Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

The Relationship Between Soluble Interleukin-17 Receptor Levels and CD3-Positive T Cells and Lymphocytes in Patients with Sepsis and Their Predictive Clinical Significance

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Background: To assess the relationship between soluble interleukin-17 receptor (sIL-7R) levels and CD3-positive t cells and lymphocytes in patients with sepsis and their predictive clinical significance.

Methods: The study cohort comprised individuals diagnosed with sepsis based on the Third International Consensus Definitions for Sepsis and Septic Shock, treated in the emergency and critical care medicine departments at Beijing Chuiyangliu Hospital and Baoding No. 1 Central Hospital between December 2020 and June 2022. Patient outcomes were classified based on survival or mortality. Biomarkers, including sIL-7R levels and illness severity scores, were documented. All statistical analyses, including predictive modeling and comparisons were carried out using SPSS v.23.0 software and R software.

Results: On the fifth day post-admission, sIL-7R levels significantly decreased in both the survival and death groups, compared with levels on day one (2.09 ± 0.65 vs 1.07 ± 0.53 ng/mL, $P < 0.01$). There was a significant correlation between the sIL-7R level and the CD3+ T-lymphocyte count (CD3+) (r = 0.44) and lymphocyte count (LYM) (r = 0.42). The combination of the sIL-7R level with the Sequential Organ Failure Assessment (SOFA) score demonstrated optimal predictive value for clinical outcomes in patients with sepsis, demonstrated by an area under the receiver operating characteristic curve of 0.998.

Conclusion: sIL-7R levels are correlated with CD3+ and LYM counts. Additionally, the combination of serum sIL-7R level and SOFA score provides a robust method for predicting sepsis outcomes.

Keywords: immune function, prognosis, sepsis, soluble interleukin-7 receptor

Introduction

Sepsis is a critical medical condition characterized by systemic inflammation and multi-organ dysfunction, which often leads to life-threatening scenarios.[1] Recent research has shown that immune function plays a key role in the development and progression of sepsis. In particular, immunosuppression is a leading cause of sepsis-related death,[2,3] presumably due to the uncontrolled release of endogenous anti-inflammatory mediators.[4] In the early phases of sepsis, the release of pro-inflammatory cytokines induces the production of inflammatory mediators by target cells, culminating in a systemic inflammatory response syndrome[5,6] The increased production of cytokines in sepsis may result in lymphocyte apoptosis.[7,8] In some patients, the weakened immune response and reduced numbers of lymphocytes during a severe infection can result in immune paralysis.[9,10]

There is growing evidence that immune-related factors can be used to assess the immune system of patients with sepsis.[11,12] The interleukin-7 receptor (IL-7R) is an immunomodulatory factor encoded by a gene located on chromosome 5p13. It exists in two forms: the membrane-bound interleukin-7 receptor (mIL-7R), which is predominantly expressed on immune cells and mediates IL-7 signaling, and the soluble interleukin-7 receptor (sIL-7R), which is secreted by fibroblasts and plays a role in maintaining immune homeostasis.[13] Clinical and

Received: 22 July 2024
Accepted: 8 October 2024
Published: 21 October 2024

animal model studies have revealed that deficiencies in IL-7 or IL-7R lead to impaired T-lymphocyte development and function.[14] Building on previous research demonstrating the diagnostic utility of sIL-7R in sepsis,[15] in this study, we explore the clinical significance of sIL-7R, in conjunction with other biomarkers and illness severity scores, for assessing immune function and predicting prognosis in patients with sepsis.

Materials and Methods

Participants

Patients with sepsis who were treated in the emergency and critical care medicine departments at Beijing Chuiyangliu Hospital and Baoding No. 1 Central Hospital from December 2020 to June 2022 were initially considered in this study. The inclusion criteria were a diagnosis of sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock and age greater than 18 years. The exclusion criteria included a history of immunodeficiency disease or autoimmune disease, recent use of glucocorticoids or immunosuppressants, presence of allergic or tumor conditions, and a history of severe organ dysfunction. This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committees of Baoding First Central Hospital and Beijing Chuiyangliu Hospital. Informed consent was obtained from the study participants prior to study commencement.

Data Collection

Patients were divided into survival and death groups based on their clinical outcomes. Data collected on the first and fifth days of admission included demographic characteristics; serum levels of sIL-7R; infection indicators such as lymphocyte count (LYM), T-lymphocyte count (CD3+), white blood cell count, C-reactive protein level, and procalcitonin level; Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score and other illness severity scores; and 28-day mortality.

