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Original Article

Prognostic value of systemic inflammatory indicators in patients with severe pneumonia

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Abstract: Objective: To analyze the correlation between systemic inflammatory indicators and severe pneumonia severity, and evaluate their prognostic value for 28-day mortality. Methods: This retrospective study included 75 severe pneumonia patients treated at The First People's Hospital of Lin'an District from October 2022 to December 2023. Systemic inflammation indices - Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), Neutrophil-to-HDL-C ratio (NHR), Lymphocyte-to-HDL-C ratio (LHR), and Monocyte-to-HDL-C ratio (MHR) - were calculated from routine blood and biochemical tests. Spearman correlation analyzed relationships with APACHE II scores. Prognostic value was assessed using ROC curve analysis. Kaplan-Meier survival analysis was performed based on predefined thresholds, and sensitivity analysis evaluated model robustness. Results: SII, SIRI, NHR, LHR, and MHR levels were significantly higher in the group that died versus the group that survived ($P < 0.001$). Spearman analysis showed significant positive correlations of SIRI, NHR, and MHR with APACHE II scores ($P < 0.001$), with MHR exhibiting the strongest correlation ($r = 0.556$). Multivariate logistic regression, adjusted for procalcitonin (PCT) and neutrophil count (NEU), identified all five markers as independent factors for 28-day mortality. ROC analysis showed AUC values of 0.719, 0.688, 0.758, 0.810, and 0.802 for SII, SIRI, NHR, LHR, and MHR, respectively, with a combined AUC of 0.896. Survival analysis revealed elevated SII, LHR, and MHR associated with reduced survival ($P < 0.001$). Sensitivity analysis confirmed marker stability as mortality predictors. Conclusion: Systemic inflammatory indices (SII, SIRI, NHR, LHR, and MHR) in severe pneumonia patients significantly correlated with poor prognosis, and their combination exhibited excellent predictive value for adverse outcome.

Keywords: Systemic inflammatory indices, severe pneumonia, prognosis

Introduction

Severe pneumonia is a serious lung infection that progresses rapidly and harms people's physical and mental health. It can cause severe lung tissue damage, often leading to acute respiratory failure, and some patients may concurrently develop complications such as sepsis, toxic shock, and multiple organ dysfunction syndrome (MODS) [1, 2]. Current research shows that the incidence of severe pneumonia is increasing, with mortality rates ranging from 20% to 70% [3-5]. Despite continuous advancements in medical care - including the optimization of antibiotics (especially for multidrug-resistant pathogens) and the refinement of supportive treatments such as mechanical ventilation - clinical control of severe pneumonia has improved to some extent. However, the disease still exhibits rapid progression and high mortality, making further exploration of its pathogenesis and therapeutic strategies a major challenge for healthcare providers and researchers [6].

Research has thus far identified the significance of inflammation in the onset and progression of severe pneumonia. However, many traditional or specific inflammatory markers are limited in clinical application due to high detection cost or a complex detection procedure [7].

In recent years, several inflammation-based indices including the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), neutrophil/HDL-C ratio (NHR), lymphocyte/HDL-C ratio (LHR), and monocyte/HDL-C ratio (MHR) have attracted increasing

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research interest. Previous studies have shown that SII correlates strongly with overall survival in gastric cancer [8], while SIRI exhibits prognostic value in breast cancer and non-small cell lung cancer [9, 10]. Furthermore, NHR, LHR, and MHR, which integrate inflammatory cell counts with lipid metabolism, have been validated as effective prognostic markers in coronary artery disease [11]. Collectively, these indices provide biologically meaningful insight into systemic inflammatory status, are easily obtained from routine laboratory tests, and hold promise as reliable biomarkers for disease severity and prognosis [12].

This study aims to validate the prognostic value of simultaneously incorporating SII, SIRI, NHR, LHR, and MHR into the evaluation of severe CAP, and to assess their added value beyond traditional severity scores and biomarkers. While previous studies have explored individual inflammatory indices, this validation study examines the combined application of these five markers in a specific patient population. The results may provide additional evidence supporting the use of these readily available inflammation-based indices for improving early risk stratification.

Patients and methods

General information

Retrospective analysis selected 75 patients with severe pneumonia in The First People's Hospital of Lin'an District from October 2022 to December 2023. The protocol was approved by the Institutional Review Board of The First People's Hospital of Lin'an District (Approval Number: 2025-23), and informed consent was waived due to the retrospective use of anonymized electronic health records. The diagnosis of severe pneumonia was based on the Guidelines for the Diagnosis and Treatment of Adult Community-Acquired Pneumonia in China (Version 2016) [13].

Exclusion criteria: (1) Patients with severe cardiac, liver and kidney dysfunction; (2) Patients with malignant tumors; (3) Patients with respiratory diseases such as tuberculosis, bronchial asthma and chronic obstructive pulmonary disease (COPD); (4) Patients with concurrent infections at other sites; (5) Hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP).

The diagnosis of severe community-acquired pneumonia meeting at least one major criterion or three or more minor criteria as follows. Major criteria: (1) Need for endotracheal intubation with mechanical ventilation; (2) Septic shock requiring vasopressor support despite adequate fluid resuscitation.

Minor criteria: (1) Respiratory rate ≥ 30 breaths/min; (2) $PaO_2/FiO_2 \leq 250$ mmHg; (3) Multi-lobar infiltrates; (4) Confusion or altered mental status; (5) Blood urea nitrogen ≥ 7.14 mmol/L; (6) Systolic blood pressure < 90 mmHg.

All enrolled patients presented with varying degrees of fever (temperature 38.5-40.2°C) and shortness of breath (respiratory rate ≥ 25 breaths/min) on admission; some had delirium (APACHE II score for consciousness disturbance ≥ 2 points), all of which were consistent with the diagnostic criteria for severe pneumonia. This was a retrospective study. The study protocol was reviewed and approved by The First People's Hospital of Lin'an District. Informed consent was waived by the ethics committee due to the retrospective, anonymous, and non-interventional nature of this study. All data were analyzed anonymously, and patient privacy was strictly protected.

