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Original Article

Combined prognostic value of the neutrophil-to-lymphocyte ratio and serum lactate for 28-day mortality in patients with sepsis-induced pulmonary dysfunction

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Abstract: Objective: To investigate the predictive value of the neutrophil-to-lymphocyte ratio (NLR) combined with serum lactate (Lac) in patients with sepsis-induced pulmonary dysfunction (SIPD) for early evaluation and personalized treatment. Methods: A total of 230 SIPD patients were retrospectively screened from January 2018 to December 2023. After exclusions, 226 patients were classified into the survivor group (154 cases) and the non-survivor group (72 cases) based on their 28-day survival status. Receiver operating characteristic (ROC) curves assessed NLR-Lac combined prognostic value for 28-day mortality in SIPD, with logistic regression screening risk factors. Results: In the non-survivor group, levels of NLR, serum Lac, sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation II (APACHE II) score, C-reactive protein (CRP), procalcitonin (PCT), white blood cells (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine (Cr) were higher (all $P < 0.05$), whereas partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) was lower ($P = 0.041$) than in the survivor group. ROC curve analysis showed the area under the curve (AUC) of combined NLR-Lac model for predicting SIPD patients' 28-day mortality was 0.803 (95% CI: 0.746, 0.860), higher than that of NLR alone (0.727, 95% CI: 0.649, 0.804) and serum Lac alone (0.734, 95% CI: 0.661, 0.808). Logistic regression indicated elevated NLR and serum Lac were independent predictors for 28-day mortality in SIPD patients (both $P < 0.001$). Additionally, the non-survivor group had longer mechanical ventilation duration ($P < 0.001$). Conclusion: Combined NLR and Lac detection may improve prognostic accuracy in SIPD patients.

Keywords: Sepsis-induced pulmonary dysfunction, neutrophil-to-lymphocyte ratio, serum lactate, prognostic evaluation

Introduction

As a life-threatening acute critical illness, sepsis poses a significant global risk to human health and arises from a dysregulated host response to infection that leads to life-threatening organ dysfunction. With its persistently high morbidity and mortality rates, sepsis has emerged as a major public health challenge in the field of critical care medicine [1]. Despite advances in medical technology, critically ill patients still face an extremely high risk of developing multiple organ dysfunction. Among the affected organs, the lungs, which serve as the key site for gas exchange between the body and the external environment, are particularly vulnerable to sepsis-induced damage due to the unique characteristics of their anatomical structure and physiological functions, making them one of the most frequently affected target organs in sepsis [2, 3].

Sepsis-induced pulmonary dysfunction (SIPD) is one of the most common and severe complications of sepsis [4, 5]. Therefore, early and accurate assessment of disease severity and prognosis in SIPD patients is crucial for preventing disease progression and reducing mortality [6]. Currently, the main clinical tools used for prognostic assessment of sepsis and related organ dysfunction include the Sequential Organ Failure Assessment (SOFA) score and the

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Acute Physiology and Chronic Health Evaluation II (APACHE II) score. By integrating various physiological indicators and clinical parameters, these scoring systems can reflect, to some extent, the degree of organ dysfunction and disease severity. However, they have limitations in practical application. Calculation of SOFA and APACHE II scores requires the collection of numerous physiological indicators, biochemical test results, and chronic health status information, making the process complex and time-consuming. In addition, the evaluation of certain indicators may be subject to interobserver variability [7]. For primary healthcare institutions or clinical settings with limited resources, these scoring systems may not meet the clinical need for early and rapid assessment. Moreover, these scores may lack sufficient sensitivity to dynamic changes in disease status and may fail to promptly reflect fluctuations in patients' conditions after therapeutic interventions, which is detrimental to real-time adjustments of clinical treatment strategies [8]. Therefore, identifying simple, rapid, objective, and reproducible biomarkers to construct efficient prognostic assessment models has become a priority in clinical research related to SIPD.

In recent years, the neutrophil-to-lymphocyte ratio (NLR) has been widely used for prognostic assessment in various diseases, including sepsis, malignant tumors, and cardiovascular diseases [9, 10]. In studies of sepsis-induced acute lung injury, the area under the curve (AUC) of the NLR as an independent risk factor was higher than 0.7, indicating that NLR has potential value in assessing the risk of pulmonary dysfunction [11]. However, other studies have indicated that the effectiveness of using NLR alone in predicting mortality in patients with sepsis is relatively limited, with an AUC of only 0.595-0.598 [12]. This may be because a single indicator cannot fully reflect the complex pathological processes of the disease, providing a theoretical basis for the combined application of NLR with other biomarkers.

Serum lactate (Lac) is an intermediate product of glucose metabolism, and fluctuations in its level are closely related to the severity and prognosis in patients with sepsis [13]. In sepsis, vasodilation, increased vascular permeability, and infection-induced cardiac dysfunction can lead to insufficient tissue perfusion, impaired aerobic cellular metabolism, and enhanced anaerobic glycolysis. These changes lead to increased Lac production and reduced clearance, ultimately resulting in an increase in serum Lac levels [14]. However, the predictive value of Lac alone is also limited. Studies indicate that Lac levels may exhibit nonspecific increases in cases of sepsis complicated by liver insufficiency or intense physical activity, thereby affecting the accuracy of evaluation. Therefore, combining Lac with other indicators is necessary to enhance its predictive value [15].

