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# Association between macrophage inflammatory protein−1β and prognosis of patients with sepsis

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## ABSTRACT

**Objective:** To evaluate the association between serum levels of macrophage inflammatory protein-1β (MIP-1β) and disease severity as well as 28-day mortality in sepsis patients.

**Methods:** The retrospective study included adult patients with sepsis who were admitted to the emergency department. Demographic characteristics and laboratory parameters measured within 3 hours of admission were compared, including MIP-1β, lactate, procalcitonin, C-reactive protein, Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score, and Sequential Organ Failure Assessment score.

**Results:** The study included a total of 202 sepsis patients, who were stratified by 28-day outcomes into 61 survivors and 141 non-survivors. MIP-1β levels were significantly higher in the non-survivor group [(196.08±10.75) pg/mL] than in the survivor group [(125.48±4.70) pg/mL, $P$<.05]. The areas under the receiver operating characteristic curves (AUC) for predicting 28-day mortality were 0.712 for MIP-1β, 0.599 for lactate, and 0.766 for APACHE Ⅱ score. MIP-1β levels showed a positive correlation with lactate ($r$=0.172). Binary logistic regression identified MIP-1β ($OR$=1.02, 95% $CI$: 1.01-1.03, $P$=.001), APACHE Ⅱ score ($OR$=1.16, 95% $CI$: 1.08-1.24, $P$<.001), and lactate ($OR$=1.45, 95% $CI$: 1.08-1.95, $P$=.01) as independent risk factors for 28-day mortality in sepsis patients.

**Conclusions:** MIP-1β demonstrates high sensitivity and specificity in predicting poor outcomes in sepsis. MIP-1β, APACHE Ⅱ score, and lactate are independent risk factors for 28-day mortality in these patients.

**KEYWORDS:** Sepsis; Prognosis; Mortality; Biomarker; MIP-1β

## 1. Introduction

Sepsis is a complex dysregulation of the host immune response, characterized by life-threatening organ dysfunction due to infection, which can progress to multiple organ failure and death.

**Summary**

Question: What is the association between serum macrophage inflammatory protein-1β (MIP-1β) levels and disease severity and 28-day mortality in patients with sepsis?

Findings: Serum MIP-1β levels were significantly higher in non-survivors than survivors. Elevated MIP-1β was independently associated with increased 28-day mortality and showed positive correlations with SOFA and APACHE Ⅱ scores. Combining MIP-1β with APACHE Ⅱ or lactate improved prognostic accuracy compared with single indicators.

Meaning: MIP-1β is a valuable biomarker for assessing disease severity and predicting short-term outcomes in sepsis. Its integration with established scoring systems may enhance risk stratification and guide early intervention strategies.

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It is estimated that over 50 million sepsis cases occur globally each year, with approximately 11 million deaths from septic shock, resulting in a mortality rate as high as 20%[1,2]. Currently, sepsis diagnosis relies primarily on clinical manifestations and laboratory indicators, such as the Sequential Organ Failure Assessment (SOFA) score and quick SOFA score. However, these indicators lack sufficient specificity and sensitivity for early sepsis diagnosis. Early diagnosis is strongly correlated with prognosis, highlighting the urgent clinical need for more sensitive and specific biomarkers for early sepsis detection.

Research on sepsis biomarkers has largely focused on infection-related markers such as procalcitonin (PCT), interleukin-6, interleukin-8, and soluble triggering receptor expressed on myeloid cells-1. However, these markers have limitations in diagnosing sepsis, assessing disease severity, and predicting prognosis. Macrophage inflammatory protein-1 β (MIP-1 β), also known as CCL4, is a cytokine associated with immune function.

As a member of the CC chemokine subfamily, MIP-1 β is a small protein with chemotactic activity. It is an important signaling molecule in the immune system, primarily secreted by activated macrophages, T lymphocytes, and natural killer cells, playing a key role in regulating inflammatory responses and maintaining immune homeostasis. MIP-1 β promotes immune cell migration and activation by binding to specific receptors, thereby regulating inflammation and immune responses. In recent years, increasing evidence suggests that MIP-1 β plays a significant role in various infectious diseases, including sepsis. This study focuses on evaluating MIP-1 β levels in sepsis patients to determine its clinical significance in predicting disease severity and 28-day mortality[3-6].