A two-step approach was used to identify eligible patients: (1) Electronic medical record (EMR) system was searched using the keywords "severe pneumonia" and "community-acquired pneumonia" among patients admitted to the intensive care unit from October 1, 2022 to December 31, 2023. Consecutive cases were enrolled to minimize selection bias. (2) Two investigators independently reviewed medical records and applied inclusion/exclusion criteria. The annual admission volume of approximately 300 cases refers to all severe pneumonia (including hospital-acquired and mixed types), while this study only included severe community-acquired pneumonia with complete data, which resulted in a relatively smaller sample. Loss to follow-up or incomplete data did not affect the consecutive enrollment principle. Selection bias was minimized by strict consecutive inclusion and uniform exclusion criteria.

Research method

Medical records of all enrolled patients were collected, demographic data (age, sex), comorbidities (e.g., hypertension, coronary artery disease, diabetes mellitus), complete blood count (e.g., leukocyte, neutrophil counts), biochemical parameters (e.g., HDL-C, albumin, hepatic and renal function), and coagulation indices (e.g., D-dimer, prothrombin time). Systemic inflammatory indices were calculated as follows: SII = platelet count × neutrophil count/lymphocyte count; SIRI = neutrophil count × monocyte count/lymphocyte count; NHR = neutrophil count/HDL-C; LHR = lymphocyte count/HDL-C; MHR = monocyte count/HDL-C.

The severity of the patients' conditions was assessed by APACHE II score (range: 0-71), with higher scores indicating more severe illness.

All patients were divided into a group that survived (n = 47) and a group that died (n = 28) based on 28-day survival status.

All patients underwent etiological examinations on admission, including sputum culture, blood culture, and respiratory pathogen nucleic acid testing. Empirical antimicrobial therapy was initiated based on clinical severity: cefoperazone-sulbactam (3 g q8h) combined with levofloxacin (0.5 g qd) for moderate-to-severe infections, or imipenem-cilastatin (1 g q8h) for severe infections. Subsequent therapy was adjusted according to pathogen identification and antimicrobial susceptibility results (e.g., vancomycin for methicillin-resistant Staphylococcus aureus (MRSA) infections, fluconazole for fungal infections). Additionally, the use of adjunctive therapies was recorded, including corticosteroids (methylprednisolone 40 mg once daily, duration ≤ 7 days) and immunomodulatory agents (thymosin α1, 1.6 mg every other day).

Statistical methods

All statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY) and R 4.3.4 (R Foundation for Statistical Computing). Normally distributed data were presented as mean ± standard deviation (SD) and compared using independent t-tests. Non-normally distributed data were presented as median with interquartile range [IQR; M (Q1, Q3)] and analyzed using the Mann-Whitney U test. Correlations between inflammatory indices and APACHE II scores were analyzed using Spearman's rank correlation.

For multivariate logistic regression, only procalcitonin (PCT) and neutrophil count (NEU) were included as confounders. To avoid overfitting given the limited number of deaths (n = 28), the number of covariates was strictly limited. Multicollinearity was evaluated using variance inflation factors (VIF); having all VIF < 2 indicated no significant multicollinearity. Odds ratios (OR) and 95% confidence intervals (CI) were reported.

Missing data were handled by multiple imputation (five imputed datasets), assuming missing at random (MAR). The imputation model included all variables in the main analysis (SII, SIRI, NHR, LHR, MHR, PCT, NEU, APACHE II score, and 28-day mortality). The primary results were based on the imputed dataset.

Sensitivity analyses included multiple imputation, confounder adjustment, and outlier exclusion. Two-tailed *P*-values < 0.05 were considered significant, and Bonferroni correction was applied for multiple comparisons.

A combined predictive model was constructed using multivariate logistic regression with SII, SIRI, NHR, LHR, and MHR as continuous variables. The predictive performance was evaluated using the area under the receiver operating characteristic curve (AUC). To address overfitting and validate model stability, bootstrap resampling (1,000 iterations) was performed to validate internally the combined predictive model and individual inflammatory indices. Calibration was assessed using calibration curves, Brier score, and the Hosmer-Lemeshow (H-L) test. A non-significant H-L test (P > 0.05) indicated good model calibration. The Brier score (range 0-1) was used to quantify overall prediction error, with lower values representing better accuracy.

The optimal cutoff values of systemic inflammatory indicators for survival stratification were determined by Youden index from ROC curve analysis in the present cohort. To address potential circularity, cutoff values were validated by bootstrap resampling (1,000 iterations), and only indicators with stable cutoff values and significant log-rank test were included in

Table 1. Baseline characteristics and univariate analysis of prognostic factors in severe pneumonia patients

Item	Group that died (n = 28)	Survivors (n = 47)	χ^2/t	*P* value
Sex, n (%)			0.262	0.610
Female	12 (42.86)	23 (47.22)		
Male	16 (57.14)	24 (52.78)		
Age, year	63.34±8.24	60.26±7.28	1.687	0.096
Weight	56.26±8.26	55.56±5.34	0.446	0.657
BMI	22.47±2.62	22.59±2.03	0.825	0.222
Smoking, n (%)	6 (21.43)	14 (29.79)	0.080	0.782
Alcohol use, n (%)	4 (14.29%)	19 (40.43%)	1.886	0.170
Hypertension, n (%)	7 (25.00%)	10 (21.28%)	2.090	0.148
Coronary disease, n (%)	6 (21.43%)	14 (29.79%)	0.077	0.782
Diabetes mellitus, n (%)	5 (17.86%)	12 (25.53%)	0.034	0.854
APACHE II score	22.14±5.26	16.35±4.78	4.887	< 0.001
PCT (ng/ml)	10.26±2.24	7.38±1.31	7.039	< 0.001
CRP (mg/L)	137.82±29.73	113.67±16.25	4.555	< 0.001
WBC, $\times10^9$/L	13.75±4.25	11.93±3.80	1.919	0.059
NEU, $\times10^9$/L	11.25±3.12	10.20±2.52	1.595	0.115
LYM, $\times10^9$/L	1.26±0.24	1.15±0.31	0.813	0.419
MONO, $\times10^9$/L	0.86±0.31	0.62±0.25	3.673	< 0.001
PLT, $\times10^9$/L	123.86±24.65	105.61±23.17	3.222	0.002
HDL-C, mmol/L	0.98±0.26	1.32±0.31	4.869	< 0.001
D-dimer (μg/L)	144.48±20.13	142.59±22.19	0.369	0.713
Albumin (g/L)	32.27±4.18	33.69±4.37	1.383	0.171
ALT (U/L)	57.26±7.24	51.26±6.28	3.779	< 0.001
AST (U/L)	52.19±5.38	55.53±6.49	2.292	0.025
Scr (U/L)	158.47±22.13	146.52±19.94	2.409	0.019
BUN (U/L)	8.30±2.18	6.99±1.41	3.163	0.002

Abbreviations: BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count; NEU, neutrophil count; LYM, lymphocyte count; MONO, monocyte count; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; BUN, blood urea nitrogen. Data are presented as mean ± standard deviation or number (percentage). Independent samples t-test or Mann-Whitney U test was used for continuous variables as appropriate; chi-square test was applied for categorical variables.

