

Diagnostic accuracy of 24-hour interleukin-1 β levels for predicting sepsis-associated encephalopathy in critically ill patients with sepsis

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Abstract

Background: Sepsis-associated encephalopathy (SAE) is a neurological complication of sepsis characterized by acute brain dysfunction in the absence of direct central nervous system infection. Interleukin-1 beta (IL-1 β) is a proinflammatory cytokine that may play an important role in this process.

Objective: To evaluate the diagnostic performance of IL-1 β in predicting SAE among patients with sepsis admitted to the intensive care unit.

Methods: This observational study included adult patients with sepsis admitted to the intensive care unit (ICU) at Dr. Wahidin Sudirohusodo General Hospital, Makassar. Serum IL-1 β was measured at 24 hours, alongside procalcitonin and C-reactive protein. Neurological status and disease severity were assessed using the Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, including area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive

likelihood ratio, negative likelihood ratio, and diagnostic accuracy.

Results: From a parent cohort of 123 consecutive septic ICU patients, 25 patients who developed SAE and 25 non-SAE controls were included in the final biomarker analysis. At 24 hours, IL-1 β levels were significantly higher in patients with SAE than in those without encephalopathy. ROC analysis showed that IL-1 β had an AUC of 0.935 (95% confidence interval [CI]: 0.872–0.990; $p < 0.001$). At a cutoff value of >28.5 pg/ml, IL-1 β showed 84.0% sensitivity, 80.0% specificity, 80.8% PPV, 83.3% NPV, and 82.0% accuracy. Procalcitonin and C-reactive protein (CRP) showed lower diagnostic performance, with AUC values of 0.827 and 0.782, respectively. In adjusted Firth penalized logistic regression models, 24-hour IL-1 β remained associated with SAE after separate adjustment for age, SOFA score, and APACHE II score.

Conclusion: IL-1 β measured at 24 hours demonstrated excellent discriminatory performance for predicting SAE in critically ill patients with sepsis and may serve as an adjunctive biomarker to support early neurological risk stratification. Larger multicenter studies with adjusted analyses are required to validate its clinical utility.

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Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. This condition remains a major cause of mortality and morbidity in the intensive care unit (ICU). (1) Neurological impairment is common in sepsis and is usually described as sepsis-associated encephalopathy (SAE), a diffuse cerebral dysfunction that occurs secondary to systemic infection without direct central nervous system infection. (2) Clinically, SAE may present across a wide spectrum, ranging from mild confusion, disorientation, reduced attention, and delirium to somnolence, impaired consciousness, seizures, or coma. (3) SAE can occur at any stage of sepsis. A study by Krzyżaniak et al has shown that 54% of septic patients experience encephalopathy. (4)

The pathophysiology of neurological impairment in sepsis is multifactorial. Systemic inflammation promotes the release of pro-inflammatory cytokines, endothelial activation, blood-brain barrier disruption, microglial activation, oxidative stress, cerebral microcirculatory dysfunction, metabolic disturbances, and neurotransmitter imbalance. These mechanisms impair neuronal function even in the absence of direct brain infection. As a result, septic patients may develop acute changes in consciousness and cognition, which may fluctuate during the course of critical illness. (2)

One of the key mechanisms in SAE is blood-brain barrier dysfunction. Under physiological conditions, the blood-brain barrier protects the central nervous system by regulating the passage of cells, molecules, and inflammatory mediators from the systemic circulation into the brain. In sepsis, activation of innate immune pathways promotes the release of inflammatory cytokines, including interleukin-1 beta (IL-1 β) that can disrupt endothelial tight junction proteins, increase vascular permeability, and allow inflammatory mediators to enter the brain parenchyma. (5)

Microglia are the resident immune cells of the central nervous system. These cells are activated by IL-1 β . Once activated, microglia may release pro-inflammatory cytokines, nitric oxide, reactive oxygen species, glutamate, and other neurotoxic mediators. These mediators can amplify neuroinflammation, damage neurons, impair synaptic function, and contribute to cognitive dysfunction, delirium, or reduced consciousness in septic patients. (6) Experimental evidence suggests that inhibition of inflammasome-related pathways that are also involved in cerebral inflammatory responses may reduce IL-1 β expression, microglial activation, blood-brain barrier disruption, and sepsis-related cognitive

impairment. Therefore, elevated IL-1 β levels may reflect not only systemic inflammation but also a neuroinflammatory process relevant to the development of SAE. (7)

Thus, IL-1 β can be positioned as a mechanistically relevant biomarker in SAE. Unlike general inflammatory biomarkers such as C-reactive protein or procalcitonin, IL-1 β is more directly involved in cytokine-mediated endothelial injury, blood-brain barrier disruption, microglial activation, and neuroinflammatory amplification. (8) This supports the rationale for evaluating IL-1 β as a potential biomarker for predicting neurological impairment in septic patients. However, this should be stated cautiously: an elevated IL-1 β level supports biological plausibility and diagnostic association, but it does not by itself prove that IL-1 β is the sole cause of SAE. SAE remains a multifactorial syndrome involving inflammation, hypoperfusion, metabolic dysfunction, mitochondrial injury, coagulation abnormalities, and neurotransmitter imbalance.