Laboratory Test

sIL-7R levels were quantitatively measured using a sandwich enzyme immunoassay (human sIL-7R ELISA kit, CUSABIO, Wuhan, China). This assay has demonstrated excellent sensitivity and specificity in detecting human sIL-7R without any cross-reactivity or interference from other substances.

Statistical Analysis

Data were analyzed using SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables underwent normality tests. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median [25%, 75%)]. Data were compared using t-tests or the Mann–Whitney *U*-test; *P*-values < 0.05 were considered statistically significant. Spearman correlation analysis was employed to assess pairwise relationships, with *P* values and correlation coefficient (r) values recorded. A logistic regression model was established to calculate the area under the receiver operating characteristic (ROC) curve (AUC). The R packages "glmnet" (https://glmnet.stanford.edu) and "pROC" (https://xrobin.github.io/pROC/) were used to construct sepsis-related mortality prediction models.

Results

General Data

The study cohort comprised 79 patients, with 51 categorized into the survival group and 28 into the death group, resulting in an overall mortality rate of 35.44%. Admission characteristics for days one and five are detailed in Tables 1 and 2, respectively.

Comparison of sIL-7R Levels Between Survival and Death Groups

sIL-7R levels did not significantly differ between the survival and death groups on admission day ($P = 0.48$), but they significantly differed on day five of admission ($P < 0.01$) (Figure 1). Furthermore, CD3+, APACHE II score, and SOFA

Table 1 Characteristics of Patients with Sepsis in the Survival and Death Groups on Admission Day 1

Sepsis Patients	Survival (N=51)	Death (N=28)	P value
General information			
Female	15(45.56%)	18(54.54%)	*P*=0.67
Male	36(78.22%)	10(21.73%)	*P*<0.01
Age	69[28, 87]	74.00[55, 89]	*P*<0.05
Blood test and sIL7R			
sIL-7R (ng/mL)	2.47±0.98	2.68±1.03	*P*=0.47
PCT (ng/mL)	2.66[0.11, 167]	19.71[0.10, 100]	*P*=0.19
WBC (10^9/L)	11.91[1.75, 39.04]	14.10[1.41, 32.40]	*P*=0.86
LYM (10^9/L)	0.75[0.25, 1.92]	0.54[0.08, 3.70]	*P*=0.34
CD3+ (ratio)	0.65±0.13	0.51±0.16	*P*<0.01
Critical illness score			
APACHE II	17.32±5.19	20.00±5.54	*P*<0.05
SOFA	4.00[2, 14]	8.00[2, 16]	*P*<0.001

Abbreviations: sIL-7R, Soluble interleukin-7 receptor; PCT, Procalcitonin, WBC:White blood cell count, LYM, Lymphocyte, CD3+:CD3 positive T lymphocytes, APACHE II:Acute Physiology and Chronic Health Evaluation II, SOFA:Sequential Organ Failure Assessment.

Table 2 Characteristics of Patients with Sepsis in the Survival and Death Groups on Admission Day 5

Sepsis Patients	Survival (N=51)	Death (N=28)	P value
Blood test and sIL7R			
sIL-7R (ng/mL)	2.09±0.65	1.07±0.53	*P*<0.01
PCT (ng/mL)	1.22[0.11, 135.00]	7.89[0.16, 479.00]	*P*<0.01
WBC (10^9/L)	10.50[4.08, 38]	15.67[1.56, 52.10]	*P*<0.01
LYM (10^9/L)	0.74[0.30, 2.12]	0.34[0.15, 1.21]	*P*<0.01
CD3+(ratio)	0.67[0.28, 0.83]	0.34[0.13, 0.86]	*P*<0.01
Critical illness score			
APACHEII	9.86±3.58	25.11±6.08	*P*<0.01
SOFA	2[0, 6]	16[6, 22]	*P*<0.01

score significantly differed between the two groups on days one and five (all $P < 0.05$). Higher illness severity scores were associated with lower CD3+ counts and a higher mortality rate.

Comparison of sIL-7R Levels Between Admission Days One and Five

In the survival group, the sIL-7R levels on day five showed a non-significant reduction compared to day one. However, in the death group, sIL-7R levels significantly decreased from day one to day five ($P < 0.05$) (Figure 2).

Correlation Between Serum sIL-7R Levels and LYM and CD3+

Spearman correlation analysis revealed a significant negative correlation between the sIL-7R level and CD3+ ($r = -0.47$) and LYM ($r = -0.48$) in the death group on day one. Nevertheless, sIL-7R levels exhibited a positive correlation with CD3+ and LYM ($r = 0.44$ and $r = 0.42$, respectively) in the death group on day five (Figure 3).