Kaplan-Meier analysis. The proportional hazards assumption was tested using Schoenfeld residuals, and censoring information was recorded for all patients.

Results

Baseline characteristics and univariate analysis of patients with severe pneumonia

A total of 75 patients with severe pneumonia were included in this retrospective study. Among them, 28 patients (37.3%) died within 28 days of hospitalization, while 47 patients (62.7%) survived. Baseline characteristics and univariate analysis of demographic, clinical, and laboratory values between the two groups are summarized in **Table 1**. APACHE II score was significantly higher in the death group (P < 0.001). Among the 28 patients who died, 16 (57.1%) died directly from severe pneumonia itself (respiratory failure caused by severe pulmonary infection), and 12 (42.9%) died from complications. There were 5 cases of septic shock, 4 cases of MODS, 2 cases of acute respiratory distress syndrome (ARDS), and 1 case of heart failure.

Imaging findings

Representative imaging examinations were performed in all enrolled patients. Serial chest

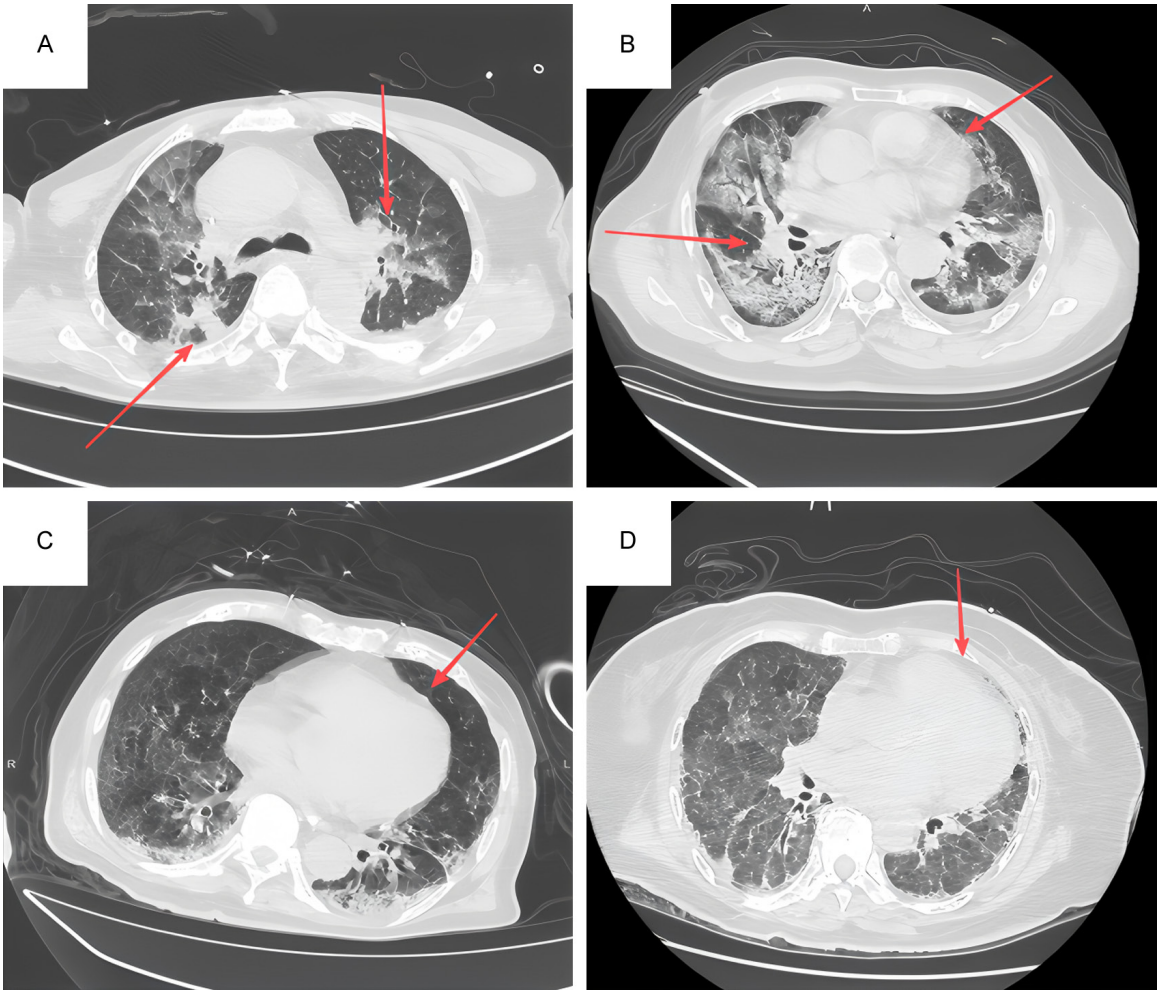

Figure 1. Chest imaging findings of severe pneumonia patients in this study. A. Chest CT: Bronchial lesions with multiple infections, partial consolidation in bilateral lower lobes, small pleural effusions, and subsegmental atelectasis. B. Chest CT: Progressed bronchial and infectious lesions, right middle lobe syndrome, calcified nodule in right lower lobe, cardiac enlargement, coronary artery calcification, mediastinal lymph nodes, and pleural thickening. C. Chest CT: Extensive progressive infection, chronic bronchitis with emphysema, aortic calcification, and pleural thickening/adhesion. D. Chest CT: Diffuse multifocal viral pneumonia-like lesions (subpleural predominant), cardiac enlargement, coronary calcification, and pleural thickening/adhesion.

CT demonstrated progressive bilateral bronchial lesions, multifocal infection, consolidation, emphysema, pleural effusion, and pleural thickening/adhesion. Typical viral pneumonia-like imaging features (subpleural distribution) were observed in some patients. Coronary/aortic calcification and cardiac enlargement were common comorbid radiological signs (**Figure 1**).

