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ORIGINAL RESEARCH

Combined Biomarker Panel of Presepsin, HE4, and Oxygenation Index for Sepsis Diagnosis and Prognosis in Intensive Care Unit Patients

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Background: Sepsis remains a lethal global health crisis with persistently high mortality, exacerbated by diagnostic challenges stemming from its heterogeneous clinical presentation and limitations of current diagnostic tools like SOFA score. While biomarkers such as Presepsin or human epididymis protein 4 (HE4) show promise, single-marker approaches exhibit insufficient accuracy for reliable early detection and prognosis.

Objective: We evaluated the diagnostic and prognostic utility of Presepsin, HE4, Oxygenation Index (OI), and their combined panel (PHO) in critically ill patients with or without sepsis.

Methods: This single-center study analyzed 411 ICU patients (165 non-sepsis, 246 sepsis or septic shock). Clinical parameters—including SOFA, and OI—alongside laboratory parameters (hematological indices, hepatic/renal function markers, inflammatory biomarkers, blood culture results) were extracted from the hospital's Laboratory Information System. Residual admission samples were used to quantify Presepsin and HE4. Receiver operating characteristic (ROC) curve analysis, Spearman's rank correlation, and gradient boosting machine learning models were employed to evaluate the diagnostic and prognostic performance.

Results: Presepsin, HE4, and OI were significantly elevated in septic patients compared to controls (all $P < 0.05$) and correlated strongly with 30-day mortality. The gradient boosting algorithm identified these three markers as the most significant predictors. Importantly, the combined biomarker panel PHO demonstrated superior performance in both diagnosis and prognosis. For sepsis diagnosis, PHO achieved an outstanding AUC of 0.892 (95% CI: 0.860–0.924), significantly outperforming individual biomarkers (Presepsin: 0.821; HE4: 0.803; OI: 0.752) and conventional inflammatory markers (all $P<0.05$). For mortality prediction, PHO maintained the highest prognostic accuracy (AUC 0.706, 95% CI: 0.641–0.772), with improved sensitivity and specificity compared to single biomarkers.

Conclusion: The combined Presepsin, HE4 and OI biomarker panel significantly outperforms individual markers in sepsis diagnosis and prognosis. This machine learning-validated composite indicator enables early risk stratification and may guide timely interventions to improve outcomes.

Keywords: presepsin, HE4, oxygenation index, sepsis, diagnosis, prognosis

Introduction

Sepsis is a life-threatening systemic complication arising from a dysregulated host response to microbial infection, leading to tissue damage, organ dysfunction, and high mortality.[1] As a critical global health challenge, it accounts for nearly 20% of global mortality, with an estimated 48.9 million cases and 11.0 million sepsis-related fatalities annually. Despite advances in antimicrobial therapy and critical care, sepsis incidence and mortality remain persistently high, posing a significant burden on healthcare systems.[2] In China, the annual incidence of hospitalized sepsis cases ranged from 4.8 to 6.1 million between 2017 and 2019, with corresponding in-hospital mortality rates of 17.32–19.16 per

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100,000 population.[3] The persistent rise in sepsis cases underscores the urgent need for improved diagnostic and prognostic strategies.

The clinical diagnosis of sepsis remains challenging due to its heterogeneous and nonspecific manifestations, which often overlap with other inflammatory conditions.[4] Early and accurate identification is critical for timely intervention, yet current diagnostic tools have limitations.[5] The Sequential Organ Failure Assessment (SOFA) score, though considered the gold standard, requires multisystem evaluation (respiratory, coagulation, hepatic, renal, cardiovascular, and neurological), limiting its practicality in rapid clinical decision-making.[1] Consequently, biomarkers have emerged as valuable adjuncts, offering objective measures of the host's inflammatory and infectious response.[6] Ideal biomarkers could facilitate early diagnosis, guide antibiotic stewardship, and improve risk stratification.[7]

Among conventional biomarkers, procalcitonin (PCT), C-reactive protein (CRP), and Presepsin have demonstrated moderate diagnostic accuracy.[8] Presepsin, a soluble CD14 subtype released upon bacterial lipopolysaccharide recognition, exhibits rapid elevation in sepsis, making it a promising early diagnostic marker.[9,10] A meta-analysis of 19 cohorts reported Presepsin's diagnostic superiority for sepsis diagnosis, achieving area under the curve (AUC) of 0.87 (95% CI: 0.83–0.91) versus 0.84 for PCT, with a sensitivity of 0.84 (95% CI: 0.80–0.88) and specificity of 0.73 (95% CI: 0.61–0.82).[11] Additionally, Presepsin demonstrates unique clinical value in distinguishing sepsis from noninfectious systemic inflammation and predicting disease severity.[6]