Based on the above research background and clinical needs, this study systematically evaluated the prognostic value of the combined use of NLR and serum Lac. Dynamic monitoring of changes in NLR and serum Lac levels can promptly reflect patients' treatment responses and disease fluctuations, providing an objective basis for adjusting personalized treatment plans. In addition, the findings of this study may provide new insights into the pathophysiological mechanisms of SIPD and offer references for the subsequent development of targeted therapeutic strategies. This study aims to clarify the value of NLR combined with serum Lac in prognostic assessment of patients with SIPD through systematic clinical data analysis, thereby providing a reliable basis for improving patient outcomes.

Materials and methods

Study process

A retrospective review was conducted using the electronic medical records of inpatients at The First Affiliated Hospital of Soochow University from January 2018 to December 2023, and 230 patients meeting the diagnostic criteria for sepsis were initially screened. Upon conducting a rigorous review against the pre-established inclusion as well as exclusion criteria, 4 patients were excluded: 1 case of pulmonary dysfunction caused by non-sepsis etiologies, 1 case of advanced gastric cancer, and 2 cases with incomplete clinical data. Ultimately, based on their 28-day survival status, 226 patients in total were enrolled in the analysis and divided into two groups: the survivor group (154 cases) and the non-survivor group (72 cases) (**Figure 1**).

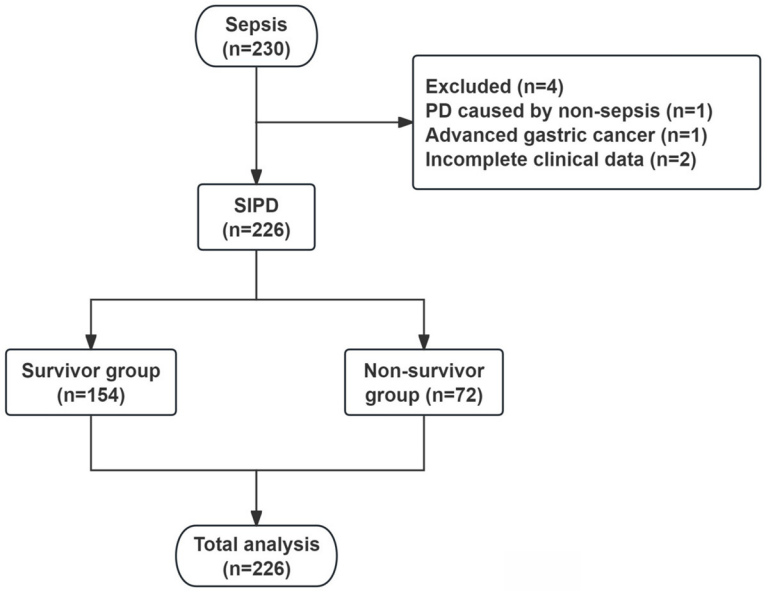

Figure 1. Research flowchart. Note: A total of 230 patients were initially screened in this study, after exclusion, 226 cases were incorporated into the analytical process, with 154 in survivor group, 72 in non-survivor group. SIPD: Sepsis-Induced Pulmonary Dysfunction; PD: Pulmonary Dysfunction.

Inclusion criteria: (1) Meeting the diagnostic criteria for sepsis as defined in the 2021 International Guidelines for the Management of Sepsis and Septic Shock, i.e., presence of confirmed infection and a SOFA score ≥ 2 [16]; (2) SIPD was defined as new-onset acute hypoxemic respiratory failure occurring within 72 hours after the confirmed diagnosis of sepsis. Referring to the Berlin definition of acute respiratory distress syndrome and the diagnostic criteria for acute lung injury, SIPD was identified when the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) was ≤ 300 mmHg under the condition of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cmH_2O. According to the oxygenation level, patients were stratified into mild (200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg), moderate (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg), and severe (PaO_2/FiO_2 ≤ 100 mmHg) subgroups. Meanwhile, cardiogenic pulmonary edema was excluded in all enrolled patients through bedside echocardiography, B-type natriuretic peptide (BNP) detection and comprehensive clinical evaluation. Pulmonary embolism was ruled out by computed tomography pulmonary angiography (CTPA) or D-dimer combined with the clinical Wells score. In addition, patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), severe underlying pulmonary diseases, or oxygenation impairment caused by non-septic factors were also excluded based on medical history, chest imaging findings, and pulmonary function data; (3) age ≥ 18 years; (4) Clear 28-day survival status with available prognostic outcomes (survival or death).

