prior studies have predominantly concentrated on evaluating prognosis based on a variety of inflammation-related factors. In addition, our research has uncovered the prognostic significance of lactate and creatinine. This underscores the necessity of not only managing inflammation but also monitoring and regulating patients' metabolic parameters, such as creatinine and lactate levels. Such findings offer valuable guidance for enhancing the prognosis of patients diagnosed with SP.

The present investigation is subject to certain limitations. Given its observational nature and data restrictions, multiple confounding factors such as etiology, susceptibility to antimicrobial drugs, patient age, and comorbidities could potentially affect the mortality of patients with CAP. These possible confounding variables may account for the diversity of our observations. Furthermore, given disparities in demographic, socioeconomic, and bioclinical attributes, our outcomes might not be universally relevant to other ethnic groups. However, NLR persists as a straightforward, readily quantifiable, and auspicious indicator for forecasting the prognosis of individuals with CAP. Its efficacy, either independently or in conjunction with additional biomarkers and scoring methodologies, merits further investigation

5. Conclusions

The prognostic evaluation of patients with SP is closely linked to their NLR, PLR, creatinine and lactate levels. The combination of these four biomarkers has demonstrated significant value in assessing the prognosis of SP patients and providing superior guidance for prognostic treatment strategies.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

BX and QH—designed the research study; wrote the manuscript. QH—performed the research. QH and PP—analyzed the data. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Biomedical Ethics Review Committee of West China Hospital of Sichuan University, Grant number: 493 in 2022. All participants provided consent to participate in the study. All methods were performed according to the relevant guidelines and regulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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