HE4, a putative serine protease inhibitor glycoprotein associated with fibrosis, is predominantly expressed in both normal and malignant epithelial tissues and has emerged as a potential biomarker.[12] While initially recognized for its role in ovarian cancer diagnostics, HE4 is significantly elevated in septic patients, particularly in those developing sepsis-induced acute respiratory distress syndrome (ARDS) and non-survivors.[13,14] These findings suggest its dual utility in both diagnosis and prognosis.

The Oxygenation Index (OI), defined as the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2), primarily reflects tissue oxygenation capacity. As a more accurate indicator of oxygenation function than SpO_2, OI plays a crucial role in the Sepsis-3.0 diagnostic criteria. In septic patients, non-survivors demonstrate significantly lower OI values compared to survivors. Incorporating OI with other clinical indicators (eg, Glasgow Coma Scale [GCS] score) into nomogram modeling may optimize predictive performance.[15]

While individual biomarkers offer valuable insights, their inherent limitations in capturing sepsis heterogeneity necessitate combinatorial approaches.[6] Given the limitations of single biomarkers, this study aimed to quantitatively determine whether a combinatorial biomarker approach provides superior diagnostic and prognostic accuracy for sepsis compared to individual biomarkers, and evaluate the clinical utility of the integrated Presepsin, HE4, and Oxygenation Index (OI) panel. To achieve these aims, we pursued these primary objectives: First, to evaluate the diagnostic performance of individual biomarkers (Presepsin, HE4, OI) versus their combined panel (designated PHO) in differentiating septic from non-septic critically ill patients. Second, to assess the prognostic value of these biomarkers for predicting 30-day mortality in sepsis. By integrating these markers, we aim to develop a more robust tool for clinical decision-making in sepsis management.

Materials and Methods

Patients and Data Collection

This prospective single-center study was conducted in the ICU of the First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China) between May 2021 and May 2022. A total of 411 ICU-admitted patients with confirmed infections were stratified into: Non-septic group (infected patients without sepsis, n=165), Sepsis group (patients with sepsis or septic shock, n=246). The inclusion criteria included: (1) Non-sepsis group: Confirmed infection based on clinical/laboratory evidence without meeting sepsis criteria. (2) Sepsis/Septic shock group: Diagnosis fulfilling Sepsis-3 criteria; (3) Age≥18 years. The exclusion criteria included: (1) Incomplete clinical data; (2) Documented history of autoimmune diseases.

Residual serum and plasma samples collected within 24 hours of admission were stored at −80°C. Clinical parameters obtained within the same timeframe were extracted from the hospital's Laboratory Information System (LIS), including:

(1) Hematological parameters: white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), hemoglobin (Hb), red cell distribution width (RDW), platelet count (PLT); (2) Liver and kidney function markers: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), cholinesterase (CHE), total bilirubin (TBIL), UREA, creatinine (CREA); (3) Inflammatory biomarkers (PCT, CRP); (4) Blood culture results; (5) Coagulation profiles: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fbg), D-dimer (PT, APTT, TT, Fbg, D-dimer); (6) Clinical parameters: age, sex, SOFA score, GCS score, OI, mean arterial pressure (MAP), diagnosis, etc). Previously stored serum specimens from these patients underwent Presepsin and HE4 quantification using electrochemiluminescence assays.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University.

Machine Learning Algorithms and Model Development

The machine learning workflow is illustrated in Supplemental Figure 1. The dataset was subjected to 5-fold cross-validation. Four machine learning algorithms-Decision Tree, Linear Support Vector Classifier (SVC), Logistic Regression, and Gradient Boosting were evaluated, with the best-performing model selected based on validation set performance (Supplemental Table 1).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 9.0 and SPSS 26.0. Data distribution normality was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were presented as median (IQR), and categorical variables as percentages. Intergroup comparisons were conducted using parametric or nonparametric tests, as appropriate. The Wilcoxon rank-sum test and chi-square test were applied for continuous and categorical variables, respectively. Correlations were evaluated using Spearman's rank analysis.