Exclusion criteria: (1) Missing key clinical data; (2) Comorbidity with severe primary lung diseases; (3) pregnancy or lactation; (4) Comorbidity with end-stage liver or kidney failure or severe coagulation disorders; (5) Advanced malignant tumors or receiving radiotherapy, chemotherapy, or immunosuppressive treatment; (6) Severe mental illness or cognitive impairment [17].

Treatment regimen

All patients with SIPD in this study received individualized comprehensive treatment, with the core therapeutic measures as follows:

1. For early fluid resuscitation, Lactated Ringer's solution (Sichuan Kelun Pharmaceutical Co., Ltd., 500 mL/bottle, Sichuan, China) or normal saline (Shijiazhuang No. 4 Pharmaceutical Co., Ltd., 500 mL/bottle, Hebei, China) was selected. The therapeutic goals were to maintain a mean arterial pressure (MAP) of no less than 65 mmHg, a central venous pressure ranging from 8 to 12 mmHg, and a Lac clearance rate of at least 10% within 24 hours.

2. Empirical anti-infection therapy was initiated within 1 hour after patient admission, which involved the combined use of broad-spectrum antibiotics, with a treatment course of 7-14 days [16].

3. Vasoactive agents included norepinephrine injection (Shanghai Hefeng Pharmaceutical Co., Ltd., 2 mg per vial, Shanghai, China), vasopressin (Ferring Pharmaceuticals, 20 U per vial,

Germany), and dopamine injection (Jiangsu Yabang Pharmaceutical Group Co., Ltd., 20 mg per vial, Jiangsu, China).

4. Adjuvant therapy for lung injury included mucolytic medication and anti-inflammatory drugs. The mucolytic agent used was Ambroxol Hydrochloride Injection (Boehringer Ingelheim Pharmaceuticals, 30 mg per vial, Germany), administered intravenously at a dose of 30 mg every 8 hours. Meanwhile, the anti-inflammatory drug (Methylprednisolone Sodium Succinate Injection, Pfizer Manufacturing Belgium NV, 40 mg per vial, Belgium) was administered by intravenous infusion at a daily dose of 40-80 mg for a short course of 3-5 days [18].

A bedside comprehensive monitoring system (Mindray Medical, Beneview T10, Guangdong, China) was adopted to record patients' indicators daily and dynamically assess their response to treatment. When the patient's condition improved, the dosage of vasoactive agents was gradually reduced, the intensity of mechanical ventilation support was lowered, or the ventilation mode was switched to non-invasive ventilation. In cases of disease progression, the anti-infection regimen was optimized, fluid resuscitation was strengthened, or respiratory support was escalated.

Observation indicators

(1) Routine blood test indicators: Five milliliters of peripheral venous blood from patients was collected using anticoagulant tubes and subjected to whole-blood testing. A fully automatic hematology analyzer (Mindray Medical, BC-6800, Guangdong, China) was employed to determine the white blood cell count (WBC), neutrophil count, and lymphocyte count. The instrument's supporting software automatically calculated NLR. The indicators were measured within 6 hours after hospital admission for all patients.

(2) Inflammation, metabolism, and hepatorenal function related indicators: 5 mL of peripheral venous blood was drawn into vacuum tubes without anticoagulants followed by centrifugation at 3,000 rpm for 10 minutes (Beckman Coulter, Allegra X-15R, USA) to separate the serum. C-reactive protein (CRP), serum Lac, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (Cr) were assayed via a fully automatic biochemical analyzer (Roche Diagnostics, Cobas 8000, Switzerland). The indicators were measured within 6 hours after hospital admission for all patients.

Five mL of peripheral venous blood was collected into anticoagulant tubes and centrifuged at 3,000 r/min for 10 minutes (Beckman Coulter, Allegra X-15R, USA) to isolate the plasma. Procalcitonin (PCT) was measured with a fully automatic biochemical analyzer (Roche Diagnostics, Cobas 8000, Switzerland). The indicators were measured within 6 hours after hospital admission for all patients.

(3) Oxygenation function indicators: PaO_2 and FiO_2 were measured using a fully automatic blood gas analyzer (Roche Diagnostics, cobas b 123, Switzerland). The indicators were measured within 6 hours after hospital admission for all patients.

(4) Organ function scores: SOFA score: This score covers six organ systems, specifically the respiratory, circulatory, hepatic, renal, coagulation, and nervous systems. The total score ranges from 0 to 24 points and is the sum of the scores of the six organ systems. A higher score indicates more severe organ dysfunction [19]. The indicators were measured within 6 hours after hospital admission for all patients.

APACHE II score: This scoring tool consists of three parts, specifically the acute physiology score (APS), age score, and chronic health status score. The total score ranges from 0 to 71 points. A higher score indicates a more critical condition and poorer prognosis [20]. The indicators were measured within 6 hours after hospital admission for all patients.