Materials and methods

Study design

This study was conducted as a nested case-control study within a prospective cohort of septic ICU patients. All eligible patients were prospectively enrolled at the time of sepsis diagnosis, and serum samples were collected 24 hours after diagnosis and stored under standardized conditions. Participants were subsequently followed for the development of SAE during the first 7 days of ICU admission. Patients who developed SAE were classified as cases. Controls were selected from patients within the same cohort who did not develop SAE during follow-up. IL-1 β concentrations were measured only after case and control groups had been identified, using stored serum specimens analyzed in a single laboratory batch to reduce inter-assay variability.

Study setting and duration

This study was conducted at Dr. Wahidin Sudirohusodo General Hospital, with specimen collection performed in the ICU and laboratory analysis of serum IL-1 β carried out at the Research Laboratory Unit of Hasanuddin University Hospital. The research was conducted from January 2026 until the required sample size was achieved.

Study population and sample

The study population consisted of all septic patients treated in the ICU during the study period. Subjects who fulfilled the inclusion criteria and agreed to participate were enrolled consecutively. The sample size was determined using a diagnostic test formula

with an expected sensitivity of 82.9%, a prevalence of SAE in septic patients of 50%, a confidence level of 95% ($\alpha=0.05$), and an allowable margin of error of 0.2, resulting in a minimum of twenty-five participants.

Eligibility criteria

Patients were eligible for inclusion if they were adults aged over 17 years, had a clinical diagnosis of sepsis with a Sequential Organ Failure Assessment (SOFA) score of at least two, and normal body mass index. Patients were excluded if they had primary disease of central nervous system, metabolic encephalopathy (hypoglycemic, diabetic ketoacidosis, hepatic encephalopathy, pulmonary encephalopathy, and uremic encephalopathy), or toxicosis. Subjects who developed other central nervous system complications, withdrew from the study, or failed to complete follow-up examinations were classified as dropouts.

Data collection procedure

Eligible patients were recruited upon diagnosis of sepsis, and baseline demographic and clinical data were recorded. Venous blood sampling was performed 24 hours after sepsis diagnosis to assess levels of IL-1 β , C-reactive protein (CRP), and procalcitonin (PCT). Serum IL-1 β was quantified using a commercial enzyme-linked immunosorbent assay (ELISA) kit with results expressed in picograms per milliliter.

Serum IL-1 β was measured 24 hours after sepsis diagnosis, and patients were subsequently followed for up to 7 days to determine the occurrence of SAE. Sedation depth was assessed using the Richmond Agitation-Sedation Scale before neurological evaluation. Patients with deep sedation were reassessed when clinically feasible. Neurological assessments were performed by trained ICU clinicians blinded to biomarker results. SAE was diagnosed if patients developed a positive Confusion Assessment Method for the ICU (CAM-ICU) result or a Full Outline of UnResponsiveness (FOUR) score <16 during the 7-day observation period after exclusion of structural, metabolic, toxic, and primary central nervous system causes.

Statistical analysis

Data were analyzed using SPSS version 27.0 for Windows. Continuous variables were assessed for normality using the Shapiro-Wilk test and presented as mean with standard deviation or median with interquartile range, while categorical data were presented as frequencies and percentages. The differences between SAE and non-SAE groups were

analyzed using independent-samples t-test or Mann-Whitney U test for continuous data, and chi-square or Fisher's exact test for categorical variables.

The diagnostic performance of IL-1 β , CRP, and PCT was evaluated through receiver operating characteristic (ROC) curve analysis, which provided the area under the curve (AUC), optimal cutoff points, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratios, and overall diagnostic accuracy. A p-value below 0.05 was considered statistically significant.

To evaluate whether 24-hour IL-1 β remained associated with SAE after adjustment for selected clinical covariates, three separate logistic regression models were constructed because of the limited sample size and the number of SAE events. Model 1 adjusted for age, Model 2 adjusted for SOFA score, and Model 3 adjusted for Acute Physiology and Chronic Health Evaluation II (APACHE II) score. IL-1 β was analyzed per 10 pg/ml increase to improve clinical interpretability. Because conventional maximum likelihood logistic regression showed quasi-complete separation, Firth penalized logistic regression was used to obtain more stable estimates. The adjusted odds ratios (ORs) with 95% confidence intervals were reported.