The Deepwise & Beckman Coulter DxAI platform (https://dxonline.deepwise.com) was employed to generate receiver operating characteristic (ROC) curves for individual and combined biomarkers (Presepsin, HE4, OI). The AUC, sensitivity, specificity, optimal cutoff values, and Youden index were calculated to assess diagnostic accuracy. Binary logistic regression was used to derive combined predictors.

Results

Baseline Characteristics

The study enrolled 411 ICU patients stratified into three groups: non-sepsis (n=165), sepsis (n=103), and septic shock (n=143). Demographic and clinical characteristics are detailed in Table 1. No significant differences were observed in WBC, ALT, TT, or Fbg between the non-sepsis and sepsis groups (P>0.05). Compared to the non-sepsis group, sepsis patients demonstrated elevated values in 20 clinical parameters including higher age, blood culture positivity, SOFA score, MAP, PCT, Presepsin, HE4, IL-6, CRP, NLR, RDW, AST, ALP, GGT, TBIL, UREA, CREA, PT, APTT, and D-dimer (all $P<0.05$). Conversely, lower GCS score, OI, PLT, and CHE (all P<0.05) levels were observed in sepsis patients (all $P<0.05$). Pulmonary infections constituted the most prevalent etiology, followed by intra-abdominal infections.

Expression Levels of Presepsin, HE4 and OI

Among the evaluated machine learning models, Gradient Boosting demonstrated superior performance (Supplemental Figure 2), with OI, Presepsin, and HE4 identified as the top three weighted features. The levels of Presepsin, HE4, and OI were significantly elevated in patients with sepsis and septic shock compared to the non-sepsis group (Figure 1A–C; $P<0.05$). Notably, patients with septic shock patients demonstrated marginally higher levels of Presepsin and HE4 compared to those with sepsis alone ($P<0.05$). Furthermore, within the sepsis group, non-survivors exhibited higher levels of all three biomarkers compared to survivors (Figure 1D–F; $P<0.05$).

Table 1 Clinical Characteristics of the Study Population

Variables	Non-Sepsis Group (n=165)	Sepsis Group (n=246)		*P* value
		Sepsis (n=103)	Septic Shock (n=143)	
Age (years)	56 (40–70)	62 (43.5–73)	62 (51–73)	0.013 [a]
Sex (male%)	57.6%	61.2%	72.7%	0.018 [b]