(5) Duration of mechanical ventilation: The duration of mechanical ventilation was calculated as the cumulative time based on the ventilator usage records [21]. The initiation time of mechanical ventilation was defined as the time when an artificial airway was established via endotracheal intubation or tracheotomy, followed by connection to a ventilator for positive pressure ventilation. The termination time was defined as the moment of successful endotracheal tube/tracheostomy cannula removal, or transition to non-invasive ventilation or high-flow nasal cannula oxygen therapy without the

need for re-invasive ventilation for more than 24 consecutive hours. For patients who died in hospital, the duration of mechanical ventilation was calculated until terminal ventilator weaning or the last ventilator application prior to death.

Ethical statement

This retrospective clinical study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Soochow University (ethics approval number: 2026-474). This study was conducted in accordance with the Declaration of Helsinki. The research data were used only for academic analysis, and their storage and use comply with relevant regulations on medical data security.

Sample size calculation method

This study referred to the results of previous studies on predicting 28-day mortality among patients with sepsis, with an AUC of 0.776 [22], and derived an effect size of Cohen's d = 0.52. G*Power 3.1.9.7 software was used for sample size estimation, with $\alpha = 0.05$ (two-tailed test), $\beta = 0.1$ (statistical power 1-β = 90%), and an estimated sample size ratio of non-survivor-to-survivor group of 1:2. The results showed that a total sample size of at least 178 cases was required. Considering potential missing data or incomplete records during the retrospective study, 226 patients were finally included (154 cases in the survivor group and 72 cases in the non-survivor group), which satisfied the required statistical power.

Statistical methods

A normality test (Kolmogorov-Smirnov test) was performed on all extracted clinical indicators. Measurement data conforming to a normal distribution were expressed as mean ± standard deviation (SD), and those not conforming to a normal distribution were expressed as M (IQR). Count data were expressed as n (%). For comparison of measurement data between the survivor group and the non-survivor group, independent-samples t-test was used for data with normal distribution and homogeneous variance, while Mann-Whitney U test was used for data not meeting the above conditions. Categorical data comparisons were conducted using the chi-square test. Multivariate logistic regression analysis was used to screen independent risk factors for 28-day mortality in patients with SIPD. To further eliminate the influence of multicollinearity on the stability of the multivariate model, collinearity diagnosis was conducted for all enrolled variables in this study. Variance inflation factor (VIF) > 10 or tolerance < 0.1 was defined as the criterion for severe multicollinearity. Receiver operating characteristic (ROC) curves were used to analyze the predictive value of NLR, serum Lac alone, and their combined detection, and the AUC was calculated. The DeLong test was used for AUC comparison. Internal validation was performed using the bootstrap method. A calibration slope closer to 1.0 indicates better consistency between model-predicted probabilities and observed probabilities. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical baseline data between the two groups

There were no statistically significant differences between the two groups in age, BMI, sex distribution, comorbidities, infection sources, or therapeutic interventions (all P > 0.05), and all effect sizes were small (absolute value < 0.1). These results indicate that the two groups were comparable and well-balanced in baseline characteristics (**Table 1**).

Inflammatory and infection indicators

The levels of NLR (11.57±3.67 vs 8.49±4.01), CRP (67.38±10.50 vs 27.39±6.45 mg/L), PCT (1.19±0.26 vs 0.36±0.11 ng/mL), and WBC ($15.34\pm1.53\times10^9$/L vs $9.19\pm1.65\times10^9$/L) were significantly higher in the non-survivor group than in the survivor group (all P < 0.001), with effect sizes of -0.789, -5.023, -4.796, and -3.806, respectively. These findings indicate that patients in the non-survivor group exhibited more severe systemic inflammatory responses and infection (**Table 2**).

Organ function and metabolic indicators

Serum Lac (3.68±1.18 vs 2.66±1.16 mmol/L, P < 0.001, effect size = -0.879), ALT (87.54±12.93 vs 43.20±8.48 U/L, P < 0.001, effect size = -4.387), AST (94.40±13.00 vs

Table 1. Baseline clinical data [mean ± SD, n (%)]

Variables	Survivor group (n = 154)	Non-survivor group (n = 72)	*Difference 95% CI*	*P*	*Effect size*	t/χ^2
Age (years)	55.12±5.34	55.49±4.25	-1.67, 0.94	0.584	-0.072	-0.549
BMI (kg/m^2)	22.85±1.28	23.02±0.97	-0.47, 0.14	0.283	-0.139	-1.077
Gender	-	-	-	1.000	< 0.001	< 0.001
Male	77 (50.0)	36 (50.0)	-	-	-	
Female	77 (50.0)	36 (50.0)	-	-	-	
Diabetes mellitus	45 (29.2)	24 (33.3)	-	0.532	0.042	0.391
Hypertension	62 (40.3)	32 (44.4)	-	0.552	0.040	0.354
Coronary heart disease	28 (18.2)	16 (22.2)	-	0.475	0.048	0.511
Infection Source	-	-	-	0.929	0.045	0.453
Pulmonary infection	68 (44.2)	34 (47.2)	-	-	-	
Abdominal infection	42 (27.3)	18 (25.0)	-	-	-	
Bloodstream infection	28 (18.2)	14 (19.4)	-	-	-	
Urinary tract infection	16 (10.4)	6 (8.3)	-	-		
Vasopressor use	89 (57.8)	48 (66.7)	-	0.203	0.085	1.619
Renal replacement therapy	18 (11.7)	12 (16.7)	-	0.304	0.068	1.056

Note: BMI: Body Mass Index; 95% CI: 95% Confidence Interval; SD: Standard Deviation.

