Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

A Simplified Immune-Dysregulation Index (IL-6/LY) as a Robust Predictor of 28-Day In-Hospital Mortality and MODS in Patients with Sepsis

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Objective: To evaluate the prognosis significance of a newly simplified immune-dysregulation index, interleukin-6-to-lymphocyte ratio (IL-6/LY), in individuals diagnosed with sepsis.

Methods: This was a retrospective cohort study enrolling consecutive patients diagnosed with sepsis who qualified the inclusion criteria and were admitted to the intensive care unit of the First Affiliated Hospital of Soochow University between March 2017 and January 2023. Multivariate COX and logistic regression models were used to estimate the association between IL-6/LY and 28-day in-hospital mortality or multiple organ dysfunction syndrome (MODS). Restricted cubic splines and survival analysis were used to show a nonlinear correlation between IL-6/LY and mortality. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic value of IL-6/LY. was performed using the Kaplan–Meier method.

Results: The study encompassed 301 participants, categorized into two groups—those with low IL-6/LY and high IL-6/LY—determined by the cutoff value of 326.04. On multivariate analyses, a high IL-6/LY was independently associated with 28-day in-hospital mortality (hazard ratio [HR]: 8.01, 95% confidence interval [CI] 4.67–13.74, $P < 0.001$) and MODS (odds ratio [OR] 3.44, 95% CI 1.85–6.38, $P < 0.001$). The area under the curve of IL-6/LY for predicting death and MODS were 0.893 (95% CI, 0.855–0.931) and 0.743 (95% CI, 0.688–0.798), respectively. The Kaplan–Meier analysis showed a significantly higher risk of mortality in the high IL-6/LY group (≥ 326.04) (log-rank $P < 0.001$).

Conclusion: The IL-6/LY is significantly associated with the risk of 28-day in-hospital mortality and MODS in patients with sepsis, making it a potential prognostic marker for risk stratification, which enables early identification of high-risk patients, timely interventions, and personalized treatment strategies to optimize patient outcomes.

Keywords: sepsis, interleukin-6, 28-day in-hospital mortality, MODS, prognosis

Introduction

Sepsis is a critical medical condition marked by dysregulated response to infection and subsequent organ dysfunction.[1] Sepsis is associated with a high morbidity and mortality rate despite the advances in intensive care medicine.[2,3] Epidemiological studies have shown that the global annual burden of sepsis is approximately 48.9 million cases and 11 million deaths, accounting for 19.7% of the global death toll. The estimated incidence of sepsis is 189 cases per 100,000 hospitalized patients, with an estimated mortality rate of 26.7%.[4] A multicenter study across 44 hospitals in China showed a high morbidity rate of sepsis at 20.6% in the intensive care unit (ICU), and the mortality rate ranged from 35.5% to over 50%.[5] Timely recognition of patients in critical condition enables clinicians to take proactive steps, thus reducing morbidity and mortality. Therefore, identification of effective predictors is a key imperative.

Received: 22 February 2025
Accepted: 18 May 2025
Published: 28 May 2025

Several clinical scoring systems, such as the sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation II (APACHE II) score, are used for risk stratification of patients with sepsis.[6,7] These scoring systems play a crucial role in sepsis management. Their proper application can significantly enhance early sepsis identification, guide interventions effectively, and ultimately lead to improved patient outcomes by quantifying disease severity and predicting patient outcomes.[8] However, these scores are derived from composite domains that limit their wide application, especially in emergency settings. Therefore, there is a need to develop a more convenient index in real-world practice.

Persistent lymphopenia after the diagnosis of sepsis predicts early and late mortality and may serve as a biomarker for sepsis-induced immunosuppression.[9] During infection or tissue damage, interleukin-6 (IL-6) is released as a pro-inflammatory cytokine, playing a role in both innate and adaptive immune responses.[10] Previous studies have suggested a prognostic role of IL-6 level in patients with systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). In sepsis, IL-6 may can cause lymphocyte overactivation and apoptosis by promoting inflammation and immune cell activation, and lymphocytopenia may weaken inflammatory control, further intensifying the inflammatory response. Unfortunately, commonly used prognostic biomarkers fail to reflect inflammation and immune status simultaneously in sepsis. For instance, despite extensive research, PCT and lactate mainly indicate bacterial infection and tissue hypoperfusion, not the interplay of inflammation and immune regulation.[11,12] In our earlier study, the IL-6-to-lymphocyte ratio (IL-6/LY) was linked to the prognosis of patients with novel coronavirus disease 2019 (COVID-19) and its prognostic value was superior to that of IL-6 or lymphocyte count alone.[13] However, the prognostic value of IL-6/LY in patients with sepsis is not clear.

In this study, we investigated the prognostic value of IL-6/LY as a predictor of 28-day in-hospital mortality and incidence of MODS in patients with sepsis.

Materials and Methods

Study Design and Population

This was a single-center, retrospective cohort study. Consecutive adult patients with sepsis who were hospitalized in the Department of Intensive Care Medicine of the First Affiliated Hospital of Soochow University between March 2017 and January 2023 were included. The follow-up time for assessing mortality outcomes was 28 days after admission to the ICU. The study protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (IRB No. 2021–274).

Inclusion and Exclusion Criteria

Sepsis is diagnosed based on the Sepsis 3.0 criteria, which requires the presence of evidence of infection along with a SOFA score of ≥2.[1] Only adult patients (age ≥18 years) for whom data regarding IL-6 levels, lymphocyte counts, and outcome measurements were available were eligible for inclusion. Patients with hematological disorders affecting lymphocyte counts, those recently treated with immunosuppressants, or those receiving any chemoradiotherapy were excluded.

Clinical Data Collection

The baseline characteristics of the patients, including age, sex, body mass index (BMI), comorbidities, primary infection site, and pathogen, as well as APACHE II and SOFA scores, were recorded. These scores were routinely calculated at our hospital during the study reference period. Data regarding the ICU length of stay (LOS), invasive mechanical ventilation, and continuous renal replacement therapy (CRRT) were also collected. We retrospectively collected the results of routine blood tests, serum cytokine measurements, blood coagulation function tests, biochemistry, and arterial blood gas analysis performed within 24h of admission were collected from the hospital database. IL-6/LY was calculated by dividing IL-6 (pg/mL) by the lymphocyte count ($\times 10^9$/L).

IL-6 Test

Sepsis patients at our hospital were routinely tested for cytokines using a 12-in-1 cytokine detection kit (multiple microsphere flow immunofluorescence method). The BD Canto II flow cytometer was used to measure the IL-6 level.