Culture (positive%)	2.4%	19.4%	30.1%	<0.001 [b]
Infection site				
Lung	63.0%	66.0%	48.3%	
Blood	2.4%	19.4%	30.1%	
Abdominal	13.3%	27.2%	30.8%	
Cavity	7.3%	11.7%	13.3%	
Urinary tract	2.4%	1.0%	7.0%	
Biliary tract	8.5%	12.6%	11.2%	
Skin soft tissue	13.3%	3.9%	4.2%	
Others	12.1%	35.0%	39.2%	
Multiple site (≥2)				
SOFA score	1 (0–1)	5 (3–8)	8 (4.5–11)	<0.001 [a]
GCS score	15 (15–15)	15 (14–15)	14 (12–15)	<0.001 [a]
OI (mmHg)	450.0 (444.8–450.0)	360.0 (241.4–450.0)	350.0 (219.5–402.5)	<0.001 [a]
MAP (mmHg)	80.0 (80.0–90.3)	83. 3 (76.7–91.7)	80.0 (72.7–90.0)	0.02 [a]
PCT (ng/mL)	0.20 (0.08–0.62)	1.92 (0.41–6.12)	2.40 (0.84–11.13)	<0.001 [a]
Presepsin (pg/mL)	331.83 (208.80–625.16)	1242.95 (481.47–3496.97)	1945.11 (649.5–5747.4)	<0.001 [a]
HE4 (pmol/L)	132.91 (70.90–282.95)	509.87 (222.47–1337.95)	893.26 (284.68–1889.27)	<0.001 [a]
IL-6 (pg/mL)	30.38 (13.30–95.03)	62.7 (19.00–153.26)	132.96 (42.27–545.91)	<0.001 [a]
CRP (mg/L)	36.19 (8.68–97.14)	84.67 (27.98–141.3)	87.51 (48.09–144.22)	<0.001 [a]
WBC (×10^9/L)	9.71 (6.65–12.63)	10.24 (6.60–14.13)	9.97 (6.92–14.79)	0.583 [a]
NLR	7.37 (4.17–12.76)	11.96 (7.06–19.6)	10.77 (6.01–23.86)	<0.001 [a]
Hb (g/L)	102 (84–117)	81 (70.25–95.5)	80 (73–94)	<0.001 [a]
RDW	0.14 (0.13–0.17)	0.16 (0.14–0.18)	0.16 (0.14–0.18)	0.002 [a]
PLT (×10^9/L)	198 (140–271)	132 (79–207)	130 (52–214.5)	<0.001 [a]
ALT (U/L)	19 (13–34)	23 (13–44)	26 (13.75–55.25)	0.059 [a]
AST (U/L)	25 (20.25–40.75)	32 (22.5–62)	38.5 (24–79.25)	<0.001 [a]
ALP (U/L)	78 (58–108)	100 (68–150.5)	102.5 (70–140.25)	<0.001 [a]
GGT (U/L)	34 (18.75–61.25)	56 (30.75–99.5)	55 (27–114)	<0.001 [a]
CHE (U/L)	4020 (2794.5–5355.75)	2976.5 (2264–3915.25)	2691 (1999–3715)	<0.001 [a]
TBIL (μmol/L)	14.3 (11.23–19.5)	16.6 (11.5–27.55)	21.6 (13.18–42.85)	<0.001 [a]
UREA (mmol/L)	5.6 (3.9–8.5)	10 (5.85–17.05)	12.55 (7.3–18.83)	<0.001 [a]
CREA (mmol/L)	68 (52–89)	90 (46.5–178)	111 (62–199.75)	<0.001 [a]
PT (s)	14.2 (12.8–15.4)	15.15 (14.1–16.3)	16 (14.8–18.35)	<0.001 [a]
APTT (s)	35.6 (29.8–42.65)	42.5 (35.28–51.85)	45.9 (38.9–55.8)	<0.001 [a]
TT (s)	16.8 (16.1–17.8)	16.7 (15.6–17.8)	17.1 (15.7–18.7)	0.239 [a]
Fbg (g/L)	3.85 (2.85–4.92)	3.67 (2.57–5.13)	3.25 (2.12–4.37)	0.067[a]
DD (mg/L)	2.27 (1.13–5.58)	3.82 (2.23–8.31)	4.17 (2.40–8.81)	0.002 [a]