Ethical approval and consent to participate

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, under protocol number 238/UN4.6.4.5.31/PP36/2026. The research protocol was reviewed through an expedited process. All study procedures adhered to institutional and national ethical standards, and written informed consent was obtained from all participants prior to inclusion, in accordance with the Declaration of Helsinki.

Results

Characteristics of research subjects

During the study period, 123 consecutive patients with sepsis were screened for eligibility. Patients who met exclusion criteria, withdrew consent, or had incomplete clinical or laboratory data were excluded from the final analysis. After follow-up for the occurrence of SAE, 25 patients who developed SAE were identified. Twenty-five patients who did not develop SAE were selected from the same cohort as controls. Therefore, a total of 50 patients (25 SAE and 25 non-SAE) were included in the final biomarker analysis.

The baseline demographic and clinical characteristics of both groups are summarized in **Table 1**. The results of the analysis showed that the group of

patients with SAE had an older average age (66.0 ± 5.2 years) compared to the group without encephalopathy (53.9 ± 5.6 years). The results of the analysis showed a statistically significant difference ($p < 0.001$). The sex distribution in both groups was relatively balanced. In the SAE group, there were 14 males (56%), while in the non-SAE group there were 13 males (52%). The proportion test showed no significant difference in sex distribution between the two groups ($p = 0.776$). Similarly, with the body mass index (BMI), where the average BMI of the SAE group was 23.9 ± 1.5 kg/m² and the non-SAE group was 24.1 ± 1.3 kg/m². The results of the statistical test ($p = 0.624$) showed that nutritional status based on BMI did not differ significantly between the two groups.

Distribution of comorbidities in septic patients in the ICU of Dr. Wahidin Sudirohusodo General Hospital Based on the analysis of comorbidities presented in **Table 2**, hypertension was the most prevalent comorbidity in both groups, with 8 patients (32%) in the SAE group and 7 patients (28%) in the non-SAE group. The second most common comorbidity was diabetes mellitus, with a prevalence of 24% in the SAE group and 20% in the non-SAE group. Statistically, there was no significant difference in the distribution of any comorbidity between the SAE and non-SAE groups ($p > 0.05$). Although severe chronic diseases such as chronic kidney disease (CKD) (kidney failure), heart disease, and a history of stroke were found only in the SAE group, their frequency was not high enough to produce a statistically significant difference compared to the control group. On the other hand, the number of patients without comorbid diseases tended to be higher in the non-SAE group (24%) compared to the SAE group (4%), but the statistical test results still showed a p-value of 0.098 ($p > 0.05$).

Distribution of infection sources in septic patients in the ICU of Dr. Wahidin Sudirohusodo General Hospital

Based on the analysis of primary infection sources triggering sepsis (**Table 3**), the gastrointestinal system and biliary tract were the most common focus of infection in the SAE group, with 12 patients (48%). The second most common source of infection in the SAE group was the respiratory system (Pneumonia or Hospital-Acquired Pneumonia) with 8 patients (32%).

In the non-SAE group, the distribution of infection sources appeared more even, but remained dominated by gastrointestinal (32%) and respiratory (28%) infections. Although the SAE group showed a trend toward higher rates of gastrointestinal and

biliary infections, statistical tests showed a p-value > 0.05 for all infection source categories. This indicates no statistically significant difference in the type of primary infection source between patients with and without encephalopathy.

Distribution of microorganisms in septic patients in the ICU of Dr. Wahidin Sudirohusodo General Hospital

Based on the microbiological identification results (**Table 4**), a significant difference in pathogen distribution was found between the two groups. The SAE group was significantly dominated by *Acinetobacter baumannii*, with 12 isolates (48%) compared to only 2 isolates (8%) in the non-SAE group ($p < 0.001$). Furthermore, the prevalence of *Staphylococcus aureus* was also significantly higher in the SAE group (24%) compared to the non-SAE group (4%), with a p-value of 0.041.

Another non-fermenting Gram-negative bacterium, *Stenotrophomonas maltophilia*, was found in 2 patients (8%) in the SAE group and 1 patient (4%) in the non-SAE group, but this difference did not reach statistical significance ($p = 1.000$). The presence of *Stenotrophomonas maltophilia* along with *Acinetobacter baumannii* and *Pseudomonas aeruginosa* reflects the profile of nosocomial infections commonly found in critically ill patients in the ICU requiring ventilator support or invasive catheters.