Follow Up

The primary outcome of this study was the 28-day in-hospital mortality after ICU admission. The secondary outcome was the incidence of MODS. MODS is defined as acute and potentially reversible dysfunction or failure of two or more organ systems,[14,15] including the cardiovascular, hepatic,[16] coagulation,[17] respiratory,[18] renal,[19] and other organs,[15] due to severe conditions like serious infections.

Statistical Analysis

All continuous variables were non-normally distributed and were presented as median (lower quartile, upper quartile). Comparisons were made using the Mann–Whitney *U*-test. Categorical variables were presented as frequency (percentage) and subjected to comparison through the chi-squared test or Fisher's exact test, as deemed suitable Patients were categorized into high IL-6/LY and low IL-6/LY groups based on a cutoff value determined by the Youden index. Multivariate COX and logistic regression models were employed to assess the association of IL-6/LY with overall survival and MODS. Restricted cubic splines were utilized to illustrate a nonlinear correlation between IL-6/LY and mortality. ROC curve analysis was conducted to evaluate the prognostic value of IL-6/LY. Survival analysis was executed using the Kaplan–Meier method, and differences in survival between groups were evaluated using the Log rank test. Additionally, a subgroup analysis was carried out using COX and logistic regression, along with an examination of the interaction between the given stratification and the study group. P values < 0.05 were considered indicative of statistical significance. Statistical analyses were performed using the R software (version 4.0.3, Vienna, Austria).

Results

Baseline Characteristics

Figure 1 displays a schematic representation of the study design and criteria used for patient selection. A total of 782 patients with sepsis qualified the diagnostic criteria for sepsis described above during the study reference period. Based on the exclusion criteria, 301 patients were included in this study. Of these, 122 (40.5%) patients were in the high IL-6/LY group and 179 (59.5%) patients in the low IL-6/LY group according to the cutoff value of 326.04 (Youden index 0.813; sensitivity: 83%; specificity: 84%).

The baseline patient characteristics are presented in Table 1. Compared to those with low IL-6/LY, patients with high IL-6/LY were older, had faster heart rate and respiratory rate, and had higher APACHE II and SOFA scores (P < 0.050, respectively). There were no significant between-group differences with respect to sex, BMI, blood pressure, or history of comorbidities. The distribution of sites of infection and pathogen types was comparable between the two groups. Patients with high IL-6/LY had significantly higher levels of lactic acid, IL-6, NT-proBNP, PT, APTT, creatinine, and AST, and significantly lower lymphocyte count, platelet count, WBC count, PH, PO_2, and oxygenation index compared to those with low IL-6/LY (P < 0.050 for all). Other laboratory parameters were not significantly different between the two groups. Compared to the low IL-6/LY group, the high IL-6/LY group showed a shorter length of free-CRRT time, length of free-mechanical ventilation time, and LOS in the ICU, while the duration of vasoactive drug use was prolonged (P < 0.050 for all). In addition, 28-day in-hospital mortality and incidence of MODS in the high IL-6/LY group were significantly higher than that in the low IL-6/LY group (P < 0.001 for both).

Association Between IL-6/LY and 28-Day In-Hospital Mortality

Multivariate COX models were employed to evaluate the correlation between IL-6/LY and the risk of 28-day in-hospital mortality (Table 2). In the unadjusted model, high IL-6/LY was associated with a 10-fold higher risk of death (hazard ratio [HR]: 10.30, 95% CI 6.27–16.94, P < 0.001). After adjusting for age, sex, hypertension, diabetes, COPD, lactic acid, platelet count, PT, AST at admission, serum creatinine at admission, and SOFA score, IL-6/LY remained a significant predictor of 28-day in-hospital mortality (HR: 8.01, 95% CI 4.67–13.74, P < 0.001).

We used a restricted cubic spline to analyze the shape of the association between IL-6/LY and 28-day in-hospital mortality. The results showed a positive relationship between the IL-6/LY and 28-day in-hospital mortality ($P_{\text{Non-linearity}}$ < 0.001) (Figure 2). The Kaplan–Meier survival curves demonstrated a significantly higher risk of 28-day in-hospital mortality in the

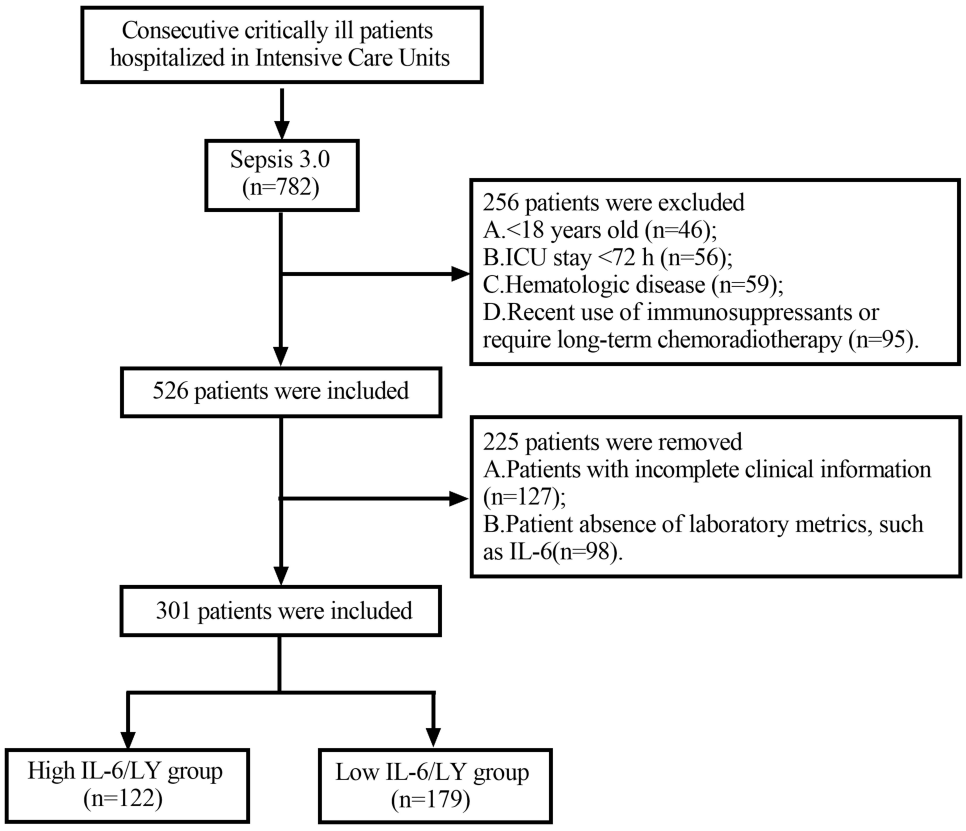

Figure 1 Flow chart showing the study design and patient-selection criteria.