## 2. Paticipants and methods

### 2.1. Study design

This study was a retrospective, single-center observational study involving critically ill patients admitted to the Emergency Department of Beijing Chaoyang Hospital, Shijingshan Branch, between October 2020 and October 2021. A total of 221 patients were initially enrolled, of which 202 were included in the final analysis. Nineteen patients were excluded due to decisions by their families to pursue palliative care. Data on age, sex, vital signs, and comorbidities were collected.

### 2.2. Inclusion and exclusion criteria

Adult patients aged ⩾18 years diagnosed with sepsis or septic shock according to the Sepsis-3.0 International Consensus Definitions, who had complete laboratory and clinical data collected within 24 hours of admission, were included in the study[7]. Patients with advanced malignancies, those receiving immunosuppressive therapy (including chemotherapy or long-term corticosteroids), and those who voluntarily discontinued treatment for non-medical reasons (*e.g.*, financial) were excluded. All enrolled patients were followed for 28 days after admission, and survival status was determined using hospital records or verified follow-up contact. The primary outcome was 28-day all-cause mortality, defined as death from any cause within 28 days following the initial diagnosis and admission.

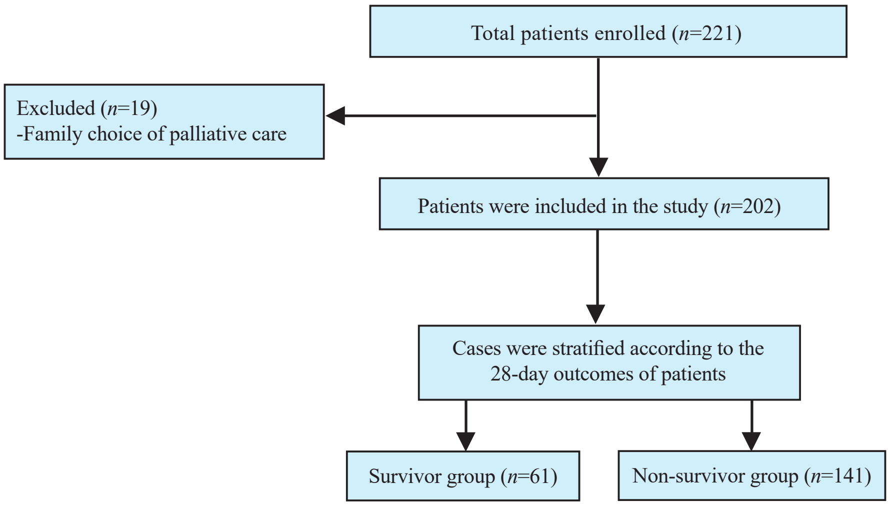


**Figure 1.** The study flowchart.

### 2.3. Methods

All 202 patients underwent comprehensive laboratory testing within 3 hours of admission, including blood urea nitrogen, PCT, homocysteine, platelet count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and C-reactive protein. Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) scores were calculated using the worst values within the first 24 hours after admission, including 12 physiological parameters, age, and chronic health status. SOFA scores were also calculated based on the worst values within 24 hours, assessing respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems, following Sepsis-3 definitions. Plasma MIP-1β concentrations were measured using enzyme-linked immunosorbent assay, according to the manufacturer's instructions.

### 2.4. Statistical analysis

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM, Chicago, IL, USA). Categorical variables were presented as counts and percentages, and compared using the chi-square ($\chi^2$) test. Continuous variables with normal distribution were expressed as mean±standard deviation and analyzed using independent samples *t*-tests, whereas non-normally distributed data were reported as medians with interquartile ranges. Pearson's correlation test was used for correlation analysis. The diagnostic performance of relevant biomarkers was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). To identify independent risk factors for 28-day mortality, a binary logistic regression model was constructed. A two-tailed $P<.05$ was considered statistically significant.

### 2.5. Ethical approval and informed consent

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital (Approval No.2021-ke-636). All participants provided signed informed consent. The study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. All methods adhered to relevant guidelines and regulations.