Comparison of length of hospital stay in septic patients in the ICU of Dr. Wahidin Sudirohusodo General Hospital

The analysis showed that patients with SAE had a longer length of stay than patients without encephalopathy. The average length of stay in the SAE group was 11.6 days, with a range of 7–18 days, while in the non-SAE group it was 6.8 days, with a range of 4–10 days. This difference indicates an increase in length of stay of approximately 4–5 days in patients with SAE ($p < 0.001$) (**Table 5**).

Comparison of mortality rates in septic patients in the ICU of Dr. Wahidin Sudirohusodo General Hospital

The analysis results showed that the mortality rate in patients with SAE was higher than in patients without encephalopathy. In the SAE group, mortality was recorded at 28% (7 of 25 patients), while in the non-SAE group it was only 4% (1 of 25 patients). This difference indicates that SAE patients have a higher mortality rate than non-SAE patients (28.0% vs. 4.0%; relative risk [RR] 7.0; $p = 0.049$) (**Table 6**).

Comparison of IL-1 β , CRP, and PCT levels at 24 hours with GCS, SOFA, and APACHE II scores in septic patients in the ICU of Dr. Wahidin Sudirohusodo General Hospital

At 24 hours after admission, inflammatory biomarker levels remained significantly higher in patients with SAE than in those without encephalopathy. As shown in **Table 7**, IL-1 β at the 24-hour time point (T24) was still markedly elevated in the encephalopathy group, suggesting persistence of the inflammatory and neuroinflammatory response during the early phase of ICU treatment.

The persistence of high IL-1 β levels at T24 may be clinically important. IL-1 β is involved in amplifying inflammatory signaling, activating endothelial cells, disrupting the blood–brain barrier, and activating microglia. These mechanisms may contribute to sustained brain dysfunction in septic patients. Therefore, IL-1 β measured at T24 may provide additional information regarding ongoing inflammatory activity and the risk of SAE.

CRP and procalcitonin at T24 were also significantly higher in patients with encephalopathy. This finding indicates that systemic inflammation and infection-related inflammatory responses remained more pronounced in the encephalopathy group after 24 hours. Compared with the non-encephalopathy group, the encephalopathy group had higher biomarker concentrations at T24, indicating a greater inflammatory burden at the time of measurement.

A stronger interpretation is that IL-1 β , CRP, and procalcitonin remained significantly higher at T24 in patients with SAE. This supports the hypothesis that persistent systemic inflammation may be associated with neurological dysfunction in sepsis.

Ability of 24-hour IL-1 β to predict the occurrence of SAE

Based on the ROC curve analysis of the 24-hour examination (**Table 8**, **Figure 1**), IL-1 β showed excellent diagnostic ability to predict the occurrence of SAE, with an AUC of 0.935 (95% CI: 0.872–0.990; $p < 0.001$). At a cutoff of >28.5 pg/ml, IL-1 β had a sensitivity of 84.0% and a specificity of 80.0%, with an overall accuracy of 82.0%. Meanwhile, procalcitonin showed good diagnostic ability with an AUC value of 0.827 (95% CI: 0.710–0.940; $p < 0.001$). At a cutoff value of >2.0 ng/ml, procalcitonin had a sensitivity of 72.0% and a specificity of 84.0%, with a total accuracy of 78.0%. CRP demonstrated adequate diagnostic capability with an AUC of 0.782 (95% CI: 0.695–0.869; $p < 0.05$). With a cutoff of >85.2 mg/l, CRP had a sensitivity of 76.0%, a specificity of 72.0%, and a total accuracy of 74.0%.

Comparison of validity (PPV, NPV, positive likelihood ratio [PLR], negative likelihood ratio [NLR]) and diagnostic accuracy of 24-hour IL-1 β , PCT, and CRP in predicting the incidence of SAE

Diagnostic validity analysis (**Table 9**) showed that IL-1 β performed well in predicting SAE, with a PPV of 80.8% and an NPV of 83.3%. The lower NLR compared to other biomarkers indicated that IL-1 β had a better ability to exclude SAE. PCT performed comparably in terms of PLR, but had a higher NLR value, indicating limitations in excluding the diagnosis. Meanwhile, CRP showed the lowest diagnostic performance, with a PLR value that was not strong enough to support a clinical diagnosis.

Association between 24-hour IL-1 β and SAE after adjustment for age and disease severity

In Firth penalized logistic regression (**Table 10**), 24-hour IL-1 β remained significantly associated with SAE across all three adjustment models. After adjustment for age, each 10 pg/ml increase in IL-1 β was associated with higher odds of SAE (adjusted OR 4.96; 95% CI 1.08–22.69; $p = 0.039$). Similar associations were observed after adjustment for SOFA score (adjusted OR 61.07; 95% CI 2.99–1245.52; $p = 0.008$) and APACHE II score (adjusted OR 43.38; 95% CI 3.47–542.66; $p = 0.003$). However, the wide confidence intervals and high correlation between IL-1 β and severity scores indicate that these findings should be interpreted cautiously.