Prognostic Value of sIL-7R Levels

Compared to admission day one, sIL-7R levels declined with disease progression on day five in the death group, as indicated by high APACHE II and SOFA scores. The sIL-7R level, APACHE II score, and SOFA score significantly differed between the survival and death groups on day five (all $P < 0.05$). Sepsis-related mortality prediction models

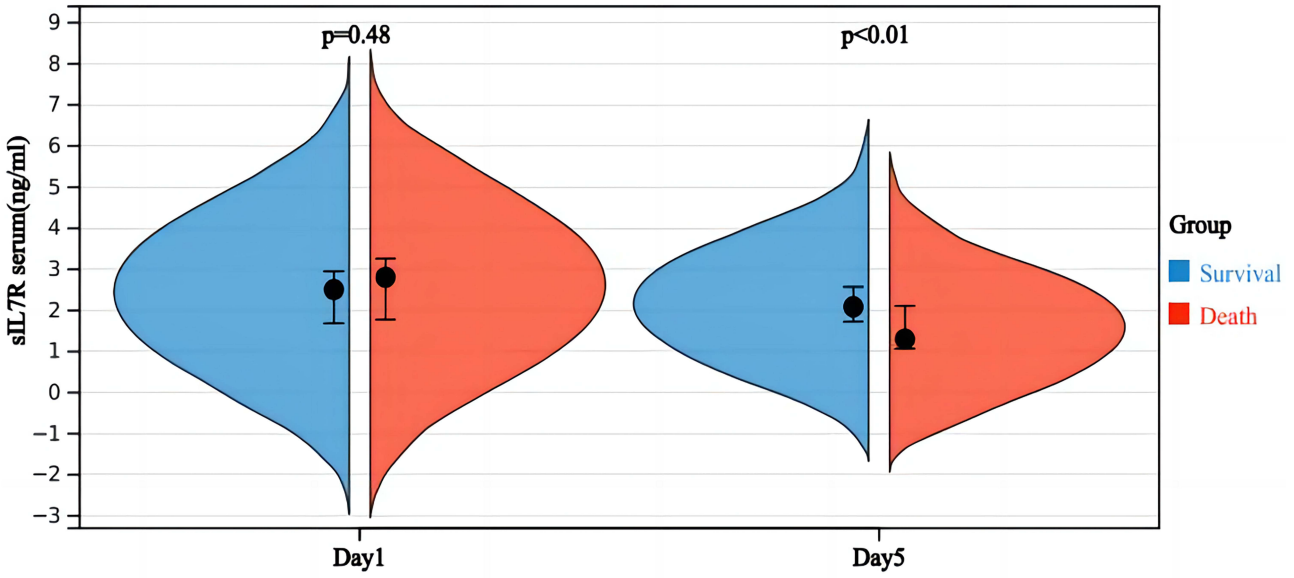

Figure 1 Comparison of sIL-7R levels between survival and death groups.