Notes: Categorical and continuous variables are presented as frequency or median (IQR), respectively. Between-group differences in categorical and continuous variables are analyzed using Chi-squared test and Wilcoxon rank sum test, respectively. [a] Wilcoxon rank sum test; [b] Chi-squared test.
Abbreviations: OI, oxygenation index; PCT, Procalcitonin; MAP, mean arterial pressure; CRP, C-reactive protein; WBC, blood white cell; NLR, Neutrophils to Lymphocytes Ratio; RDW, red blood cell distribution width; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CHE, cholinesterase; TBIL, total bilirubin; UREA: urea nitrogen; CREA, creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; Fbg, fibrinogen; DD, D-dimer.

Correlations Between Biomarkers

Correlations of HE4 with Inflammatory and Clinical Parameters

In the sepsis group, HE4 levels were significantly positively correlated with Presepsin ($r^2=2.875\times10^{-3}$, $P<0.001$), CRP ($r^2=1.700\times10^{-2}$, $P=0.043$), and SOFA score ($r^2=0.999$, $P<0.0001$). However, no significant associations were observed

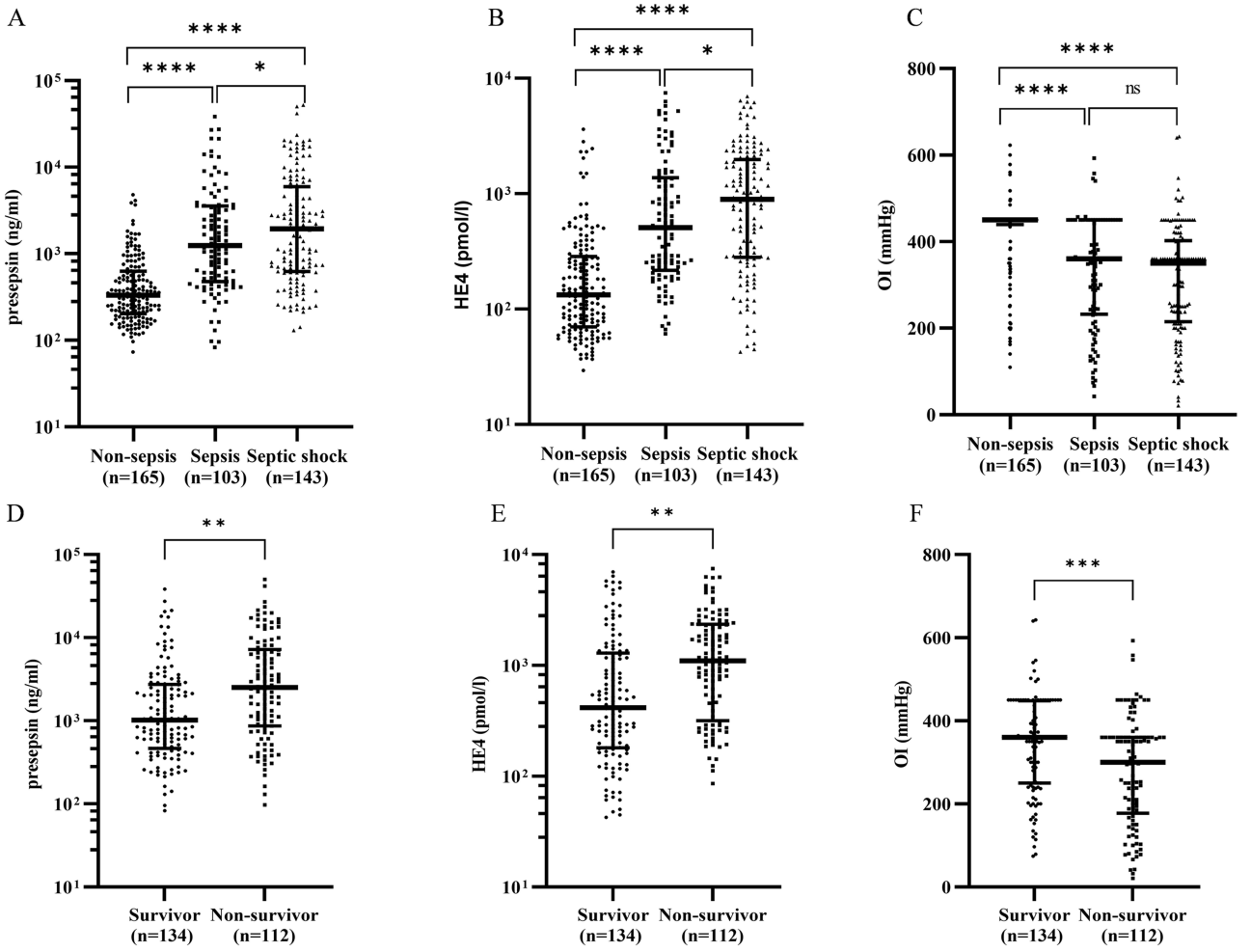

Figure 1 Presepsin, HE4, OI levels in different populations. Presepsin (**A**), HE4 (**B**), OI (**C**) levels in Non-sepsis, Sepsis and Septic shock groups; Presepsin (**D**), HE4 (**E**), OI (**F**) levels in Survivor and Non-survivor of sepsis patients. ns, No significance. *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001.

between HE4 and OI ($r^2=9.100\times10^{-4}$, $P=0.640$), PCT ($r^2=7.681\times10^{5}$, $P=0.892$), or IL-6 ($r^2=5.740\times10^{-3}$, $P=0.302$) (Figure 2). In contrast, in the non-sepsis group, HE4 levels were positively correlated with Presepsin ($r^2=4.767\times10^{-1}$, $P<0.001$), PCT ($r^2=4.970\times10^{-2}$, $P=0.004$), and SOFA score ($r^2=4.910\times10^{-2}$, $P=0.005$), while negatively correlated with OI ($r^2=4.73\times10^{-2}$, $P=0.005$). No significant correlations were detected between HE4 and IL-6 ($r^2=1.87\times10^{-3}$, $P=0.666$) or CRP ($r^2=1.380\times10^{-3}$, $P=0.139$) (Figure 2).