Discussion

In this study, 24-hour IL-1 β demonstrated excellent discriminatory performance for SAE, with the highest AUC, sensitivity, NPV, and overall accuracy among the evaluated biomarkers. Procalcitonin showed slightly higher specificity and PLR, indicating that IL-1 β was not superior across all diagnostic parameters. These findings suggest that 24-hour IL-1 β may serve as an adjunctive biomarker for neurological risk stratification in septic ICU patients. While traditional markers like C-reactive protein and procalcitonin offer broad insights into systemic inflammatory intensity, (7) they often fail to capture the nuanced neuro-inflammatory cascade that specifically compromises the blood-brain barrier during critical illness. However, it should not replace validated clinical tools such as CAM-ICU or FOUR score. This precision in identifying inflammatory triggers offers a more personalized approach to care, acknowledging that individual immune responses play a pivotal role in the trajectory of cognitive recovery. (9)

Given that IL-1 β is fundamentally linked to synaptic plasticity deficits and the impairment of long-term

potentiation, its measurement serves as an essential bridge between systemic immune activation and subsequent neurological decline. This mechanistic link highlights that such elevations are not merely bystanders of the disease, but active contributors that directly interfere with the synaptic maintenance required for cognitive stability. (10) Furthermore, evidence suggests that this inflammatory signaling facilitates the activation of cerebral endothelial cells, which subsequently leads to blood-brain barrier dysfunction and secondary neuronal loss in vulnerable regions such as the hippocampus. (2) Consequently, clinical focus on these inflammatory mediators may prove essential for preventing the chronic cognitive decline that often persists long after the acute phase of sepsis has resolved. Although targeted modulation of this cytokine has shown promise in preclinical models of cognitive dysfunction, translating these benefits to the complex, multisystem failure seen in human sepsis remains a profound clinical challenge. (11) Nevertheless, the observed correlation between early IL-1 β expression and subsequent cognitive impairment provides a critical foundation for future trials aimed at mitigating neuro-inflammatory damage during the acute septic window. (12,13)

The logistic regression analysis suggested that 24-hour IL-1 β remained associated with SAE after adjustment for age, SOFA score, or APACHE II score in separate models. However, the estimates showed wide confidence intervals, reflecting the limited sample size and strong separation between groups. Moreover, IL-1 β was highly correlated with SOFA and APACHE II scores, indicating that elevated IL-1 β may partly reflect overall sepsis severity rather than isolated neuroinflammatory activity. Therefore, these findings support the potential role of IL-1 β as an adjunctive biomarker for SAE risk stratification,

but they should not be interpreted as definitive evidence of independent predictive ability without validation in larger cohorts.

This study has several limitations. First, it was conducted in a single center with a relatively small sample size, which may limit generalizability. Second, although Firth-penalized logistic regression was used to address quasi-complete separation, the adjusted estimates had wide confidence intervals and should be interpreted cautiously. Third, IL-1 β was highly correlated with SOFA and APACHE II scores, suggesting that elevated IL-1 β may partly reflect overall sepsis severity rather than isolated neuroinflammatory activity. Fourth, the proposed cutoff value requires external validation. Fifth, this study compared IL-1 β with systemic inflammatory biomarkers but did not include brain injury biomarkers such as neuron-specific enolase (NSE), S100 calcium-binding protein B (S100 β), or neurofilament light chain. Finally, technical variability in IL-1 β measurement may affect clinical implementation, and future studies should standardize assay methods and sample handling procedures.

Conclusion

Twenty-four-hour IL-1 β showed excellent diagnostic performance for predicting SAE and demonstrated the most favorable overall diagnostic profile among the evaluated biomarkers. IL-1 β remained associated with SAE after separate adjustment for age, SOFA score, and APACHE II score, although the estimates should be interpreted cautiously because of the limited sample size and wide confidence intervals. These findings support IL-1 β as a potential adjunctive biomarker for neurological risk stratification in septic ICU patients, but further multicenter validation is required.

Table 1. Baseline characteristics of the study population

Variable	Sepsis-associated encephalopathy		p-value
	Yes (n=25)	No (n=25)	
Age (years), mean±SD	66.0±5.2	53.9±5.6	<0.001
BMI (kg/m ²), mean±SD	23.9±1.5	24.1±1.3	0.624
Sex, n (%)			
- Male	14 (56.0%)	13 (52.0%)	0.776
- Female	11 (44.0%)	12 (48.0%)	
FOUR score, mean±SD	10.2±3.1	14.8±0.5	<0.001

Legend: BMI=body mass index; FOUR=Full Outline of UnResponsiveness.