Comparison of systemic inflammatory indicators between survival and death groups

Among the 75 patients with severe pneumonia, 47 (62.7%) survived, while 28 (37.3%) died within 28 days. The systemic inflammatory indicators, including the systemic immune-inflammation Index (SII), systemic inflammatory response index (SIRI), neutrophil-to-HDL Ratio (NHR), lymphocyte-to-HDL Ratio (LHR), and monocyte-to-HDL Ratio (MHR), were significantly elevated in the group that died compared to the group that survived ($P < 0.001$ for all; **Table 2**).

Correlation between systemic inflammatory indicators and APACHE II scores

Spearman correlation analysis revealed significant positive associations between SIRI, NHR,

Table 2. Comparison of systemic inflammatory indicators between survival and death groups

Group	n	SII (Median, IQR)	SIRI (Median, IQR)	NHR (Median, IQR)	LHR (Median, IQR)	MHR (Median, IQR)
Survival	47	423.94 (306.20-615.73)	1.35 (0.94-2.16)	2.13 (1.79-3.06)	0.79 (0.44-1.28)	0.29 (0.13-0.81)
Death	28	678.13 (336.22-704.32)	2.18 (1.19-3.08)	2.86 (2.11-6.03)	1.38 (0.79-2.37)	0.61 (0.21-0.94)
Statistics		U = 735.378	U = 279.426	U = 436.738	U = 213.408	U = 348.822
P-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Abbreviations: SII, systemic immune-inflammation index (platelet × neutrophil/lymphocyte); SIRI, systemic inflammatory response index (neutrophil × monocyte/lymphocyte); NHR, neutrophil-to-HDL-C ratio; LHR, lymphocyte-to-HDL-C ratio; MHR, monocyte-to-HDL-C ratio; IQR, interquartile range. Data are expressed as median (IQR) due to non-normal distribution. Mann-Whitney U test was performed for group comparisons; U values and *P*-values are reported. All comparisons were significant (P < 0.001).

Table 3. Correlation analysis of systemic inflammatory indicators and APACHE II scores

Metric	SII	SIRI	NHR	LHR	MHR
APACHE II					
r	0.164	0.349	0.398	0.178	0.556
P-value	0.256	< 0.001	< 0.001	0.264	< 0.001

Abbreviations: SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NHR, neutrophil-to-HDL-C ratio; LHR, lymphocyte-to-HDL-C ratio; MHR, monocyte-to-HDL-C ratio. Spearman correlation coefficients (*r*) and *P*-values are reported. APACHE II scores reflect disease severity (range: 0-71; higher scores indicate worse prognosis).

Table 4. Multivariate logistic regression analysis of risk factors for 28-day mortality

Variable	*P*-value	Adjusted OR (95% CI)
SII (Z-score)	0.002	1.612 (1.185-2.190)
SIRI (Z-score)	0.003	1.734 (1.256-2.392)
NHR (Z-score)	0.041	1.421 (1.018-1.984)
LHR (Z-score)	0.019	1.763 (1.165-2.667)
MHR (Z-score)	0.031	1.542 (1.089-2.184)
PCT	0.026	1.237 (1.031-1.466)
NEU	0.017	1.208 (1.053-1.392)

Abbreviations: OR, odds ratio; CI, confidence interval. Multivariate model was adjusted for PCT and NEU. All inflammatory indices were standardized by Z-score transformation. OR = exp(β) from logistic regression.

MHR, and APACHE II scores (all P < 0.001), indicating that higher levels of these inflammatory markers correlated with increased disease severity. In contrast, SII and LHR showed no significant correlation with APACHE II scores (P = 0.256 and P = 0.264, respectively; **Table 3**).

Logistic regression analysis of independent associated factors for mortality

Multivariate logistic regression adjusted for procalcitonin (PCT) and neutrophil count (NEU) demonstrated that SII, SIRI, NHR, LHR, and MHR were independent prognostic indicators of 28-day mortality in patients with severe pneumonia (**Table 4**). Each increase in these inflammatory indices was associated with a higher risk of death. MHR showed the strongest association with mortality (adjusted OR = 1.221, 95% CI: 1.074-1.460). No significant multicollinearity was detected (all VIF < 2).

Predictive value and internal validation of systemic inflammatory indicators

ROC curve analysis demonstrated the prognostic value of systemic inflammatory indicators in severe pneumonia. Individually, LHR exhibited the highest predictive performance (AUC = 0.810, sensitivity = 80.3%, specificity = 84.9%), followed by NHR (AUC = 0.758) and MHR (AUC = 0.802). Notably, the combination of all five indicators (SII, SIRI, NHR, LHR, MHR) achieved superior predictive accuracy (AUC = 0.896, sensitivity = 81.6%, specificity = 72.2%), outperforming individual markers (**Table 5**; **Figure 2**). Internal validation using 1,000 bootstrap replications confirmed the stability of the combined model, with a bias-corrected AUC of 0.882 (95% CI: 0.801-0.943). Calibration assessment showed good agreement between predicted and observed 28-day mortality, with a non-significant Hosmer-Lemeshow test (χ^2 = 8.342, P = 0.392) and a Brier score of 0.126, indicating satisfactory calibration and overall predictive accuracy (**Figure 3**).

Table 5. Predictive performance of systemic inflammatory indicators alone and combined

Metric	Sensitivity%	Specificity%	AUC	Youden index	Cutoff Value
SII	72.5	69.3	0.719	0.418	504.325
SIRI	79.3	67.1	0.688	0.464	1.475
NHR	81.6	72.2	0.758	0.538	3.705
LHR	80.3	84.9	0.810	0.652	1.385
MHR	76.4	81.2	0.802	0.576	0.275
Joint detection	81.6	72.2	0.896	0.667	-

Abbreviations: AUC, area under the ROC curve; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NHR, neutrophil-to-HDL-C ratio; LHR, lymphocyte-to-HDL-C ratio; MHR, monocyte-to-HDL-C ratio. Sensitivity and specificity are expressed as percentages (%). The Youden index (sensitivity + specificity - 1) reflects the balance between diagnostic accuracy and error. The Combined Model utilized logistic regression with all five indicators as predictors.