high IL-6/LY group compared to that in the low IL-6/LY group ($P < 0.001$) (Figure 3). To further analyze the role of IL-6/LY in different populations, a subgroup analysis was performed. Results of subgroup analysis stratified by patient age, sex, history of hypertension, and diabetes are presented in Figure 4. In this sensitivity analysis, the IL-6/LY remained a significant predictor

Table 1 Baseline Characteristics of Septic Patients in Low and High IL-6/LY Groups

	Low IL-6/LY group (<326.04)	**High IL-6/LY group (≥326.04)**	***P* value**
Number, n (%)	179 (59.5%)	122 (40.5%)	
Sex (male), n (%)	74 (41.3%)	50 (41.0%)	0.951
Age, years	58.00 (45.00, 73.00)	68.00 (59.00, 77.00)	<0.001
BMI, kg/m^2	23.31 (21.26, 25.80)	23.04 (20.90, 25.40)	0.315
Vital signs			
HR	101.00 (85.00, 117.00)	107.00 (95.00, 125.25)	0.015
RR	20.00 (17.00, 22.00)	21.50 (16.75, 27.25)	0.045
SBP	115.00 (100.00, 132.00)	106.00 (92.00, 128.00)	0.111
DBP	66.00 (56.00, 80.00)	64.00 (53.75, 75.25)	0.166
Comorbidity, n (%)			
Hypertension	87 (48.6%)	58 (47.5%)	0.856
Diabetes	51 (28.5%)	35 (28.7%)	0.970
COPD	7 (3.9%)	4 (3.3%)	0.774
Coronary artery disease	8 (4.5%)	1 (0.8%)	0.068
Chronic kidney disease	14 (7.8%)	5 (4.1%)	0.192
Chronic liver disease	7 (3.9%)	3 (2.5%)	0.054
Cerebrovascular disease	18 (10.1%)	18 (14.8%)	0.217

(*Continued*)

Table 1 (Continued).

	Low IL-6/LY group (<326.04)	High IL-6/LY group (≥326.04)	*P* value
Infection site, n (%)			0.092
Respiratory	59 (33.0%)	51 (41.8%)	
Abdominal/GI	38 (21.2%)	21 (17.2%)	
Urinary	17 (9.5%)	6 (4.9%)	
Skin and soft tissue	22 (12.3%)	7 (5.7%)	
Blood	22 (12.3%)	23 (18.9%)	
Others	21 (11.7%)	14 (11.5%)	
Organism, n (%)			0.690
Gram-positive	20 (15.6%)	11 (10.7%)	
Gram-negative	53 (41.4%)	42 (40.8%)	
Complicated	35 (27.3%)	31 (30.1%)	
Fungal	20 (15.6%)	19 (18.4%)	
APACHE II score	16.00 (11.00, 21.00)	22.00 (17.75, 28.00)	<0.001
SOFA score	8.00 (6.00, 11.00)	12.00 (8.00, 15.25)	<0.001
Blood routine index			
Hemoglobin, g/L	104.00 (86.00, 126.00)	101.00 (77.75, 120.25)	0.165
WBC count, 10^9/L	12.86 (7.78, 21.79)	10.76 (5.39, 18.18)	0.027
Platelet count, 10^9/L	123.00 (70.00, 207.00)	86.00 (43.00, 168.25)	0.005
Lymphocyte count, 10^9/L	0.76 (0.51, 1.36)	0.47 (0.27, 0.85)	<0.001
Neutrophil count, 10^9/L	11.40 (6.21, 18.96)	9.36 (4.78, 16.08)	0.072
Cytokines			
IL-6, pg/mL	67.20 (27.00, 134.00)	606.80 (240.83, 1476.55)	<0.001
Cardiac function			
NT-proBNP, pg/mL	2341.50 (1025.00, 4668.25)	6819.00 (1695.50, 16,622.00)	<0.001
Coagulation function			
PT, s	16.10 (14.50, 18.10)	17.50 (14.90, 20.73)	<0.001
APTT, s	43.80 (37.10, 50.80)	46.60 (39.20, 53.93)	0.027
Arterial blood gas			
PH	7.42 (7.34, 7.48)	7.39 (7.28, 7.46)	0.006
PO_2, mmHg	99.20 (79.70, 135.00)	67.95 (64.58, 115.00)	0.003
PCO_2, mmHg	34.20 (28.20, 40.00)	34.65 (29.45, 44.68)	0.076
P/F	245.61 (172.44, 310.00)	188.67 (117.45, 263.71)	<0.001
Lac, mmol/L	1.60 (1.00, 2.50)	2.90 (1.68, 5.68)	<0.001
Renal function			
Creatinine, μmol/L	91.00 (55.00, 175.40)	119.65 (63.60, 210.03)	0.020
Liver function			
TBil, μmol/L	17.70 (10.80, 31.30)	19.75 (13.80, 41.33)	0.137
AST, U/L	43.70 (24.00, 131.20)	59.80 (32.30, 203.10)	0.020
ALT, U/L	35.80 (17.30, 91.00)	34.45 (22.20, 115.50)	0.334
Albumin, g/L	29.90 (27.00, 33.30)	29.90 (24.98, 33.70)	0.612
Prognostic indicators			
ICU LOS, days	12.00 (7.00, 22.00)	9.00 (4.00, 14.00)	<0.001
Length of free-CRRT, days	18.00 (8.00, 31.00)	9.00 (3.00, 21.25)	<0.001
Length of free-mechanical ventilation, days	13.00 (5.00, 25.00)	4.00 (0.00, 15.25)	<0.001
Length of vasoactive drug use, days	4.00 (0.00, 10.00)	5.00 (3.00, 10.00)	0.006
28-day in-hospital mortality	19 (10.6%)	92 (75.4%)	<0.001
Incidence of MODS	65 (36.3%)	93 (76.2%)	<0.001