Continuous variables were compared using an independent-samples t-test, and categorical variables were compared using the Pearson chi-square test.

Table 2. Distribution of comorbid diseases in septic patients

Comorbid diseases	Sepsis-associated encephalopathy, n (%)		p-value
	Yes (n=25)	No (n=25)	
Hypertension	8 (32%)	7 (28%)	0.758*
Diabetes mellitus	6 (24%)	5 (20%)	0.733*
Cardiovascular disease	3 (12%)	0 (0%)	0.235**
Kidney disease	3 (12%)	0 (0%)	0.235**
Lung disease (COPD/asthma)	2 (8%)	3 (12%)	1.000**
Gastrointestinal disease	0 (0%)	4 (16%)	0.110**
Stroke	2 (8%)	0 (0%)	0.490**
No comorbid	1 (4%)	6 (24%)	0.098**

Legend: COPD=chronic obstructive pulmonary disease.

*Chi-square test; **Fisher's exact test (used because the expected value <5).

Table 3. Distribution of sources of infection in septic patients

Sources of infection	Sepsis-associated encephalopathy, n (%)		p-value
	Yes (n=25)	No (n=25)	
Gastrointestinal and biliary tract	12 (48%)	8 (32%)	0.252
Respiratory system (pneumonia or HAP)	8 (32%)	7 (28%)	0.758
Urinary tract	3 (12%)	6 (24%)	0.269
Soft tissue and dermatology	2 (8%)	4 (16%)	0.384

Legend: HAP=hospital-acquired pneumonia.

Table 4. Distribution of microorganisms in septic patients

Microorganism	Sepsis-associated encephalopathy, n (%)		p-value
	Yes (n=25)	No (n=25)	
<i>Acinetobacter baumannii</i>	12 (48%)	2 (8%)	<0.001
<i>Staphylococcus aureus</i>	6 (24%)	1 (4%)	0.041
<i>Stenotrophomonas maltophilia</i>	2 (8%)	1 (4%)	1.000
<i>Pseudomonas aeruginosa</i>	1 (4%)	3 (12%)	0.609
<i>Escherichia coli</i>	1 (4%)	4 (16%)	0.349
<i>Klebsiella pneumoniae</i>	1 (4%)	3 (12%)	0.609
<i>Burkholderia cepacia</i>	1 (4%)	1 (4%)	1.000
<i>Enterobacter cloacae</i>	1 (4%)	1 (4%)	1.000
<i>Candida</i> spp. (<i>albicans/tropicalis</i>)	0 (0%)	4 (16%)	0.110
Other (<i>Proteus</i> , <i>Serratia</i> , etc.)	0 (0%)	5 (20%)	0.050

Table 5. Comparison of length of hospital stay in septic patients

Variable	Sepsis-associated encephalopathy		p-value
	Yes (n=25)	No (n=25)	
Average length of stay (days), mean±SD	11.6±3.2	6.8±1.8	<0.001*
Median (min-max) (days)	11 (7–18)	7 (4–10)	
Average difference (days)	-	4.8	

Legend: SD=standard deviation.

*Mann-Whitney test/t-test.

Table 6. Comparison of mortality rates in septic patients

Variable	Sepsis-associated encephalopathy		p-value
	Yes (n=25)	No (n=25)	
Mortality (n)	7	1	0.049*
Mortality (%)	28%	4%	
Relative risk	7.0	-	

Legend: *Fisher exact test.

Table 7. Comparison of 24-hour biomarker levels and clinical severity scores according to SAE status

Variable	Sepsis-associated encephalopathy		p-value
	Yes (n=25)	No (n=25)	
IL-1 β T24 (pg/ml), mean $\pm$ SD	56.53 $\pm$ 25.8	12.84 $\pm$ 4.2	<0.001*
CRP T24 (mg/l), mean $\pm$ SD	101.31 $\pm$ 58.4	46.52 $\pm$ 13.8	<0.001*
Procalcitonin T24 (ng/ml), mean $\pm$ SD	5.21 $\pm$ 3.4	1.12 $\pm$ 0.7	<0.001*
GCS score, median (min-max)	10 (4–14)	15 (14–15)	<0.001†
SOFA score, mean $\pm$ SD	8.1 $\pm$ 2.6	4.0 $\pm$ 1.8	<0.001*
APACHE II score, mean $\pm$ SD	19.8 $\pm$ 4.2	12.1 $\pm$ 3.5	<0.001*

Legend: SAE=sepsis-associated encephalopathy; IL-1 β =interleukin-1 beta; SD=standard deviation; CRP=C-reactive protein; T24=24-hour time point; GCS=Glasgow Coma Scale; SOFA=Sequential Organ Failure Assessment; APACHE II=Acute Physiology and Chronic Health Evaluation II.