Table 2. Comparison of inflammatory and infection indicators (mean ± SD)

Variables	Survivor group (n = 154)	Non-survivor group (n = 72)	*Difference 95% CI*	*P*	*Effect size*	*t*
NLR	8.49±4.01	11.57±3.67	-4.18, -1.98	< 0.001	-0.789	-5.525
CRP (mg/L)	27.39±6.45	67.38±10.50	-42.65, -32.33	< 0.001	-5.023	-29.800
PCT (ng/mL)	0.36±0.11	1.19±0.26	-0.89, -0.76	< 0.001	-4.796	-25.683
WBC (10^9/L)	9.19±1.65	15.34±1.53	-6.61, -5.70	< 0.001	-3.806	-26.661

Note: NLR: Neutrophil to Lymphocyte Ratio; CRP: C-reactive Protein; PCT: Procalcitonin; WBC: White Blood Cell.

49.19±8.43 U/L, P < 0.001, effect size = -4.475), and Cr (145.07±15.79 vs 92.54±8.61 μmol/L, P < 0.001, effect size = -4.613) were significantly higher in the non-survivor group than in the survivor group. In contrast, the PaO_2/FiO_2 ratio (223.76±53.51 vs 241.70±45.36, P = 0.015, effect size = 0.373) was significantly lower in the non-survivor group. These results indicate that patients in the non-survivor group had more severe tissue hypoperfusion, oxygenation dysfunction, and multiple organ injury (**Table 3**).

Disease severity scores and the duration of mechanical ventilation

The SOFA score (8.01±4.03 vs 6.75±4.97, P = 0.043, effect size = -0.270) and APACHE II score (19.63±2.45 vs 18.68±2.79, P = 0.043, effect size = -0.315) were significantly higher in the non-survivor group than in the survivor group. Although the differences between the two groups were statistically significant, the effect sizes were small (absolute values < 0.4), and the 95% confidence intervals were close to zero (SOFA: -2.49, 0.04; APACHE II: -1.87, -0.03). These findings suggest that although these two traditional critical illness scores can distinguish prognostic risks in patients with SIPD to a certain extent, their predictive performance is relatively limited. For mechanical ventilation duration, 3.64±2.45 days were recorded in the survivor group versus 9.43±1.99 days in the non-survivor group. This indicates that the overall duration of mechanical ventilation in the survivor group was significantly shorter (95% CI: -6.44, -5.14, P < 0.001) (**Table 4**).

Logistic regression analysis of clinical baseline data

Table 5 presents the results of logistic regression analysis of general clinical data in patients

Table 3. Comparison of organ function and metabolic indicators (mean ± SD)

Variables	Survivor group (n = 154)	Non-survivor group (n = 72)	*Difference 95% CI*	*P*	*Effect size*	*t*
Serum Lac (mmol/L)	2.66±1.16	3.68±1.18	-1.35, 0.70	< 0.001	-0.879	-6.154
ALT (U/L)	43.20±8.48	87.54±12.93	-47.65, -41.03	< 0.001	-4.387	-26.541
AST (U/L)	49.19±8.43	94.40±13.00	-48.54, -41.89	< 0.001	-4.475	-26.984
Cr (μmol/L)	92.54±8.61	145.07±15.79	-56.47, -48.58	< 0.001	-4.613	-26.452
PaO_2/FiO_2	241.70±45.36	223.76±53.51	3.52, 32.38	0.015	0.373	2.462

Note: Lac: Lactate; ALT: Alanine Transaminase; AST: Aspartate Transaminase; Cr: Creatinine; PaO_2: Partial Pressure of Arterial Oxygen; FiO_2: Fraction of Inspired Oxygen.

Table 4. Comparison of disease severity scores (mean ± SD)

Variables	Survivor group (n = 154)	Non-survivor group (n = 72)	*Difference 95% CI*	*P*	*Effect size*	*t*
SOFA (scores)	6.75±4.97	8.01±4.03	-2.49, 0.04	0.043	-0.270	-2.039
APACHE II (scores)	18.68±2.79	19.63±2.45	-1.87, -0.03	0.043	-0.315	-2.663
Duration of mechanical ventilation (days)	3.64±2.45	9.43±1.99	-6.44, -5.14	< 0.001	-2.497	-17.493

Note: SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 5. Logistic regression analysis