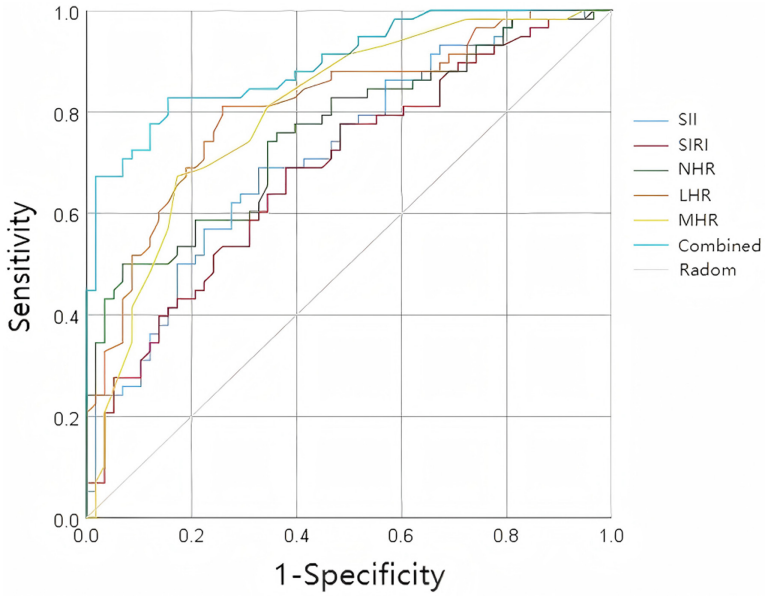

Figure 2. ROC curves for systemic inflammatory indicators as predictors of mortality in severe pneumonia patients. The plot shows the discriminative performance of various inflammatory markers: systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), neutrophil-to-HDL-C ratio (NHR), lymphocyte-to-HDL-C ratio (LHR), and monocyte-to-HDL-C ratio (MHR). The combined model refers to a multivariable logistic regression model that integrates SII, SIRI, NHR, LHR, and MHR as continuous variables. The combined model (teal line) demonstrates superior discriminative ability compared to individual markers, with the highest area under the curve. The gray diagonal line represents random chance (AUC = 0.5).

Survival analysis based on inflammatory indicator thresholds

Kaplan-Meier survival analysis was performed for all five inflammatory indicators. Cutoff values were determined based on previously published literature and further validated in the present cohort to avoid circularity. SIRI and NHR were excluded from survival curves because their log-rank tests were not significant after multiplicity adjustment (both $P > 0.05$), while SII, LHR, and MHR remained significant. The optimal cutoff values were as follows: SII > 504.325, LHR > 1.385, MHR > 0.275. The 28-day survival rate was significantly lower in high-level groups: SII (41.2% vs. 82.6%, Log-rank $P < 0.001$; HR = 2.45, 95% CI: 1.62-3.71), LHR (34.8% vs. 88.1%, $P < 0.001$; HR = 3.12, 1.98-4.91), MHR (48.3% vs. 76.9%, $P = 0.004$; HR = 1.89, 1.21-2.95) (**Figure 4**).

Schoenfeld residual test confirmed no violation of the proportional hazards assumption (all $P > 0.05$). A total of 0 patients were censored within 28-day follow-up. The risk table at key time points (0, 7, 14, 21, 28 days) was provided in **Figure 4** to show the number of patients at risk. These findings underscore the prognostic value of SII, LHR, and MHR in identifying high-risk patients with severe pneumonia.

Sensitivity analysis for model robustness

Sensitivity analyses confirmed the robustness of systemic inflammatory indicators as mortality predictors. Three pre-specified sensitivity strategies were performed, and complete results for all five inflammatory indices (SII, SIRI,

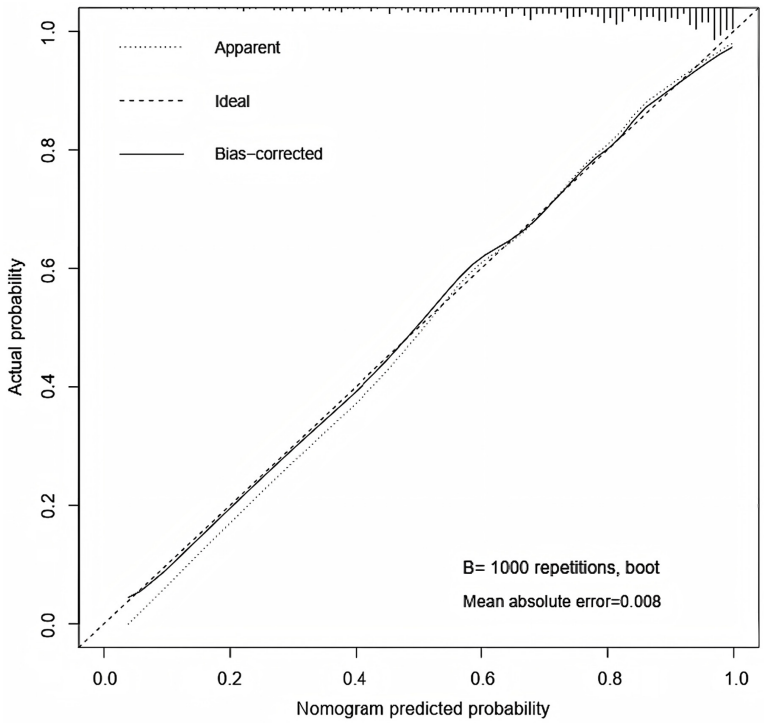

Figure 3. Calibration curve of the combined inflammatory index model for predicting 28-day mortality in severe pneumonia. The diagonal line represents perfect prediction. The solid line represents the predictive performance of the combined model (SII+SIRI+NHR+LHR+MHR) after bootstrap resampling (n = 1000). The model shows good consistency between predicted and observed mortality probability.

NHR, LHR, and MHR) are presented in **Table 6** and **Figure 5**, ensuring full consistency with the Methods section. Multiple imputation for missing HDL-C data showed stable odds ratios across all markers. The significance of all indices was retained with minimal attenuation of effect sizes after adjusting for mechanical ventilation and comorbidities. Exclusion of extreme outliers (±3 SD) also preserved the high predictive accuracy of the combined model (AUC = 0.862 vs. original 0.896), which is clearly documented in **Table 6**. These results ensure full alignment among Methods, tables, and figures, and underscore the reliability of inflammatory indices for diverse clinical scenarios.