*Independent-samples t-test; †Mann-Whitney U test.

Table 8. Comparison of the results of 24-hour IL-1 β , CRP, and PCT diagnostic tests in predicting the incidence of SAE

Test parameters	IL-1 β (T24)	PCT (T24)	CRP (T24)
AUC	0.935	0.827	0.782
CI 95%	0.872–0.990	0.710–0.940	0.695–0.869
p-value for AUC	<0.001*	<0.001*	<0.05*
Cutoff	>28.5 pg/ml	>2.0 ng/ml	>85.2 mg/l
Sensitivity	84.0%	72%	76.0%
Specificity	80.0%	84%	72.0%
Total accuracy	82.0%	78%	74.0%

Legend: IL-1 β =interleukin-1 beta; CRP=C-reactive protein; PCT=procalcitonin; SAE=sepsis-associated encephalopathy; T24=24-hour time point; AUC=area under the receiver operating characteristic curve; CI=confidence interval.

*All ROC curves demonstrated statistically significant discriminatory ability (p<0.05).

Table 9. Predictive values, likelihood ratios, and diagnostic accuracy of 24-hour IL-1 β , PCT, and CRP for SAE

Parameter	IL-1 β	PCT	CRP
Cutoff	>28.5 pg/ml	>2.0 ng/ml	>85.2 mg/l
Sensitivity	84.0%	72.0%	76.0%
Specificity	80.0%	84.0%	72.0%
PPV	80.8%	81.8%	73.1%
NPV	83.3%	75.0%	75.0%
PLR	4.20	4.50	2.71
NLR	0.20	0.33	0.33
Accuracy	82.0%	78.0%	74.0%

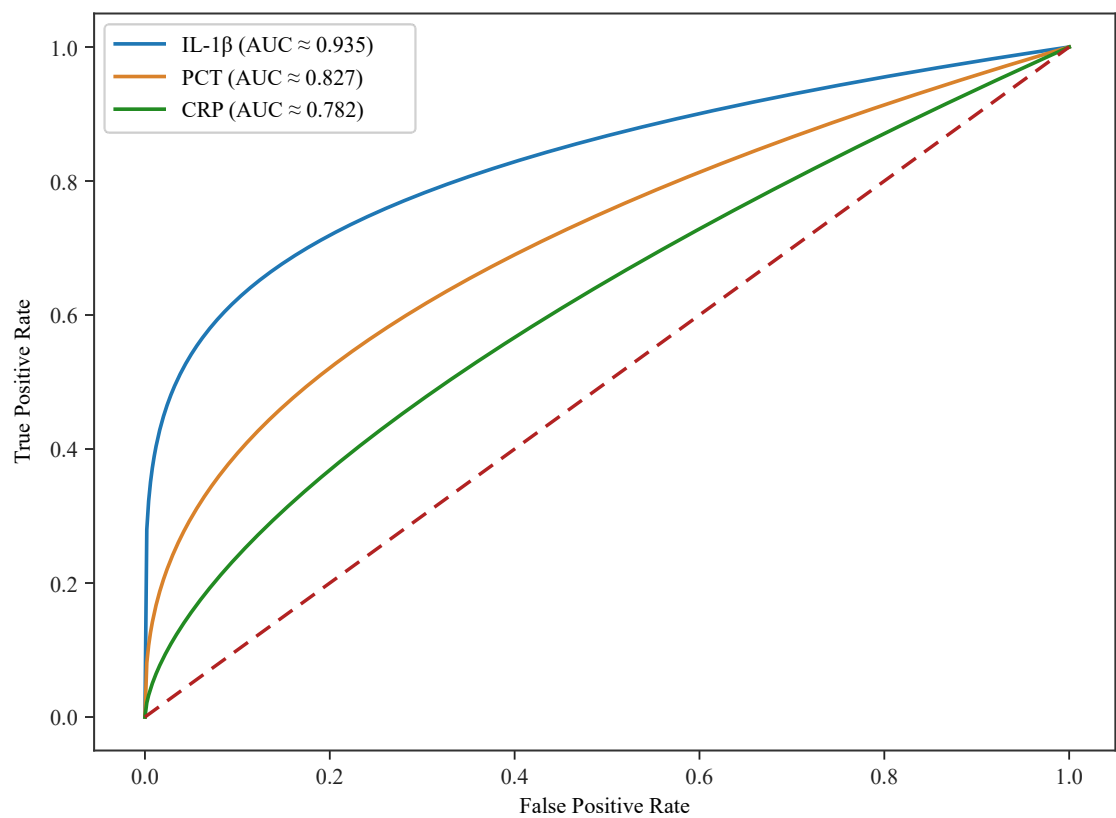
Legend: IL-1 β =interleukin-1 beta; PCT=procalcitonin; CRP=C-reactive protein; SAE=sepsis-associated encephalopathy; PPV=positive predictive value; NPV=negative predictive value; PLR=positive likelihood ratio; NLR=negative likelihood ratio.