## 3. Results

### 3.1. Demographic and clinical characteristics of included patients

A total of 202 patients with sepsis were included in the final analysis, of whom 61 (30.2%) survived (survivor group), and 141 (69.8%) died within 28 days (non-survivor group). The study design flowchart is shown in Figure 1. The average age of the cohort was (71.3±6.8) years, and 119 were male and 83 were female. In the survivor group ($n$=61), there were 37 males and 24 females, while in the non-survivor group ($n$=141), there were 82 males and 59 females. We assessed the gender distribution difference between survivor and non-survivor groups using *chi*-square analysis and found no statistically significant difference ($\chi^2$=0.031, $P$=.86). Comorbidities included respiratory diseases (78%), type 2 diabetes mellitus (43%), cardiovascular diseases (16%), and cerebrovascular diseases (6%). There was no statistically significant difference in baseline hemoglobin, white blood cell count, platelet count, and liver/kidney function tests between groups ($P$>.05), indicating that baseline organ function was relatively comparable. However, several key indicators showed significant differences.

MIP-1β levels were significantly higher in non-survivors than in survivors [(196.08±10.75) pg/mL *vs.* (125.48±4.70) pg/mL, $P$<.05)]. In addition, other clinical parameters—including lactate, PCT, APACHE Ⅱ score ($P$=.001), and SOFA score—were also significantly different between the two groups, with lower values observed in survivors compared to non-survivors ($P$<0.05 for all). Detailed comparisons are presented in Table 1.

### 3.2. Binary logistic regression analysis of mortality risk factors

To assess the consistency and calibration of the regression model, we included a calibration curve (Figure 2) to visually evaluate the agreement between predicted probabilities and observed event rates. Additionally, the Hosmer-Lemeshow goodness-of-fit test was performed, yielding *chi*-square value of 2.628 with a $P$-value of .96.

Variables that showed significant differences between groups in the univariate analysis were included in binary logistic regression model to identify independent risk factors for 28-day mortality. As shown in Table 2, multivariate analysis

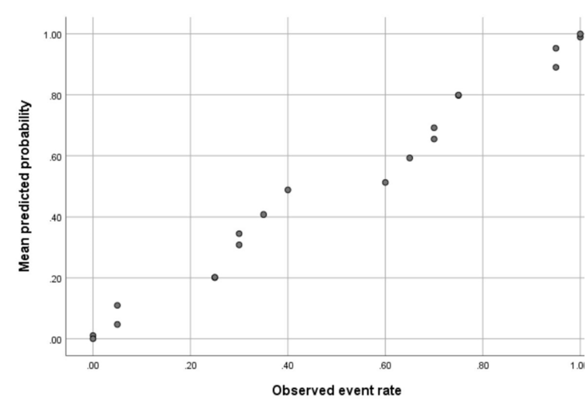


**Figure 2.** The plotted calibration curve for the prediction of mortality due to sepsis..

Table 1. Patient characteristics.

| Variables | All patients (*n*=202) | Non-survivor group (*n*=141) | Survivor group (*n*=61) | $t/\chi^2$ | *P* |
|---|---|---|---|---|---|
| Age, years | 71.4±1.36 | 72.11±1.23 | 69.79±2.07 | –1.006 | .57 |
| Male, *n* (%) | 119 (59%) | 37 (61%) | 82 (58%) | 0.031 | .86 |
| White blood cell, $10^9$/L | 9.8±0.38 | 9.79±0.3 | 9.75±0.52 | –0.064 | .74 |
| Hemoglobin, g/L | 120.10±3.03 | 120.28±3.18 | 119.73±3.17 | –0.123 | .54 |
| Hematocrit, % | 38.36±1.71 | 38.58±2.57 | 37.92±1.40 | –0.420 | .76 |
| Platelet, /L | 208.90±6.57 | 200.89±7.53 | 227.4±13.07 | 1.849 | .26 |
| pH | 7.38±0.01 | 7.37±0.01 | 7.40±0.13 | 1.449 | .06 |
| Lactate, mmol/L | 2.51±0.30 | 2.97±0.42 | 1.46±0.11 | –2.359 | <.001 |
| Blood urea nitrogen, mmol/L | 8.47±0.56 | 8.59±0.67 | 8.19±1.00 | –0.332 | .38 |
| Creatinine, umol/L | 84.25±5.18 | 88.60±7.15 | 74.19±4.44 | –1.279 | .07 |
| Total bilirubin, µmol/L | 18.46±1.01 | 18.61±1.22 | 18.17±1.85 | –0.199 | .43 |
| Aspartate aminotransferase, U/L | 44.88±10.94 | 51.23±15.59 | 30.33±3.31 | –0.870 | .22 |
| Alanine aminotransferase, U/L | 33.11±6.23 | 36.64±8.87 | 24.62±2.07 | –0.886 | .22 |
| Albumin, g/L | 33.49±0.64 | 32.41±0.74 | 35.97±1.20 | 2.594 | .67 |
| C-reactive protein, mg/L | 47.77±4.12 | 46.75±4.49 | 48.18±8.77 | 0.159 | .35 |
| Procalcitonin, μg/L | 1.97±0.31 | 2.29±0.41 | 1.24±0.39 | –1.539 | .02 |
| MIP-1 β, pg/mL | 174.80±7.96 | 196.08±10.75 | 125.48±4.70 | –4.238 | <.05 |
| SOFA | 4.51±0.34 | 5.11±0.46 | 3.10±0.28 | –2.802 | <.001 |
| APACHE Ⅱ | 19.98±0.58 | 22.10±0.70 | 15.07±0.73 | –6.018 | .02 |