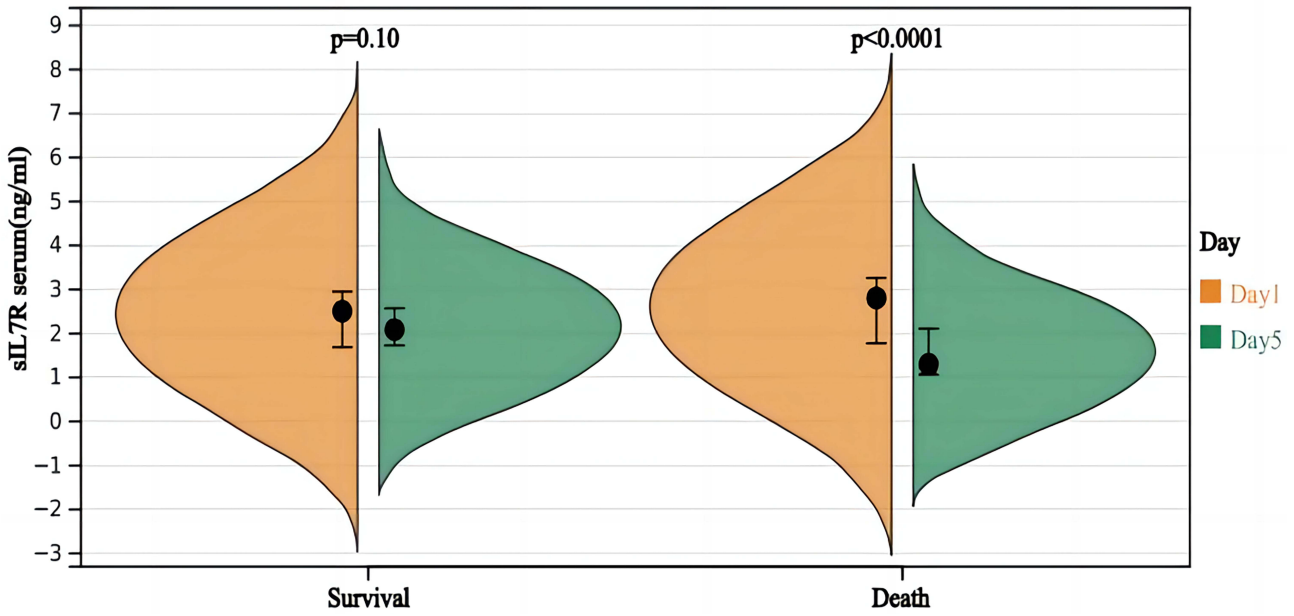

Figure 2 sIL-7R levels in survival and death groups on admission days 1 and 5.

were constructed using different combinations of variables. The predictive models incorporating sIL-7R level with SOFA score, and sIL-7R level with both APACHE II and SOFA score. Internal validation using bootstrapping techniques showed that both combinations had a mean AUC of 0.998 (Figure 4), affirming the robust prognostic capability of these variable combinations for predicting sepsis-related mortality.

Discussion

Sepsis, a severe and potentially fatal condition, has increasingly become a primary cause of death among critically ill patients, with its prevalence rising in recent years.[16] The initial stages of sepsis are marked by immune dysfunction, with immunosuppression notably linked to high mortality, particular in cases of severe sepsis. Although immune assessment is

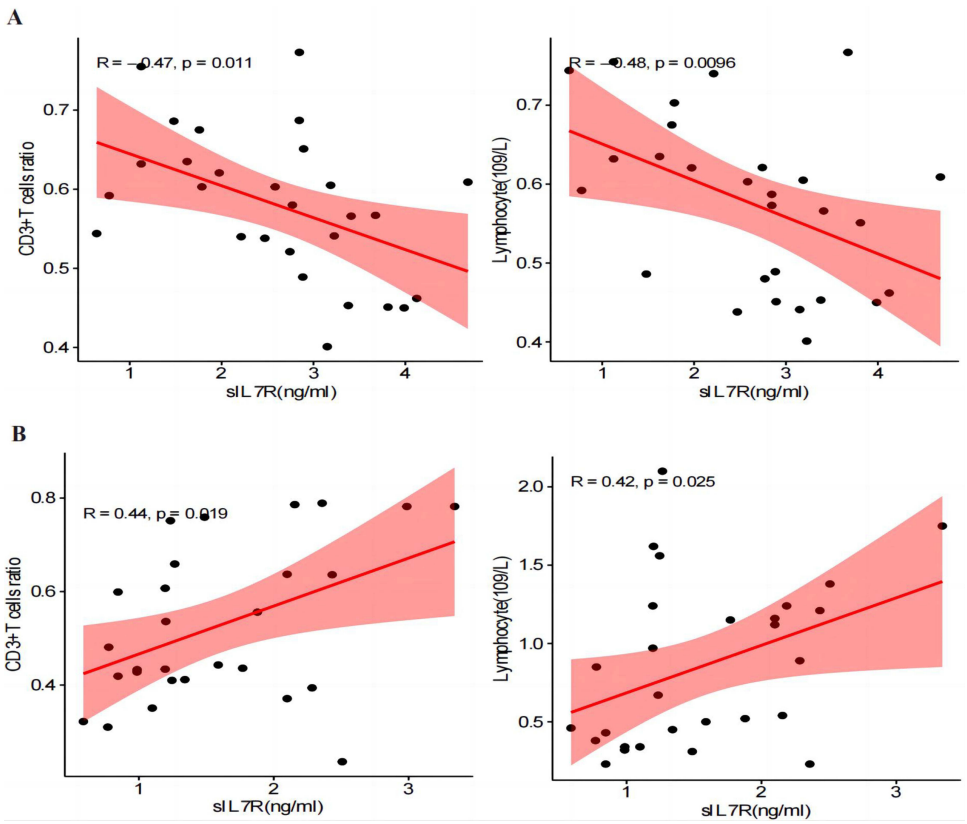

Figure 3 Correlations of serum sIL-7R level with CD3+ and LYM on admission days 1 and 5. (**A**) Day 1; (**B**) day 5.

a key aspect of sepsis management, relying solely on individual biomarkers has its limitations. In this study, we aimed to investigate novel immune biomarkers for evaluating immune function and predicting mortality in patients with sepsis. Specifically, we examined the correlations between sIL-7R level and CD3+ and LYM. Our findings demonstrate that combining sIL-7R levels with the SOFA score yields the most accurate predictions for sepsis outcomes.