Abbreviations: BMI, body mass index; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; WBC, white blood cell count; IL-6, interleukin-6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PT, prothrombin time; APTT, activated partial thromboplastin time; P/F, PaO_2/FiO_2; TBil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Lac, lactic acid; LOS, length of stay; MODS, multiple organ dysfunction syndrome; CRRT, continuous renal replacement therapy.

https://doi.org/10.2147/JIR.S521684

Table 2 Multivariate Cox Regression Analysis for the Association Between IL-6/LY and 28-Day in-Hospital Mortality

	HR (95% CI)		*P* value	Concordance
	Low IL-6/LY Group (<326.04)	High IL-6/LY Group (≥326.04)		
Univariate Non-adjusted	1.00 (Ref)	10.30 (6.27, 16.94)	<0.001	0.739
Multivariate				
Model I	1.00 (Ref)	9.92 (5.97, 16.48)	<0.001	0.755
Model II	1.00 (Ref)	9.98 (6.00, 16.60)	<0.001	0.757
Model III	1.00 (Ref)	8.01 (4.67, 13.74)	<0.001	0.802

Notes: Model I adjusted for age and sex. Model II adjusted for age, sex, hypertension, diabetes, and COPD. Model III adjusted for age, sex, hypertension, diabetes, COPD, lactic acid, platelet count, PT, AST at admission, serum creatinine at admission, and SOFA score.
Abbreviations: HR, hazard ratio; CI, confidence interval.

of mortality, and there was no difference in trends between subgroups ($P < 0.050$ for all; P-interaction > 0.050). As shown in Figure 5, IL-6/LY (AUC = 0.893, 95% CI, 0.855–0.931, $P < 0.001$) outperformed the SOFA score (AUC = 0.717, 95% CI, 0.655–0.778, $P < 0.001$) in predicting 28-day in-hospital mortality.

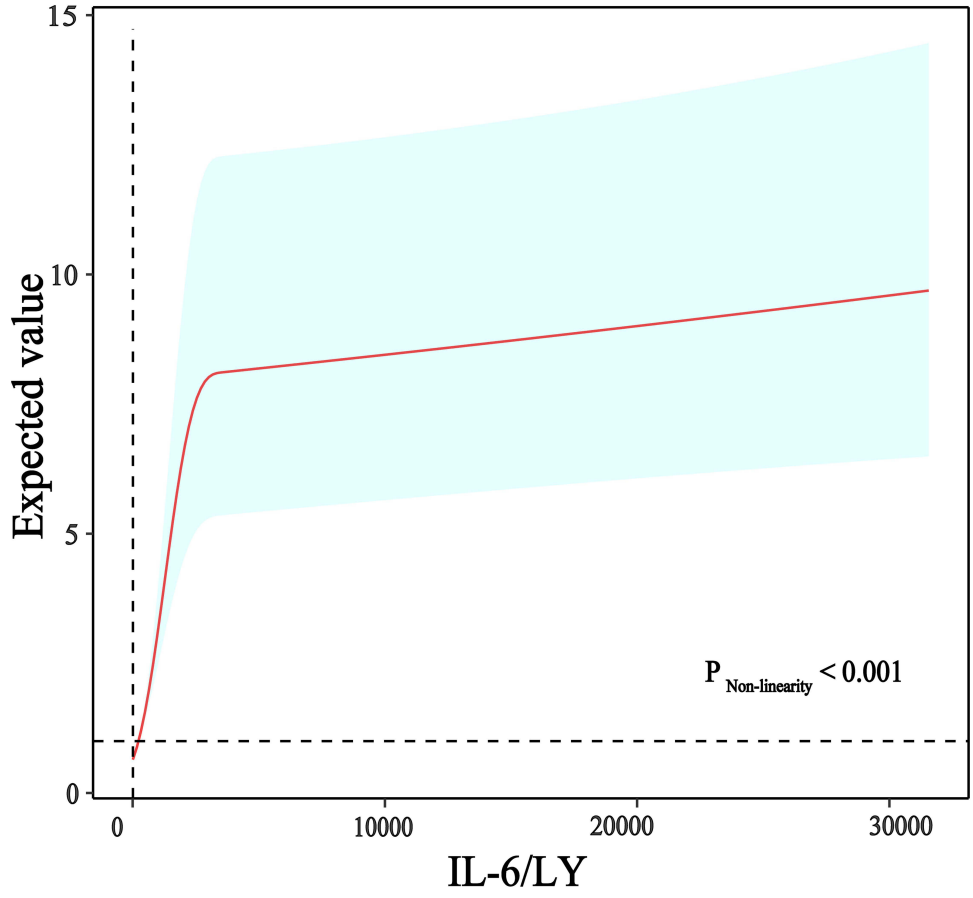

Figure 2 Restricted cubic spline analysis of the relationship between IL-6/LY and 28-day in-hospital mortality in patients with sepsis. Dashed lines are 95% confidence intervals (P non-linearity < 0.001).