Variable (n = 226)	Beta Coefficient	Standard Error	*P*	*OR*	*95% CI for OR*
Age (years)	0.015	0.029	0.611	1.015	0.959, 1.073
BMI (kg/m^2)	0.118	0.121	0.330	1.125	0.887, 1.427
Gender	0.000	0.286	1.000	1.000	0.571, 1.750
Diabetes mellitus	0.214	0.312	0.492	1.239	0.672, 2.284
Hypertension	-0.156	0.298	0.601	0.855	0.476, 1.537
Coronary heart disease	0.287	0.356	0.421	1.333	0.663, 2.679
Infection Source	0.189	0.298	0.526	1.208	0.673, 2.169
Vasopressor use	0.356	0.312	0.253	1.428	0.775, 2.631
Renal replacement therapy	0.423	0.456	0.354	1.527	0.625, 3.730

Note: EXP(B): Exponent of Beta coefficient.

with SIPD, to control for the influence of potential confounding factors on 28-day mortality risk. The analysis showed that age (P = 0.611, OR = 1.015, 95% CI: 0.959-1.073), BMI (P = 0.330, OR = 1.125, 95% CI: 0.887-1.427), sex (P = 1.000, OR = 1.000), diabetes mellitus (P = 0.492, OR = 1.239), hypertension (P = 0.601, OR = 0.855), coronary heart disease (P = 0.421, OR = 1.333), source of infection (P = 0.526, OR = 1.208), use of vasoactive agents (P = 0.253, OR = 1.428), and renal replacement therapy (P = 0.354, OR = 1.527) showed no significant independent association with 28-day mortality risk (all P > 0.05). In addition, the 95% confidence intervals of all variables included 1.0, indicating that these baseline characteristics and routine therapeutic measures were not independently associated with short-term prognosis of patients with SIPD. After adjusting for the above confounding factors, these results provide an important basis for covariate control in the subsequent construction of an accurate predictive model.

Multivariate logistic regression analysis

Based on the results shown in **Tables 1-5**, potential risk factors (NLR, serum Lac, ALT, AST, PaO_2/FiO_2, SOFA score, and APACHE II score) screened out by univariate Logistic regression, a multivariate Logistic regression analysis was performed on 226 patients after adjusting for confounding factors including ALT, AST, PaO_2/FiO_2, SOFA score, and APACHE

Table 6. Multivariate logistic regression analysis

Variable (n = 226)	Beta Coefficient	Standard Error	*P*	*OR*	*95% CI for OR*	*VIF*	*Tolerance*
NLR	0.186	0.037	< 0.001	1.204	1.119, 1.296	1.312	0.762
Serum Lac (mmol/L)	0.664	0.126	< 0.001	1.942	1.519, 2.484	1.245	0.803
ALT (U/L)	4.696	175.132	0.979	109.557	0.000, 240.236	18.654	0.054
AST (U/L)	4.025	166.988	0.981	56.007	0.000, 77.321	16.832	0.059
PaO_2/FiO_2	-0.004	0.002	0.053	0.996	0.991, 1.000	1.876	0.533
SOFA	0.054	0.032	0.092	1.055	0.991, 1.123	3.245	0.308
APACHE II (scores)	0.123	0.052	0.068	1.131	1.022, 1.252	3.562	0.281

Note: VIF: Variance Inflation Factor.

Table 7. Comparison of AUCs among different models

Variables (n = 226)	AUC	95% CI	*P*	*Z*	*Cut off value*	*Sensitivity (%)*	*Specificity (%)*	*Youden index*	*Bootstrap AUC*	*Bootstrap calibration slope*
NLR	0.727	0.649, 0.804	0.024*	2.265	9.85	69.4	71.4	0.408	0.711	0.92
Serum Lac	0.734	0.661, 0.808	0.011*	2.548	3.12	72.2	68.8	0.410	0.718	0.89
NLR + serum Lac	0.803	0.746, 0.860	-	-	8.52/2.95	76.4	79.2	0.556	0.786	0.95
SOFA	0.713	0.642, 0.785	0.035*	2.112	7.50	62.5	64.3	0.268	0.698	0.85
APACHE II	0.684	0.605, 0.762	0.022*	2.284	19.20	63.9	66.9	0.308	0.671	0.83

Note: **P* vs. NLR + serum Lac; AUC: Area Under the Curve.

II score. Collinearity diagnosis was performed for all included variables in this study. The results demonstrated that the VIF of NLR, serum Lac and PaO_2/FiO_2 were all less than 2, and their tolerance values were all higher than 0.5. The VIF values of the SOFA score and APACHE II score were 3.245 and 3.562, with tolerance values of 0.308 and 0.281, respectively; no obvious collinearity was observed for the two indicators (all VIF < 5). By contrast, the VIF values of ALT and AST were 18.654 and 16.832, and the corresponding tolerance values decreased to 0.054 and 0.059. Collectively, ALT and AST presented significant collinearity, which was defined as VIF > 10 or Tolerance < 0.1. Given the significant collinearity between ALT and AST, they were not simultaneously included in the final multivariate model. The results (**Table 6**) showed that NLR (95% CI: 1.119-1.296, P < 0.001) and serum Lac (95% CI: 1.519-2.484, P < 0.001) were independently associated with 28-day mortality in patients with SIPD. These findings indicate that inflammatory response and tissue perfusion abnormalities may play important roles in the prognosis of SIPD patients.