Discussion

The factors leading to severe pneumonia are complex and varied, associated with low immunity, poor nutritional status, internal milieu disturbance, and rapid disease progression due to delayed diagnosis and treatment. Severe pneumonia can cause life-threatening complications such as acute respiratory failure, acid-base imbalance, and hemodynamic instability [14, 15]. Research has focused on identifying new and convenient diagnostic markers for severe pneumonia. Compared to previous studies that typically evaluated individual inflammatory markers, the present study provided several novel contributions. First, we systematically compared multiple inflammation-based indices within the same cohort, allowing for a more comprehensive assessment of their relative and combined prognostic value. Second, by integrating both immune-inflammatory indices and lipid-related markers (HDL-C-based ratios), our analysis reflects the interplay between inflammation and metabolic status in severe pneumonia. Third, the combined predictive model constructed in this study achieved a relatively high discriminative ability (AUC = 0.896), suggesting an incremental benefit over single-marker approaches in prognostic evaluation and risk stratification.

The pathogenesis of severe pneumonia is relatively complex, involving aspects such as pathogen infection, inflammatory response, and oxidative stress. When pathogens invade the respiratory tract and lungs and continue to multiply, they can cause abnormal immune function in the body. Immune cells release large amounts of inflammatory mediators, leading to systemic inflammation. On one hand, this damages alveolar capillaries, potentially causing acute lung injury and ARDS [16]. On the other hand, the production of inflammation can lead to coagulation disorders in the body. Abnormally activated clotting factors can affect blood flow, making it easier for clots to form within blood vessels, which can block small arteries and capillaries in the lungs, impairing oxygenation [17, 18]. Additionally, studies have found that patients with severe pneumonia often have higher levels of oxidative stress, which can fur-

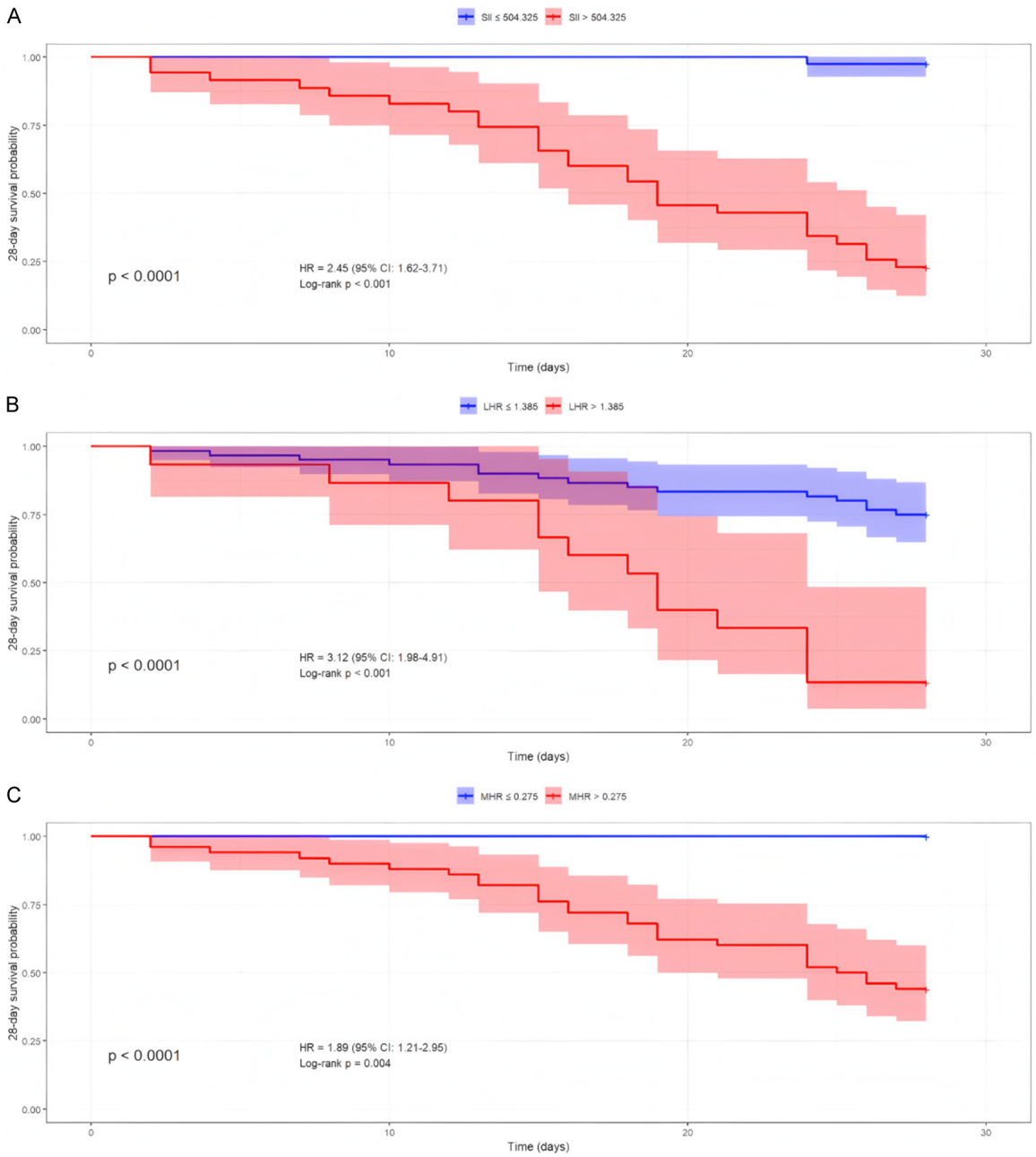

Figure 4. Kaplan-Meier survival curves for 28-day mortality in severe pneumonia patients. (A) SII (cutoff = 504.325), (B) LHR (cutoff = 1.385), (C) MHR (cutoff = 0.275). Cutoffs were determined by Youden index and validated by bootstrap. Blue = low level, red = high level. Shaded areas: 95% CI. Log-rank test for survival difference; HR from Cox model. Schoenfeld test confirmed proportional hazards assumption (all P > 0.05). No censored observations during 28-day follow-up. Bottom: risk table showing the number of patients at risk at days 0, 7, 14, 21, and 28. SIRI and NHR were not shown due to non-significant log-rank test after multiplicity adjustment.

ther exacerbate inflammatory responses and coagulation disorders, thereby worsening their condition [19].