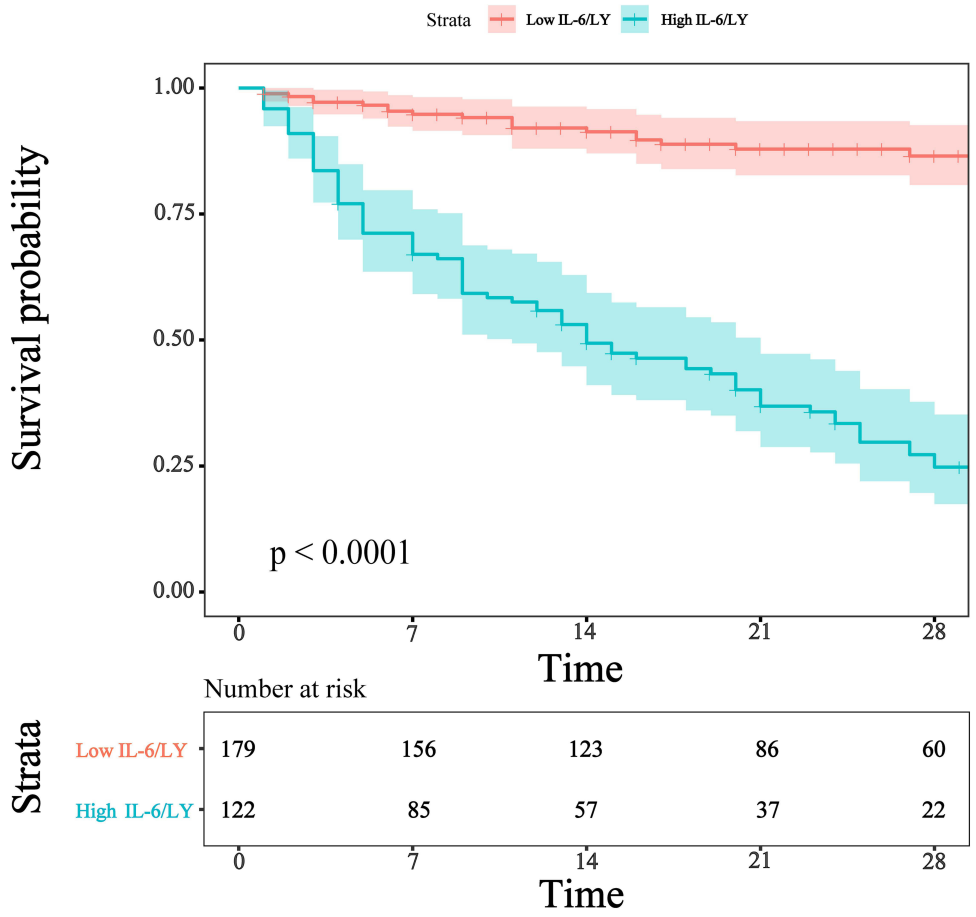

Figure 3 Kaplan–Meier cumulative survival curves for 28-day in-hospital mortality in patients with sepsis according to IL-6/LY. (log-rank P < 0.001).

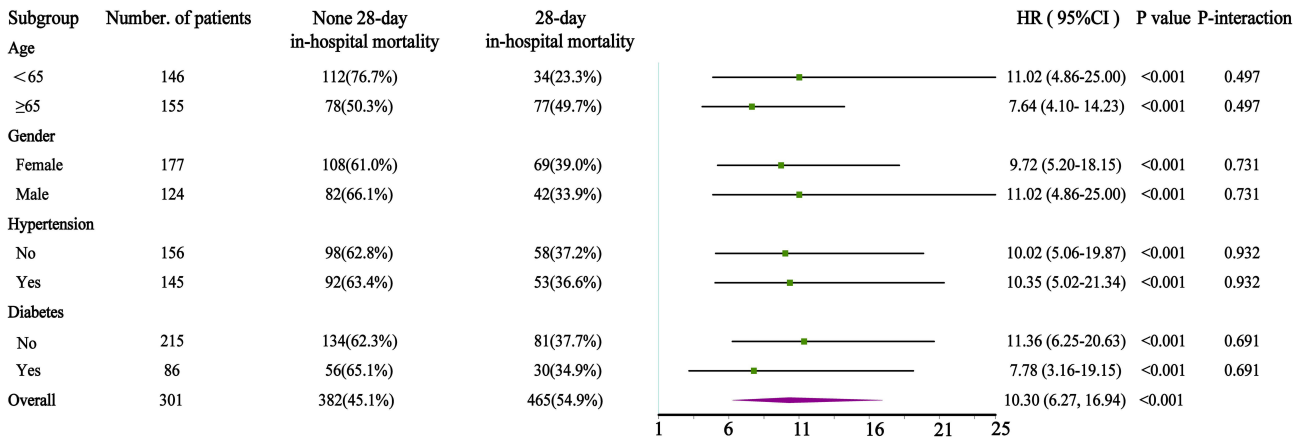

Figure 4 Subgroup analysis of the association between IL-6/LY and 28-day in-hospital mortality.
Abbreviation: HR, hazard ratio.

Association Between IL-6/LY and MODS

Multivariate logistic analysis was conducted to evaluate the correlation between IL-6/LY and the risk of developing MODS. As shown in Table 3, both univariate (OR 5.62, 95% CI 3.36–9.43, $P < 0.001$) and multivariate (OR 3.44, 95% CI 1.85–6.38, $P < 0.001$) analyses showed that a higher IL-6/LY was associated with an increased risk of MODS.

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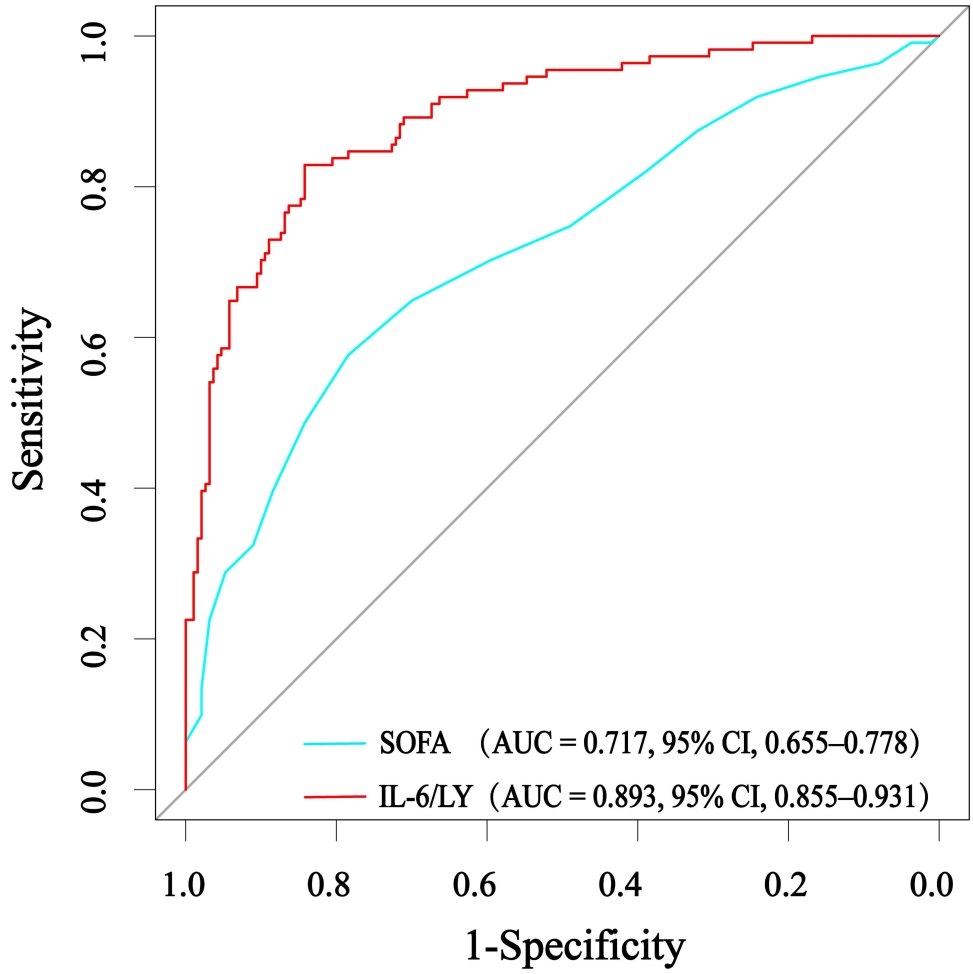

Figure 5 The ROC curves of SOFA and IL-6/LY to predict the 28-day in-hospital mortality in sepsis patients (AUC = 0.717, 95% CI, 0.655–0.778; AUC = 0.893, 95% CI, 0.855–0.931, respectively).