ROC curve analysis

As shown in **Table 7**, the combined model of NLR plus serum Lac yielded the highest AUC of 0.803, with the optimal cutoff values of 8.52 and 2.95, respectively. This model also showed the highest sensitivity of 76.4%, specificity of 79.2% and Youden index of 0.556. The individual indicators of NLR and serum Lac showed moderate predictive performance with AUCs of 0.727 and 0.734, respectively. Conventional critical illness scoring systems presented relatively lower discriminatory ability, with an AUC of 0.713 for SOFA score and 0.684 for APACHE II score. All single indicators and clinical scores showed statistically significant differences in AUC compared with the combined model (P < 0.05). After internal validation via bootstrap resampling, the corrected AUC of each model decreased slightly, while all calibration slopes were close to 1.0, indicating good predictive stability and satisfactory calibration. Collectively, the combined model of NLR and serum Lac exhibited superior predictive performance among the evaluated models.

Discussion

As one of the most common manifestations of organ damage in patients with sepsis, SIPD is characterized by alveolar-capillary barrier injury, inflammatory cell infiltration, and oxygenation dysfunction. It progresses rapidly and is associated with marked differences in progno-

sis; therefore, early prognostic assessment and is crucial for clinical intervention [23, 24]. Currently, commonly used clinical prognosis assessment tools have significant limitations [25]. Both NLR and serum Lac have shown potential in the prognosis assessment of sepsis.

This retrospective study enrolled 226 SIPD patients. The non-survivor group had higher levels of inflammatory indicators (NLR, CRP, PCT, WBC), organ injury indicators (ALT, AST, Cr), disease severity scores (SOFA, APACHE II), and serum Lac. In contrast, the oxygenation indicator (PaO_2/FiO_2) was lower in the non-survivor group. Multivariate Logistic regression analysis revealed that elevated NLR and serum Lac were independently associated with 28-day mortality in patients with SIPD. ROC curve analysis demonstrated that the combination of NLR and serum Lac achieved a good level of predictive performance. Additionally, the duration of mechanical ventilation in the non-survivor group was significantly longer than that in the survivor group.

The elevation of NLR reflects the dual pathological states of excessive inflammatory response and immune suppression, which is highly consistent with the pathogenesis of SIPD. In this study, NLR was significantly elevated in the non-survivor group and identified as an independent risk factor, whose mechanism can be explained from two aspects. On one hand, under septic conditions, pathogen-associated molecular patterns activate Toll-like receptor signaling pathways, inducing massive proliferation of neutrophils and their migration to lung tissue. These neutrophils release elastase, reactive oxygen species, and neutrophil extracellular traps, which can damage alveolar epithelial and capillary endothelial cells and exacerbate lung diffusion dysfunction. A study by Fang Bangjiang's team confirmed [26] that increased NLR is directly correlated with the accumulation of immature neutrophils and the activation of the S100A8/A9-MMP9 axis, where MMP9 degrades collagen in the alveolar basement membrane, further aggravating lung injury. From other perspectives, the ongoing inflammatory response during sepsis can lead to lymphocyte apoptosis, thymus atrophy, and increased immune paralysis, thereby causing functional failure of CD4+ T cells and CD8+ T cells. These damaged immune cells are unable to effectively eliminate pathogens and regulate inflammatory responses, leading to persistent infection and aggravated lung injury [27]. In this study, the serum lactate levels in the non-survivor group were significantly elevated and were treated as an independent risk factor. The possible reason is that ventilation/perfusion mismatch and diffusion dysfunction caused by SIPD can directly reduce arterial oxygen saturation, thereby causing systemic tissue hypoxia. Under hypoxic conditions, the anaerobic glycolysis of cells is enhanced, thereby increasing the production of Lac. Secondly, sepsis is often accompanied by capillary leakage syndrome, leading to insufficient effective circulating blood volume and poor tissue perfusion. Even if the arterial oxygen partial pressure is normal, microcirculation disorders may still lead to hidden hypoxia, characterized by elevated Lac [28]. It may also be that Lac is not merely a metabolic byproduct; it can also regulate immune cell function through GPR81 receptor and histone lactylation modifications. High concentrations of Lac can inhibit macrophage phagocytosis and dendritic cell antigen presentation ability, promote regulatory T cell differentiation, and enhance immunosuppression, which is detrimental to the repair of pulmonary infections and injuries. The predictive effect of combined NLR and serum Lac testing is significantly better than that of individual testing. They are able to reflect different dimensions of the pathophysiology of SIPD, with NLR focusing on inflammation and immune imbalance, whereas serum Lac reflects oxygenation and perfusion disorders [29]. When elevated NLR indicates immune imbalance and elevated Lac indicates tissue hypoxia, patients may experience both impaired pathogen clearance and a deteriorating tissue repair microenvironment, which jointly contribute to an increased risk of death. In addition, the intergroup differences in the duration of mechanical ventilation further supports this association. Due to severe inflammation and hypoxia, the non-survivor group required long-term respiratory support, and prolonged mechanical ventilation further exacerbates the risk of lung injury and infection, creating a vicious cycle of poor prognosis.