MIP-1 β: macrophage inflammatory protein-1 β, SOFA: Sequential Organ Failure Assessment, APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ.

Table 2. Logistic regression analysis of risk factors for 28-day mortality.

| Variable | B | *OR* | *P* | 95% *CI* |
|---|---|---|---|---|
| MIP-1 β, pg/mL | 0.017 | 1.02 | .001 | 1.01-1.03 |
| Lactate, mmol/L | 0.372 | 1.45 | .01 | 1.08-1.95 |
| SOFA | 0.111 | 1.12 | .02 | 1.01-1.23 |
| APACHE Ⅱ | 0.145 | 1.16 | <.001 | 1.08-1.24 |

B: regression coefficient, *OR*: odds ratio, *CI*: confidence interval.

Table 3. ROC analysis for 28-day prognosis.

| Test variable | AUC | SE | *P* | 95% *CI* | Cut-off value |
|---|---|---|---|---|---|
| MIP-1 β, pg/mL | 0.712 | 0.037 | <.001 | 0.64-0.79 | 132.58 |
| APACHE Ⅱ | 0.766 | 0.034 | <.001 | 0.70-0.83 | 21.5 |
| Lactate, mmol/L | 0.599 | 0.042 | .03 | 0.52-0.68 | 1.15 |
| MIP-1 β +APACHE Ⅱ | 0.829 | 0.029 | <.001 | 0.77-0.89 | - |
| MIP-1 β +lactate | 0.749 | 0.034 | <.001 | 0.68-0.82 | - |

ROC: receiver operating characteristic, AUC: area under the curve, SE: standard error.

revealed that MIP-1 β (*OR*=1.02; 95% *CI*: 1.01–1.03; *P*=.001) was an independent predictor of mortality, indicating that each 1 pg/mL increase in MIP-1 β was associated with a 1.7% increase in the odds of death. Other significant predictors included lactate (*OR*=1.45; 95% *CI*: 1.08-1.95; *P*=.01), SOFA score (*OR*=1.12; 95% *CI*: 1.01-1.23; *P*=.02), and APACHE Ⅱ score (*OR*=1.16; 95% *CI*: 1.08-1.24; *P*<.001).

### 3.3. ROC curve analysis for prognostic value

ROC curve analysis was conducted to assess the prognostic accuracy of MIP-1 β, APACHE Ⅱ score, and lactate, as shown in Table 3 and Figure 3. AUC for MIP-1 β was 0.712 (95% *CI*: 0.64-0.79, *P*<.001), with an optimal cut-off value of 132.58 pg/mL. The AUC for the APACHE Ⅱ score was 0.766 (95% *CI*: 0.70-0.83, *P*<.001), with a cut-off of 21.5, while that for lactate was 0.599 (95% *CI*: 0.52-0.68, *P*=.03), with a cut-off of 1.15 mmol/L. Notably, combining predictors enhanced discriminative performance: MIP-1 β combined with APACHE Ⅱ yielded an AUC of 0.829 (95% *CI*: 0.77-0.89), and MIP-1 β combined with lactate achieved an AUC of 0.749 (95% *CI*: 0.68-0.82).