As shown in Figures 6 and 7, patients with MODS had higher IL-6/LY levels than those without MODS, and the incidence of MODS was higher in the high IL-6/LY group than in the low IL-6/LY group. Subgroup analysis of the role of IL-6/LY in predicting MODS is shown in a stratified forest plot in Figure 8. The results showed that IL-6/LY remained a significant risk factor for MODS, except in patients with diabetes. The ROC curves for SOFA score and IL-6/LY for

Table 3 Predictors of MODS in Univariable and Multivariable Logistic Regression Analyses

	OR (95% CI)		*P* value	Log-Likelihood
	Low IL-6/LY Group (<326.04)	High IL-6/LY Group (≥326.04)		
Univariate Non-adjusted	1.00 (Ref)	5.62 (3.36, 9.43)	<0.001	368.38
Multivariate				
Model I	1.00 (Ref)	5.27 (3.11, 8.93)	<0.001	366.34
Model II	1.00 (Ref)	5.31 (3.10, 9.08)	<0.001	359.82
Model III	1.00 (Ref)	3.44 (1.85, 6.38)	<0.001	294.70

Notes: Model I adjusted for age, sex. Model II adjusted for age, sex, hypertension, diabetes, and COPD. Model III adjusted for age, sex, hypertension, diabetes, COPD, lactic acid, platelet count, PT, AST at admission, serum creatinine at admission, and SOFA score.
Abbreviations: OR, odds ratio; CI, confidence interval.

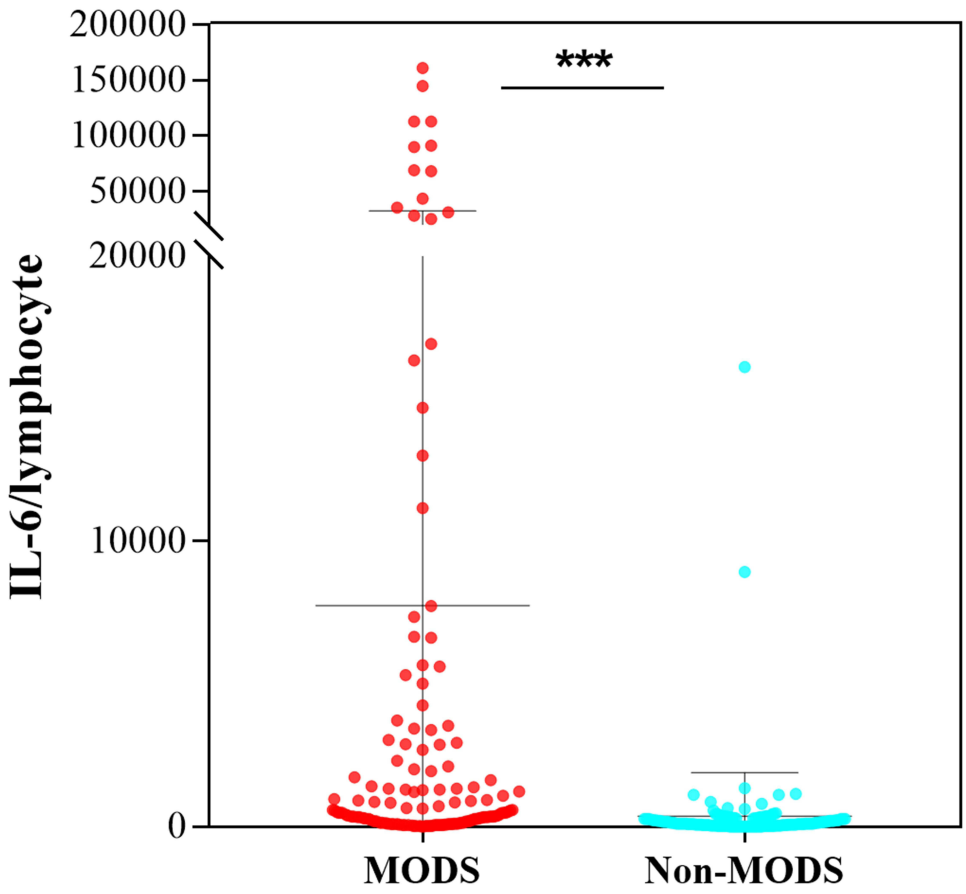

Figure 6 IL-6/LY levels in MODS and non-MODS patients. ***P < 0.001.

predicting the risk of MODS are shown in Figure 9. SOFA score and IL-6/LY showed similar predictive efficacy for the incidence of MODS (AUC = 0.740, 95% CI, 0.685–0.795; AUC = 0.743, 95% CI, 0.688–0.798, respectively).

Discussion

In this retrospective cohort study, a high IL-6/LY in patients with sepsis was associated with an increased risk of 28-day in-hospital mortality and MODS. Following adjustments for demographic and clinical characteristics in the multivariate model, IL-6/LY retained its significance as a predictor for adverse outcomes. Patients in the high IL-6/LY group had more unstable vital signs, poor survival, and a high incidence of organ dysfunction. Subgroup analysis revealed the prognostic value of IL-6/LY in most patients with sepsis.

Cytokine storm and immunosuppression are two key drivers of the development and progression of sepsis, contributing to increased morbidity and mortality.[20] Research conducted in the past decade has unraveled the critical role of immune function and inflammatory response in the development of sepsis.[21,22] IL-6 is induced by stress, including infection and trauma. It plays an essential role in host defense by stimulating acute-phase responses, hematopoiesis, and immune reactions.[23] Nevertheless, exaggerated production of IL-6 predisposes to cytokine storm,[10] a pernicious reaction associated with an adverse prognosis. Song et al established the diagnostic and prognostic values of IL-6 in individuals diagnosed with sepsis.[11] In a prospective multicenter observational study, elevated IL-6 expression was identified as being correlated with mortality in ICU patients with sepsis,[24] which is consistent with our findings. Cifaldi et al reported that elevated levels of IL-6 were associated with impaired cytolysis due to hyperactivation of the immune system, resulting in MODS.[25] In our study, IL-6/LY showed better predictive efficacy and was equally statistically significant in logistic and COX regression and subgroup analysis.