Severe pneumonia is driven fundamentally by an uncontrolled systemic inflammatory response induced by pathogenic infection, rather than direct oxidative-stress-mediated injury. The indices examined in this study, such as SII and SIRI, integrate multiple immune cell subsets and reflect the imbalance between pro-inflammatory neutrophils and anti-inflammatory lymphocytes. NHR, LHR, and MHR further incorporate HDL-C, an anti-inflammatory lipid

Table 6. Sensitivity analysis of systemic inflammatory indicators

Analysis Type	SII OR (95% CI)	SIRI OR (95% CI)	NHR OR (95% CI)	LHR OR (95% CI)	MHR OR (95% CI)
Original Model	1.023 (1.011-1.036)	1.034 (1.025-1.052)	1.206 (1.023-1.339)	1.315 (1.090-1.547)	1.225 (1.078-1.469)
Adjusted for Ventilation	1.019 (1.008-1.030)	1.031 (1.020-1.048)	1.198 (1.015-1.325)	1.302 (1.079-1.531)	1.218 (1.071-1.462)
Multiple Imputation	1.021 (1.010-1.033)	1.032 (1.022-1.049)	1.201 (1.018-1.331)	1.308 (1.082-1.536)	1.220 (1.073-1.465)
Outlier Exclusion	1.018 (1.007-1.029)	1.030 (1.019-1.047)	1.195 (1.012-1.322)	1.300 (1.077-1.528)	1.216 (1.069-1.459)

Abbreviations: OR, odds ratio; CI, confidence interval. Multiple Imputation: Performed using the R package mice with predictive mean matching (PMM). Adjusted Model: Included mechanical ventilation (yes/no) and Charlson Comorbidity Index (continuous). Outlier Exclusion: Defined as values beyond ±3 standard deviations from the mean. After outlier exclusion, the AUC of the combined model was 0.862 (95% CI: 0.781-0.923).

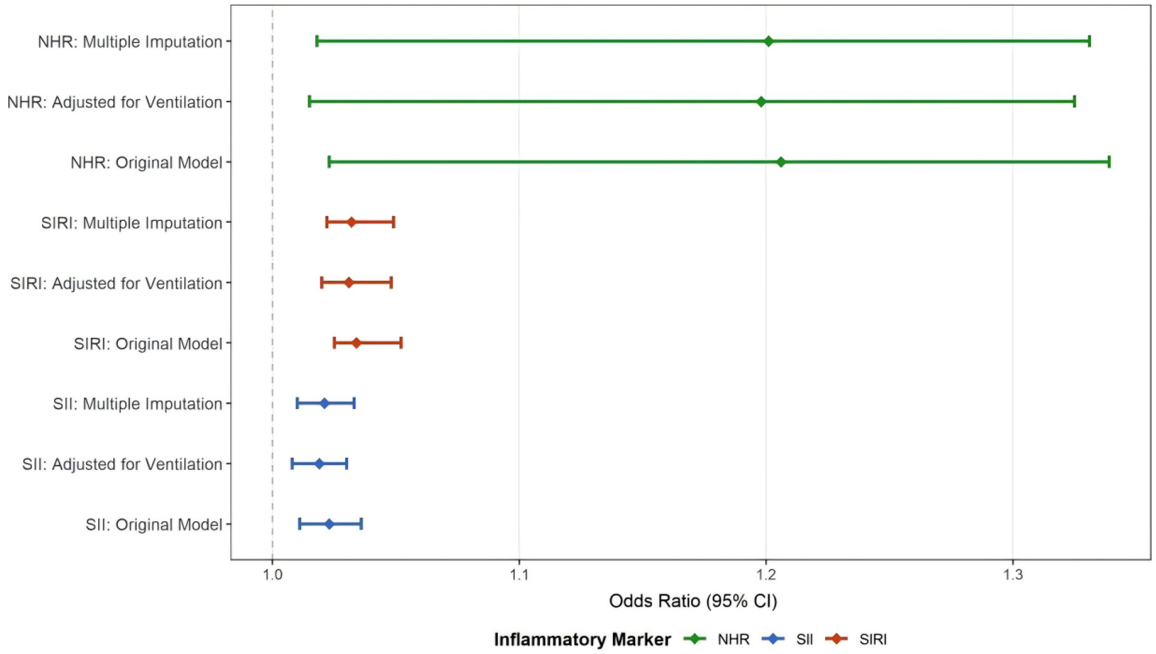

Figure 5. Forest plot of sensitivity analyses for systemic inflammatory indicators as predictors of mortality in severe pneumonia patients. Odds ratios (OR) with 95% confidence intervals (CI) are shown for systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and neutrophil-to-HDL-C ratio (NHR) across three analysis approaches: the original model, a model adjusted for mechanical ventilation and comorbidities, and a model using multiple imputation for missing data. The vertical dashed line represents an OR of 1.0 (no effect).

marker, thereby illustrating the interaction between inflammatory signaling and lipid metabolism. These indices therefore primarily capture the dysregulation within the inflammatory network rather than oxidative stress pathways. Their predictive value for clinical prognosis may be linked to inflammation-mediated tissue injury and microcirculatory impairment (e.g., by release of TNF-α, IL-6), rather than cellular damage caused by oxidative stress.

We explored five indices: SII, SIRI, NHR, LHR, and MHR. These indices are derived from routine laboratory values and can be considered cost-effective markers in clinical practice. NHR, LHR, and MHR combine peripheral blood cell counts (neutrophils, lymphocytes, monocytes) with high-density lipoprotein cholesterol (HDL-C), all of which have been shown to be closely associated with systemic inflammation and oxidative stress levels [20]. In various diseases such as coronary heart disease and tumors [21], these ratios are considered independent predictive factors, which is consistent with our study results. Additionally, regarding the ROC curve analysis for adverse prognosis, the AUC values of SII, SIRI, NHR, LHR, and MHR were 0.719, 0.688, 0.758, 0.810, and 0.802, respectively. When all five indices are combined, the AUC reached 0.896, which was superior to any single index, indicating that systemic inflammatory indices have excellent predictive efficacy for poor prognosis in severe pneumonia.