Analyses of two immune biomarkers, CD3+ and LYM in the present study revealed that these two markers significantly decline immediately after sepsis onset. Their levels were notably lower in the death group than in the survival group. Although the decline of these two markers is widely regarded as an indicator of reduced immune function, it can be influenced by various factors. Immunosuppression is mainly characterized by a significant increase in lymphocyte apoptosis, along with reduced cell proliferation and diminished cytokine secretion.[7,8]

Given their role in regulating lymphocyte regeneration, proliferation, and apoptosis, immune-related markers have become focal points in sepsis research.[11,17] IL-7R, an essential immunoregulatory factor, plays a crucial role in signaling pathways that suppress immune function in sepsis.[18,19] IL-7 can bind to IL-7R to form a biologically active ternary complex, which is a key regulator of lymphocyte development,[20] and can influence the development and homeostasis of B- and T-lymphocytes. Thus, IL-7R is closely associated with systemic immune function. Changes in IL-7 and IL-7R levels may lead to lymphocytopenia and immunosuppression in patients with sepsis.

In the present study, the serum sIL-7R level increased and LYM decreased on day 1, suggesting that immunosuppression in early sepsis is associated with an increased sIL-7R level. This increased sIL-7R level can inhibit IL-7-mediated T-lymphocyte proliferation and cause immunosuppression.[12,21] The sIL-7R level in early sepsis (admission day 1) was significantly negatively correlated with CD3+ and LYM, while early immunosuppression was linked to an increase in sIL-7R levels. Thus, sIL-7R levels could be useful in detecting immunosuppression during the initial stage of sepsis.

As sepsis progresses, the balance between pro-inflammatory and anti-inflammatory mechanisms becomes dysregulated, leading to apparent immunosuppression and widespread lymphocyte apoptosis.[22] Further reductions in LYM and CD3+ typically lead to mortality.[7,8] There is also evidence that decreased serum sIL-7 expression can trigger a decline in