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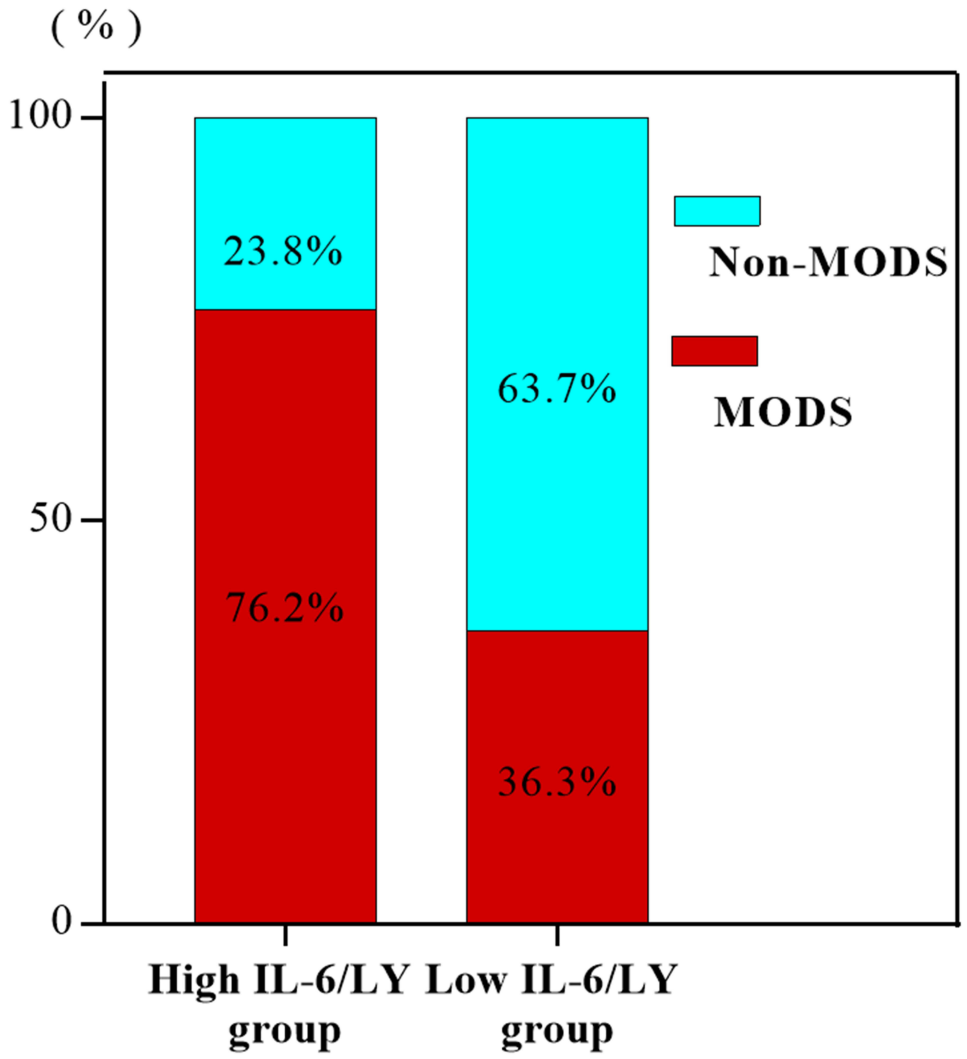

Figure 7 Bar graph of MODS incidence in low and high IL-6/LY groups.

Subgroup	Number of patients	Incidence of non-MODS	Incidence of MODS	OR (95%CI)	P value	P-interaction
Age						
＜65	146	77(52.7%)	69(47.3%)	4.90 (2.21- 10.84)	<0.001	0.776
≥ 65	155	66(42.6%)	89(57.4%)	6.12 (3.02- 12.40)	<0.001	0.776
Gender						
Female	177	81(45.8%)	96(54.2%)	5.69 (2.88-11.24)	<0.001	0.958
Male	124	62(50.0%)	62(50.0%)	5.58 (2.52-12.35)	<0.001	0.958
Hypertension						
No	156	70(44.9%)	86(55.1%)	3.76 (1.88-7.51)	<0.001	0.251
Yes	145	73(50.3%)	72(49.7%)	8.99 (4.11-19.69)	<0.001	0.251
Diabetes						
No	215	106(49.3%)	109(50.7%)	9.40 (4.91-18.00)	<0.001	0.103
Yes	86	37(43.0%)	49(57.0%)	1.84 (0.76-4.48)	0.177	0.103
Overall	301	143(47.5%)	158(52.5%)	5.62 (3.36, 9.43)	<0.001	

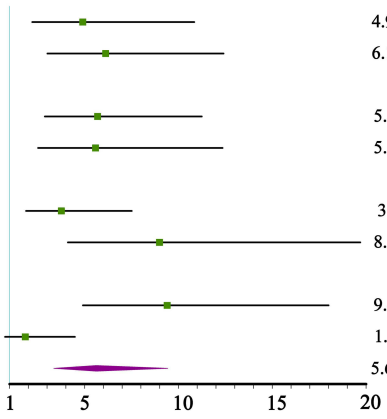

Figure 8 Subgroup analyses of the association between IL-6/LY and MODS.
Abbreviation: OR, odds ratio.