In terms of the predictive value of NLR, a meta-analysis indicated a significant association between higher NLR levels and poor prognosis and increased risk of death in adult sepsis

patients (HR: 1.6884, 95% CI: 1.4338, 1.9882) [30]. In a single-center prospective observational study involving 114 patients admitted for sepsis or septic shock, the NLR demonstrated good sensitivity (47%) and specificity (78%), with an AUC value of 0.631 ($P < 0.05$). Compared to other specific biomarkers, NLR is more cost-effective and easier to implement, and may serve as an alternative for assessing the severity of sepsis [31]. Regarding serum Lac, a retrospective study enrolled 156 patients diagnosed with severe pneumonia, among whom 54 developed sepsis (sepsis group) and 102 did not (non-sepsis group). Logistic regression analysis identified Lac as an influencing factor for severe pneumonia-related sepsis ($P < 0.05$). Among sepsis patients, those with poor prognosis had significantly higher Lac levels than those with favorable prognosis ($P < 0.05$) [32]. Multivariate Logistic regression analysis revealed that elevated Lac levels were a predictive factor for poor prognosis ($P < 0.05$), with Lac achieving a prognostic AUC of 0.771. Another retrospective study involving 127 sepsis patients reported that the AUC of serum Lac for predicting the prognosis of sepsis patients was 0.694 (95% CI: 0.589, 0.799) [33]. However, some studies have questioned the independent predictive value of NLR. A multicenter retrospective cohort study including 536 critically ill patients found there existed no significant difference in terms of NLR values between the survival and mortality groups, and ROC analysis showed NLR had limited ability to predict critical illness prognosis [34]. The potential reasons for this inconsistency are as follows: first, the study included 536 critically ill patients with heterogeneous disease types, covering different pathological states such as sepsis, trauma, and post-surgery, and the predictive value of NLR varies significantly across different diseases; second, indicators (e.g., APACHE II score, CRP, PCT, Lac) showed good predictive performance, and NLR was highly correlated with these indicators, leading to its elimination in the multivariate model; third, critically ill patients often receive multiple medications, which can significantly affect neutrophil and lymphocyte counts, and thereby influence distorted NLR values [35].

The necessity of this study lies in the fact that, as a common and highly fatal complication of sepsis, SIPD currently relies on clinical prognostic tools, which suffer from cumbersome indicators and insufficient early sensitivity. CRP and PCT are susceptible to interference when used alone. NLR and serum Lac, as routine testing indicators, are free of additional cost and can be quickly obtained. They help address the clinical challenges in primary hospitals and compensate for the lack of SIPD prognosis assessment tools. The innovation of this study is reflected in its focus on the specific population of SIPD, demonstrating the prognostic value of the combined use of NLR and serum Lac through clinical data, thereby addressing the limitations of previous widespread sepsis studies. Furthermore, it quantifies the predictive performance of the joint model and provides a reference for the subsequent construction of composite models.

Study limitations

There are several limitations in this study. First, single admission measurements of the NLR and Lac were adopted, without dynamic monitoring. Therefore, the dynamic changes in these indicators throughout treatment and their longitudinal predictive value for prognosis could not be observed. Second, stratified analysis based on infection type, pathogen species, sepsis severity and comorbidities was not performed, making it difficult to clarify the applicable scope of the combined model in different clinical subgroups. Third, this is a single-center retrospective study. It is subject to selection bias and limited generalizability, and lacks an independent external validation cohort. Consequently, the generalizability and robustness of the combined model require further validation. In addition, the specific mechanisms of NLR and Lac in SIPD were only theoretically explained based on existing literature. No experimental verification at the mechanistic level was conducted through basic research methods such as inflammatory factor detection, immune phenotyping analysis or lactylation modification validation. Finally, confounding factors including therapeutic interventions, pathogen characteristics, genetic subtypes and chronic comorbidities were not fully incorporated into the analysis, which may limit the ability to control for selection bias and confounding factors. This study did not perform propensity score matching (PSM), which resulted in methodological limitations in controlling for selection bias and confounding factors.

Future research should conduct multicenter prospective studies to obtain more SIPD patient

samples and validate the effectiveness of the combined model. Dynamic detection data should be collected to improve prediction accuracy, and stratified analysis should be conducted by different subtypes to clarify the applicable scope of this model. Moreover, combining basic research to explore the association mechanism between NLR and serum Lac will help achieve a more complete clinical pathway from prediction to intervention. Further methods such as PSM or inverse probability of treatment weighting (IPTW) will be adopted to verify the conclusions, so as to improve the evidence level of this study and the extrapolation reliability of the results.

Conclusions

Through retrospective analysis, this study showed that elevated NLR and elevated serum Lac are independently associated with 28-day mortality in SIPD patients, and their combined prognostic value is superior to individual detection. The combined model has the advantages of convenient testing, low cost, and early availability.

Disclosure of conflict of interest

None.

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