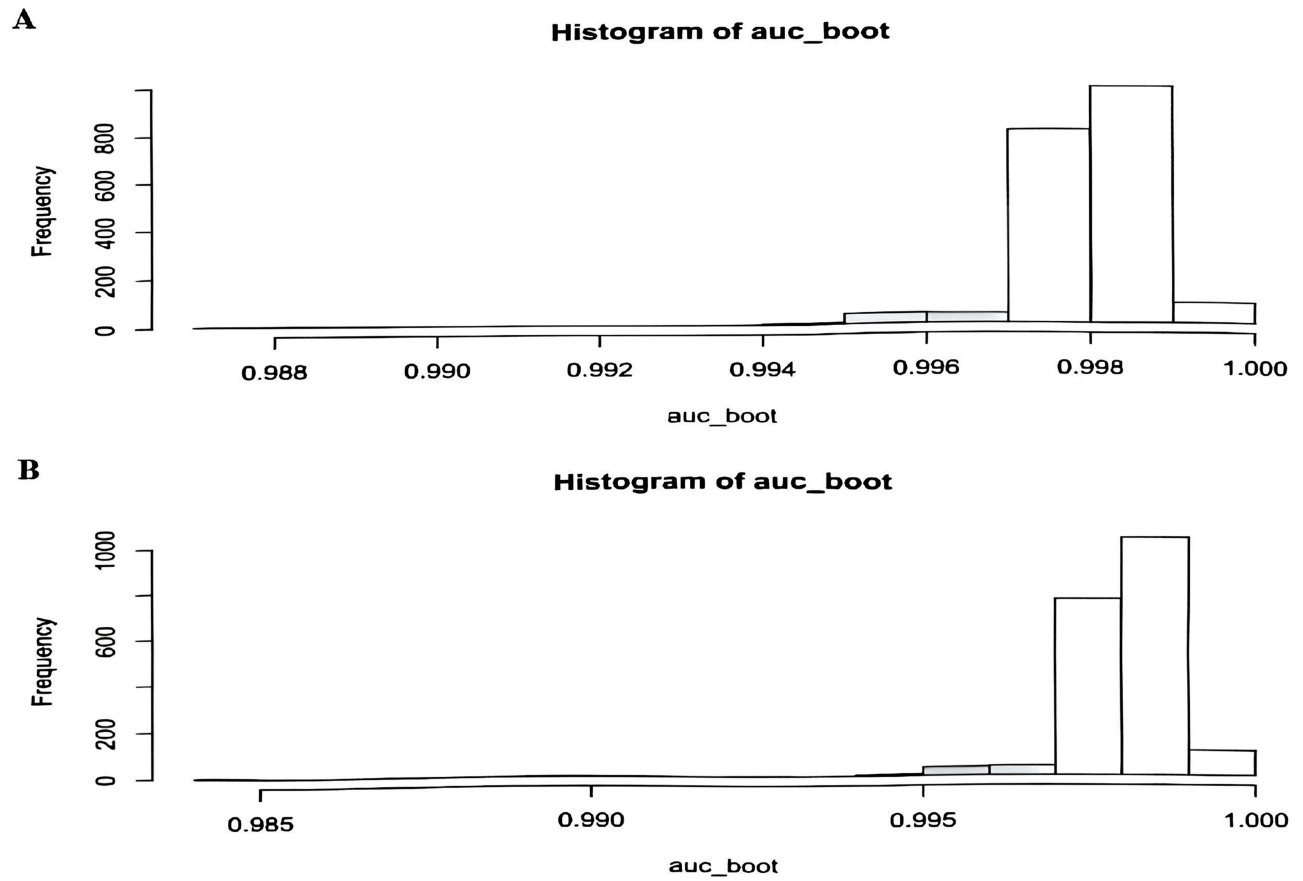

Figure 4 Internal validation of prognostic models (via bootstrapping) constructed using (**A**) sIL-7R level + SOFA score and (**B**) sIL-7R level + APACHE II score + SOFA score on admission day 5.

T-lymphocyte viability among patients with sepsis.[20] However, the relationships among these three indicators remain poorly defined.

In the present study, the death group exhibited significant decreases in LYM and CD3+ on day 5, along with a notable downward trend in sIL-7R. sIL-7R is mainly secreted by fibroblasts but can also originate from the selective splicing and release of membrane-bound IL-7 from lymphocytes. The decline in immune function during sepsis progression is characterized by reduced levels of LYM, CD3+, and sIL-7R, indicating positive correlations among these three indicators. An imbalance in the sIL-7R levels can lead to a decrease in CD3+ levels and inhibit lymphocyte proliferation, creating a vicious cycle that may result in immune paralysis, disease exacerbation, and death. Thus, accurately predicting mortality is a critical aspect of managing sepsis.

During the progression of sepsis, the SOFA and APACHE II scores are widely used to assess the disease and predict clinical outcomes. In the present study, the risk of mortality significantly increased on admission day five, when substantial immunosuppression was observed. By using sIL-7R as a novel indicator of immune function, in combination with illness severity scores, we were able to enhance the predictive performance of sepsis outcomes. Subsequently, we established mortality prediction models that demonstrated that the APACHE II and SOFA scores were significantly higher in the death group than in the survival group. We also observed a significant correlation between the sIL-7R level on admission day five and an increased risk of sepsis-related death. The combined use of sIL-7R levels and the SOFA score proved more effective in predicting mortality in patients with sepsis than single indicators. This approach has the potential to enhance clinical outcomes by enabling early mortality prediction and timely intervention to preserve immune function.

However, the present study also has some limitations. First, the sample size of this study is small, which should be expanded in subsequent studies. Second, unfortunately, we are now unable to provide clinical data such as patient body

temperature, heart rate, respiratory rate, as well as other examination indicators like liver function, kidney function, and cardiac enzymes. This limitation restricts further understanding of the study. We will include these parameters in our future research. Third, we will determine whether the relevant indicators are risk factors for mortality in future studies.

Conclusions

sIL-7R levels are correlated with CD3+ and LYM counts. Additionally, the combination of serum sIL-7R level and SOFA score provides a robust method for predicting sepsis outcomes.

Funding

This research was supported by the Beijing Municipal Science & Technology Commission (Z221100007422129) and Beijing Clinical Key Specialty Project (2023).

Disclosure

Authors declare that they have no conflict of interest.

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