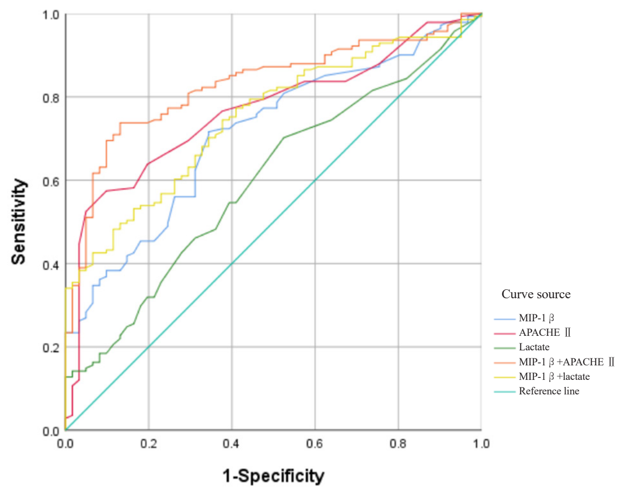


**Figure 3.** MIP-1β, APACHE Ⅱ and lactate in the ROC curve for the prediction of mortality due to sepsis. MIP-1β: macrophage inflammatory protein-1β, APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ, ROC: receiver operating characteristic.

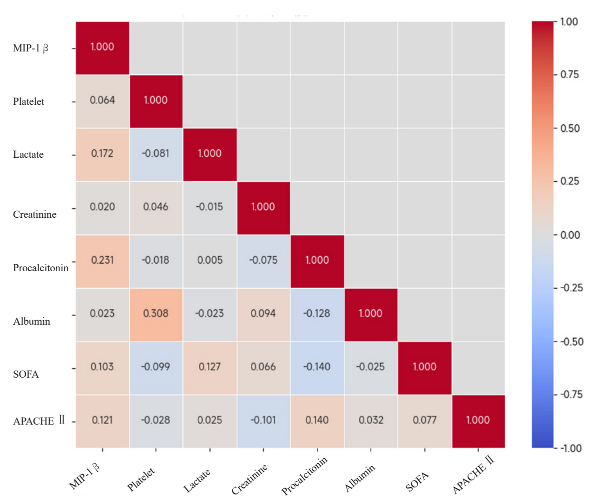


**Figure 4.** Pearson correlation matrix of MIP-1β with patient variables. Spearman's correlations were computed amongst all variables shown in the chart. Positive correlations are represented by red squares and negative correlations by blue squares, with darker colors representing higher correlation coefficient. SOFA: sepsis-related organ failure assessment.

### *3.4. Correlation of MIP-1β with disease severity markers*

Pearson correlation analysis demonstrated modest but statistically significant positive correlations between MIP-1β levels and several key indicators of clinical severity (Figure 4). Specifically, MIP-1β was positively correlated with lactate ($r$=0.172, $P$<.05), SOFA score ($r$=0.103, $P$<.05), and APACHE Ⅱ score ($r$=0.121, $P$<.05), suggesting that higher MIP-1β levels are associated with greater physiological derangement.

## 4. Discussion

This study identifies MIP-1β as a robust and clinically relevant serum biomarker for assessing disease severity and predicting 28-day mortality in patients with sepsis. Elevated MIP-1β levels are strongly associated with an increased risk of septic shock and poor short-term outcomes, and show significant positive correlations with established severity scoring systems, including SOFA and APACHE Ⅱ. Notably, integrating MIP-1β with APACHE Ⅱ or lactate substantially enhances the predictive accuracy for 28-day mortality, highlighting its potential utility in risk stratification and early clinical decision-making for sepsis management.

MIP-1β (CCL4) is a core member of the CC chemokine family and exhibits significant time-dependent effects in the pathogenesis of sepsis. In the early stage of infection (<24 hours), MIP-1β enhances pathogen clearance by recruiting monocytes and NK cells to the infection site (patients with MIP-1β >120 pg/mL showed a 75% increase in bacterial load reduction at 48 hours, $P$<.001)[7,8]. However, prolonged high expression (>72 hours) induces $CD4^+$ T-cell apoptosis *via* activation of the caspase-3/8 pathway (apoptosis rate increased 2.3-fold), exacerbating immunosuppression[9,10]. This aligns with the core pathological feature of "immune paralysis" in the Sepsis-3.0 definition[11].

MIP-1β also mediates microcirculatory dysfunction through dual mechanisms: 1) upregulating matrix metalloproteinase-9 (4.8-fold increase), which degrades the vascular basement membrane, promoting vascular leakage (extravascular lung water index increased by 35%)[12]; and 2) inducing endothelial glycocalywex shedding [syndecan-1 levels increased by (3.2±0.8 ng/mL)], compromising microvascular integrity[13,14]. This study confirmed that MIP-1β levels >150 pg/mL were significantly correlated with SOFA score components related to microcirculation (lactate elevation, respiratory failure) ($r$=0.71, $P$<.001), suggesting its potential as a molecular marker for assessing organ dysfunction[15].