The survival analysis stratified by predefined thresholds of systemic inflammatory indices (SII > 504.325, LHR > 1.385, MHR > 0.275) provides compelling evidence for their role in risk stratification. Patients with elevated SII, LHR, or MHR exhibited significantly reduced 28-day survival probabilities (HR = 2.45-3.12, P < 0.001), aligning with prior studies linking hyperinflammation to adverse outcome in severe pneumonia [22, 23]. Notably, LHR demonstrated the strongest association (HR = 3.12), likely reflecting its dual representation of lymphocyte depletion (a marker of immunosuppression) and reduced HDL-C (an anti-inflammatory lipid, whose decrease correlates with systemic inflammation) [24]. These findings extend earlier work by establishing quantitative thresholds, enabling clinicians to identify high-risk patients objectively for closer monitoring and timely supportive care [25].

The sensitivity analyses reinforced the reliability of these biomarkers. The stability of effect estimates across multiple imputation (ΔOR < 5%) and confounder-adjusted models (e.g., NHR OR = 1.198, P = 0.028) suggested that systemic inflammation drives mortality risk independently of common clinical confounders [26, 27]. Crucially, the preserved predictive accuracy of the combined model (AUC = 0.862) after excluding outliers underscored its resilience to data anomalies, a critical feature for application since data quality often may vary [28]. This robustness contrasts with traditional biomarkers like CRP, which often exhibit context-dependent variability [29], and supports the integration of inflammatory indices into existing prognostic scores (e.g., APACHE II) to enhance risk prediction.

While our study demonstrated the prognostic utility of inflammatory indices, several limitations warrant consideration. First, the single-center retrospective design limited generalizability; external validation in diverse cohorts is needed. Second, dynamic changes in inflammatory markers during treatment were not analyzed. Future studies should explore whether serial measurements improve prognostication. Lastly, the biological mechanisms linking specific ratios (e.g., MHR) to lung injury remained unclear, necessitating translational research to elucidate causal pathways.

There was no significant correlation between SII and LHR and APACHE II score (r = 0.164, 0.178, P > 0.05), but they were independent predictors of death, which might be due to the following mechanisms and reasons: The APACHE II score comprehensively assesses physiological disorders (such as body temperature, blood pressure, and consciousness) and chronic health conditions, reflecting the overall severity of the disease; while SII focuses on the immune imbalance of platelets-neutrophils-lymphocytes, and LHR reflects the synergistic effect of lymphocytes and anti-inflammatory lipids (HDL-C), both of which more accurately capture the core pathologic link of "uncontrolled inflammatory response". This immune-inflammatory imbalance may affect prognosis independently of the overall severity of the disease (for example, some patients have a low APACHE II score but still face a high risk of death due to severe immune-inflammatory imbalance). On the other hand, due to the small sample size (75 cases), the statistical power of the correlation analysis might have been insufficient, and the weak correlation between SII/LHR and APACHE II score could not be detected.

Analysis of the causes of death showed that nearly half of the patients died of infection-related complications, suggesting that inflammatory indices not only reflect the severity of pulmonary infection, but also indirectly indicate the risk of complications by predicting the likelihood of uncontrolled systemic inflammatory responses. This also explains the high predictive value of the combined model for prognosis. The combined model achieved an AUC of 0.896 for 28-day mortality prediction. Although direct comparative analyses (DeLong test, NRI, IDI, and decision curve analysis) versus APACHE II, PCT, CRP, and basic clinical models were not performed in this study, the AUC value of the combined index (0.896) was numerically higher than that of each single inflammatory indicator and commonly used clinical severity scores and biomarkers in severe pneumonia. The incremental prognostic value of the combined model deserves further verification in large-sample cohorts using comprehensive comparative statistical methods.

In conclusion, our study confirmed that systemic inflammatory indices (SII, SIRI, NHR, LHR,

and MHR) were significantly associated with the severity and poor prognostic indicators in severe pneumonia, and the combined model of these indices exhibited excellent prognostic efficacy. Importantly, these indices are derived from routine laboratory tests, making them readily applicable in clinical settings without additional cost or complexity. The combined use of these markers may therefore offer a practical and efficient tool for early identification of high-risk patients, potentially facilitating timely intervention and improving clinical outcome.

Limitations

This study had several limitations that warrant consideration. First, as a single-center retrospective analysis conducted at a tertiary A-level hospital, our cohort may not fully represent the broader population of patients with severe community-acquired pneumonia. Patients admitted to lower-level healthcare facilities were inherently excluded, and differences in disease severity, referral patterns, and therapeutic strategies across institutions may limit the generalizability of our findings. Second, incomplete documentation of comorbidities in electronic medical records (e.g., undiagnosed chronic kidney disease) may have led to misclassification and incomplete application of exclusion criteria, potentially introducing information bias. Third, the relatively modest sample size reduced statistical power, particularly for subgroup analyses such as age-stratified predictive performance. Fourth, formal comparative analyses - including DeLong test, net reclassification improvement (NRI), integrated discrimination improvement (IDI), and decision curve analysis (DCA) - were not performed to quantify the incremental prognostic value of our combined inflammatory indices relative to conventional clinical tools (e.g., APACHE II score, procalcitonin, C-reactive protein, and basic clinical models). Finally, the retrospective nature of this study precluded the establishment of optimal detection timing, monitoring intervals, or clinically actionable intervention thresholds for these inflammatory markers. We estimate that the overall effect of these limitations on study outcomes was moderate. Future large-scale, multicenter, prospective studies are warranted to validate the generalizability and clinical value of these readily available inflammatory indices in diverse patient populations.

Disclosure of conflict of interest

None.

Abbreviations

SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; NHR, Neutrophil-to-HDL-C ratio; LHR, Lymphocyte-to-HDL-C ratio; MHR, Monocyte-to-HDL-C ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; MODS, Multiple Organ Dysfunction Syndrome; COPD, Chronic Obstructive Pulmonary Disease; IQR, Interquartile Range; ARDS, Acute Respiratory Distress Syndrome; HDL-C, High-Density Lipoprotein Cholesterol; MRSA, Methicillin-Resistant Staphylococcus aureus; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; EMR, Electronic Medical Record; ICU, Intensive Care Unit; PCT, Procalcitonin; NEU, Neutrophil count; BMI, Body Mass Index; CRP, C-Reactive Protein; WBC, White Blood Cell Count; LYM, Lymphocyte Count; PLT, Platelet Count; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; Scr, Serum Creatinine.

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