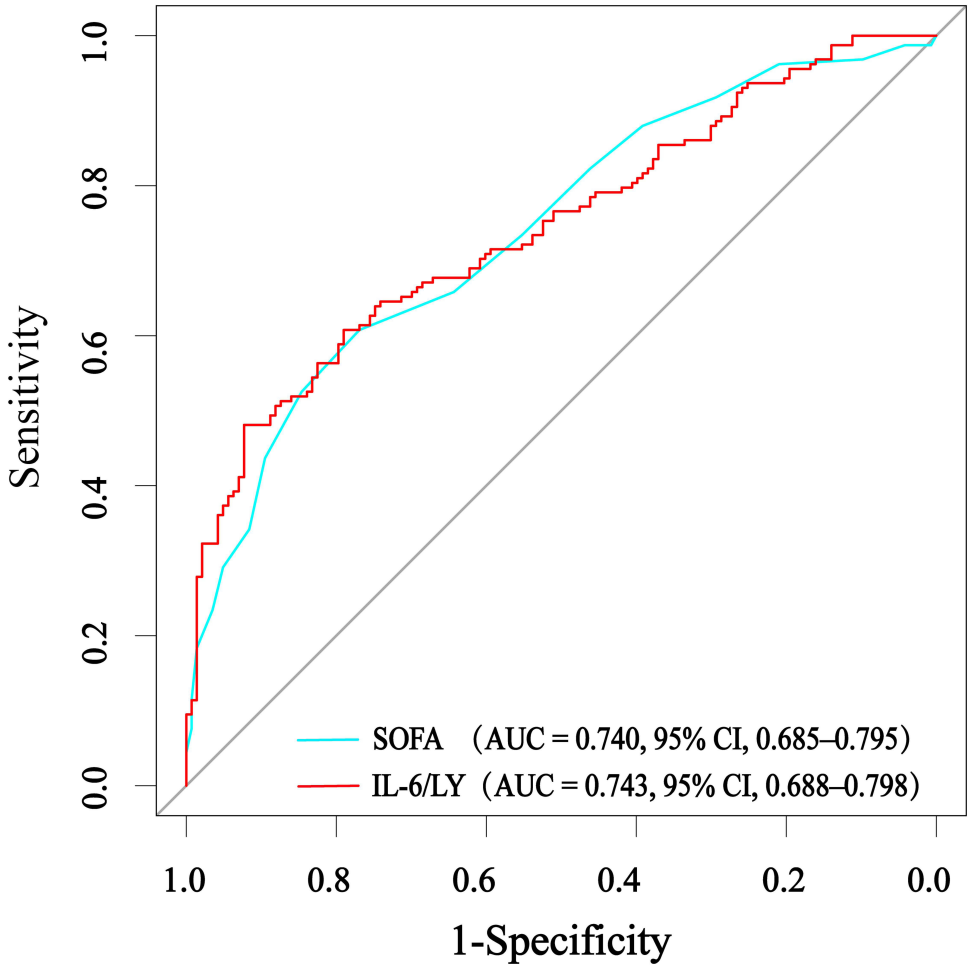

Figure 9 The ROC curves of SOFA and IL-6/LY in predicting MODS (AUC = 0.740, 95% CI, 0.685–0.795; AUC = 0.743, 95% CI, 0.688–0.798, respectively).

Immunosuppression induced by sepsis is characterized by the depletion of apoptosis-associated immune cells, including $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, and follicular dendritic cells.[26] Persistent lymphopenia, a marker of sepsis-induced immunosuppression, is considered a predictor of mortality.[9] Compared to survivors, deceased patients with sepsis showed a lower quantity of mature B cells and circulating Tfh (cTfh) cells. Lymphocyte counts are inversely associated with mortality.[27] Additionally, dysregulated lymphocyte function was shown to be associated with the occurrence and prognosis of MODS in patients with sepsis.[28] Humanized mouse models of sepsis suggest that the decrease in septic lymphocytes may be related to their regulation.[29] Overall, in sepsis, IL-6 may promote inflammatory responses and cause immune cell overactivation and tissue damage by activating multiple signaling pathways, such as the JAK/STAT3 pathway.[30] This novel indicator, which combines inflammatory responses and lymphocyte regulation, can more comprehensively reflect the stress response during sepsis. To the best of our knowledge, this study represents the initial exploration of the prognostic significance of IL-6/LY in sepsis.

Multi-dimensional scoring systems, including the APACHE II and SOFA scores, are well-known risk stratification tools for sepsis management. However, these models rely on an array of demographic, clinical, and laboratory data, rendering them inconvenient to implement in emergency settings. This significantly limits their application in routine clinical practice, especially for more intensive scenarios, typically in the emergency department.[31,32] In contrast, the predictive efficacy of IL-6/LY is similar to that of SOFA score, but it employs two simple serum biomarkers, making it more convenient to use in this setting. In addition, IL-6 assays have gradually become routine and more readily available in clinical practice, thereby making IL-6/LY a more appropriate method for point-of-care applications. Therefore, IL-6/

https://doi.org/10.2147/JIR.S521684

LY facilitates more timely sepsis monitoring and earlier intervention, enhancing the potential for improved patient outcomes.

Compared with the low IL-6/LY group, WBC count was lower in the high IL-6/LY group, which is a perplexing finding. This might be related to the intensity of antibiotic use and bone marrow suppression caused by severe infection.[33,34] Moreover, the high IL-6/LY group had a shorter ICU LOS, likely due to the severity of the condition. Relevant studies have shown that the mortality rate of septic patients is high in the early stage.[35] Some limitations of this study should be considered while interpreting the results. Firstly, it was performed in a single tertiary center and the study population comprised exclusively of Han Chinese patients. Secondly, the study's retrospective nature precludes causal inferences and may leave some confounding factors unavoidable. Finally, the follow-up period for the survival analysis was confined to 28 days, and further study is required to assess the long-term prognostic value. A prospective multicenter cohort with a longer follow-up duration is currently underway to address these limitations.

Conclusion

The IL-6/LY may become a novel prognostic biomarker for predicting 28-day in-hospital mortality and MODS in patients with sepsis. This composite index integrates IL-6 and lymphocyte counts, reflecting the dual pathological drivers of sepsis: hyperinflammation and immune paralysis. Elevated IL-6/LY values correlate with systemic inflammation, impaired host defense, and increased risk of organ failure, offering a more holistic assessment than traditional biomarkers. Its dual-parameter integration enhances prognostic accuracy for early identification of high-risk patients and may guide real-time therapeutic decisions, with potential for future validation in personalized critical care management.

Data Sharing Statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request after official publication.

Acknowledgments

This paper has not been published elsewhere in whole or in part. The authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. There are no ethical/legal conflicts involved in the article. The procedures with human participants followed the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (IRB No. 2021-274). The ethics committee waived the requirement for individual informed consent as the data were retrospectively analyzed without identifiers, and the study posed no additional risks to participants. We would like to thank hospital staff, patients, and medical staff who cared for patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Science Foundation of Jiangsu Commission of Health (M2022086), the Suzhou Basic Research Project (SSD2024053) and Nature Science Foundation of Jiangsu Project (BK20241798).

Disclosure

The authors report no conflicts of interest in this work.

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