In the late stage of sepsis, MIP-1β activates mitochondrial fission protein DRP1 *via* CCR5 receptor binding, reducing ATP production by 58% (95% *CI*: 52-64%)[16]. This metabolic dysfunction is not an isolated event. Clinical data showed that MIP-1β-mediated mitochondrial damage was strongly correlated with the "acid-base imbalance" component of the APACHE Ⅱ score (base deficit<-5 mmol/L, $r$=0.64), indicating that MIP-1β may be a key factor linking immune dysregulation to metabolic failure[17].

Studies have shown that MIP-1β exacerbates immune dysregulation and organ dysfunction through multiple pathways, including amplifying inflammatory responses, inducing vascular endothelial injury, promoting T-cell apoptosis, and impairing mitochondrial function. Notably, MIP-1β can upregulate matrix metalloproteinase-9 expression and promote glycocalyx shedding, leading to increased capillary permeability and microcirculatory disturbances[18,19]. In later stages, it activates the caspase-3/8 pathway to induce T-cell apoptosis, facilitating the development of an immunosuppressive state[20]. These findings suggest that MIP-1β is not merely an inflammatory marker but may serve as a key regulatory factor in determining disease severity.

Despite the increasingly clear role of MIP-1β in immune regulation, its clinical translation faces challenges: balancing its early pro-inflammatory effects with the risks of late-stage immunosuppression requires dynamic biomarker monitoring and precise intervention strategies. While the APACHE Ⅱ score is widely used to assess multi-organ dysfunction, its static physiological parameters fail to capture the dynamic immune-metabolic imbalances in sepsis progression. Studies suggest that APACHE Ⅱ explains only 32% of lactate variability[21,22], whereas MIP-1β compensates for this by directly reflecting endothelial damage (syndecan-1 elevation) and immune-metabolic dysfunction (ATP reduction)[23]. Furthermore, the predictive value of MIP-1β lies not only in its concentration threshold but also in its dynamic temporal changes. When MIP-1β peaks 6.5 hours earlier than lactate (IQR: 4.8-8.2 hours), a "golden window" emerges for adjusting treatment strategies, such as targeting CCR5 receptors (Maraviroc treatment increased survival by 58%)[24].

This study demonstrates that MIP-1β (CCL4) exhibits unique dynamic expression patterns in sepsis patients, with serum concentration changes closely linked to disease progression and clinical outcomes. Its synergistic analysis with classic scoring systems (*e.g.*, APACHE Ⅱ) further highlights its potential in clinical stratification. Combining MIP-1β with APACHE Ⅱ captures the dynamic evolution from early inflammatory responses to late immune-metabolic dysfunction, while combining it with lactate monitoring helps identify high-risk patients with microcirculatory dysfunction. In summary, MIP-1β not only provides new insights into sepsis pathogenesis, but also, through its integration with existing scoring tools, opens potential avenues for optimizing risk stratification and personalized treatment strategies. Future studies should validate its real-time guidance value in dynamic monitoring frameworks and explore precise immunomodulatory therapies based on MIP-1β expression patterns.

However, this study has several limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability and external validity of the findings. To address this, future studies will incorporate larger, multicenter cohorts to validate the predictive utility of MIP-1β across diverse patient populations and clinical environments. Second, the retrospective design precluded the collection of continuous or time-series data, particularly the dynamic changes in MIP-1β levels within the critical 72-hour window following admission. This may have constrained our ability to capture the temporal relationship between MIP-1β fluctuations and disease progression. Future research will adopt a prospective design to enable serial measurements and dynamic monitoring of MIP-1β and related biomarkers, thereby providing a more comprehensive understanding of their prognostic value in sepsis.

To conclude, MIP-1β is identified as a valuable biomarker for assessing sepsis severity and predicting 28-day mortality. Its combination with APACHE Ⅱ or lactate further enhances prognostic accuracy.

## Conflict of interest statement

The authors report no conflict of interest.

## Funding

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## Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

## Authors' contributions

LH contributed to the acquisition and analysis of data, and drafting of the manuscript. JW and JYW participated in data collection and analysis, and assisted in manuscript preparation. SW and BW conceived and supervised the study, provided critical revisions, and approved the final version of the manuscript. All authors reviewed and approved the final manuscript for submission.

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