Table 10. Association of 24-hour IL-1 β with SAE after adjustment for clinical covariates

Model	Variable	Adjusted OR	95% CI	p-value
Model 1	IL-1 β T24, per 10 pg/ml	4.96	1.08–22.69	0.039
	Age, per year	1.31	0.89–1.95	0.173
Model 2	IL-1 β T24, per 10 pg/ml	61.07	2.99–1245.52	0.008
	SOFA score	0.11	0.009–1.41	0.091
Model 3	IL-1 β T24, per 10 pg/ml	43.38	3.47–542.66	0.003
	APACHE II score	0.36	0.11–1.17	0.089

Legend: IL-1 β =interleukin-1 beta; SAE=sepsis-associated encephalopathy; OR=odds ratio; CI=confidence interval; T24=24-hour time point; SOFA=Sequential Organ Failure Assessment; APACHE II=Acute Physiology and Chronic Health Evaluation II.

Figure 1. ROC curves of 24-hour IL-1 β , PCT, and CRP for predicting SAE



Legend: ROC=receiver operating characteristic; IL-1 β =interleukin-1 beta; PCT=procalcitonin; CRP=C-reactive protein; SAE=sepsis-associated encephalopathy; AUC=area under the ROC curve.

References

1. Prescott HC, Antonelli M, Alhazzani W, Möller MH, Alshamsi F, Azevedo LCP, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2026. *Crit Care Med* 2026;54:725–812.
2. Sonnevile R, Benghanem S, Jeantin L, de Montmollin E, Doman M, Gaudemer A, et al. The spectrum of sepsis-associated encephalopathy: a clinical perspective. *Crit Care* 2023;27:386.
3. Wang R, Bi W, Huang S, Han Q, Deng J, Wang Z, et al. Recent advances in the pathogenesis, diagnosis, and treatment of sepsis-associated encephalopathy. *Brain-X* 2024;2:e67.
4. Krzyżaniak K, Szymczyk A, Wściślak A, Szczygieł N, Zembruska S, Abramczyk-Suszek A, et al. Prevalence, symptoms, risk factors and impact of sepsis-associated encephalopathy in emergency department patients: a case-control study. *BMC Emerg Med* 2025;25:262.
5. Galea I. The blood-brain barrier in systemic infection and inflammation. *Cell Mol Immunol* 2021;18:2489–501.
6. Yan X, Yang K, Xiao Q, Hou R, Pan X, Zhu X. Central role of microglia in sepsis-associated encephalopathy: from mechanism to therapy. *Front Immunol* 2022;13:929316.
7. Zhang L, Tang M, Falsaperla R, Zhang K. The role of microglia in sepsis-associated encephalopathy: a narrative review. *Transl Pediatr* 2025;14:2363–73.
8. Xiao D, Wang X, Liang W, Yang Y, Du Y, Liu C, et al. Convergence of sepsis-associated encephalopathy pathogenesis onto microglia. *J Transl Med* 2025;23:622.
9. Calsavara AJC, Costa PA, Nobre V, Teixeira AL. Factors associated with short and long term cognitive changes in patients with sepsis. *Sci Rep* 2018;8:4509.
10. Zhu Q, Wan L, Huang H, Liao Z. IL-1 β , the first piece to the puzzle of sepsis-related cognitive impairment? *Front Neurosci* 2024;18:1370406.
11. Terrando N, Rei Fidalgo A, Vizcaychipi MP, Cibelli M, Ma D, Monaco C, et al. The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction. *Crit Care* 2010;14:R88.
12. Andonegui G, Zelinski EL, Schubert CL, Knight D, Craig LA, Winston BW, et al. Targeting inflammatory monocytes in sepsis-associated encephalopathy and long-term cognitive impairment. *JCI Insight* 2018;3:e99364.
13. Voiriot G, Oualha M, Pierre A, Salmon-Gandonnière C, Gaudet A, Jouan Y, et al. Chronic critical illness and post-intensive care syndrome: from pathophysiology to clinical challenges. *Ann Intensive Care* 2022;12:58.