Associations of OI with Inflammatory Markers and Clinical Parameters

In the sepsis group, OI exhibited significant negative correlations with IL-6 ($r^2=5.040\times10^{-2}$, $P=0.002$) and SOFA score ($r^2=1.018\times10^{-1}$, $P<0.0001$), whereas no associations were detected with Presepsin ($r^2=2.600\times10^{-3}$, $P=0.43$), PCT ($r^2=4.390\times10^{-3}$, $P=0.310$), or CRP ($r^2=6.960\times10^{-3}$, $P=0.193$) (Figure 3). Similarly, in the non-sepsis group, OI was inversely correlated with PCT ($r^2=4.530\times10^{-2}$, $P=0.007$) and SOFA score ($r^2=9.580\times10^{-2}$, $P<0.0001$), but not with Presepsin ($r^2=3.800\times10^{-3}$, $P=0.430$), IL-6 ($r^2=4.000\times10^{-3}$, $P=0.530$), or CRP ($r^2=2.600\times10^{-3}$, $P=0.520$) (Figure 3).

Relationship Between Presepsin and Other Biomarkers

In the sepsis group, serum Presepsin levels were strongly positively correlated with SOFA score ($r^2=6.810\times10^{-1}$0.681, $P<0.001$), but no significant associations were observed with PCT ($r^2=2.830\times10^{-3}$, $P=0.409$), IL-6 ($r^2=8.670\times10^{-4}$, $P=0.689$), or CRP ($r^2=2.510\times10^{-2}$0.0251, $P=0.13$) (Supplemental Figure 3). In the non-sepsis group, Presepsin demonstrated positive correlations with CRP ($r^2=5.790\times10^{-2}$0.0579, $P=0.002$) and SOFA score ($r^2=3.380\times10^{-2}$, $P=0.018$), while no significant relationships were found with PCT ($r^2=2.190\times10^{-2}$, $P=0.060$) or IL-6 ($r^2=1.680\times10^{-3}$, $P=0.682$) (Supplemental Figure 3).

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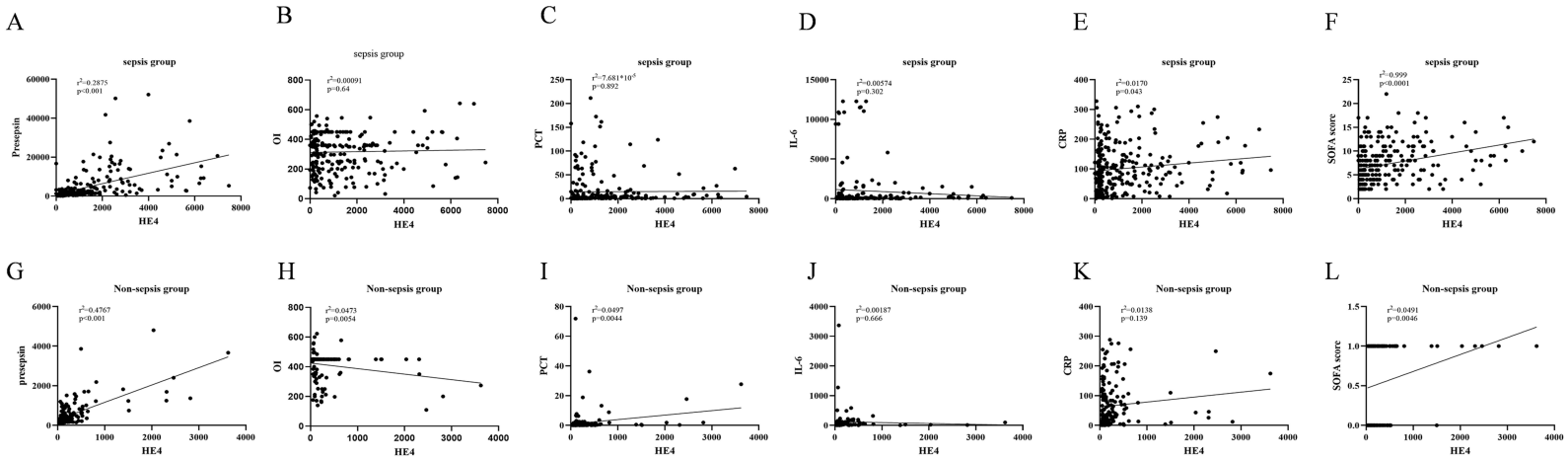

Figure 2 Correlation of HE4 with other commonly used laboratory infection indicators between the sepsis group and Non-sepsis group. (**A**–**F**) Correlation of HE4 with Presepsin(**A**), OI(**B**), PCT(**C**), IL-6(**D**), CRP(**E**), SOFA score(**F**) in Sepsis group. (**G**–**L**) Correlation of HE4 with Presepsin(**G**), OI(**H**), PCT(**I**), IL-6(**J**), CRP(**K**), SOFA score(**L**) in Non-sepsis group.

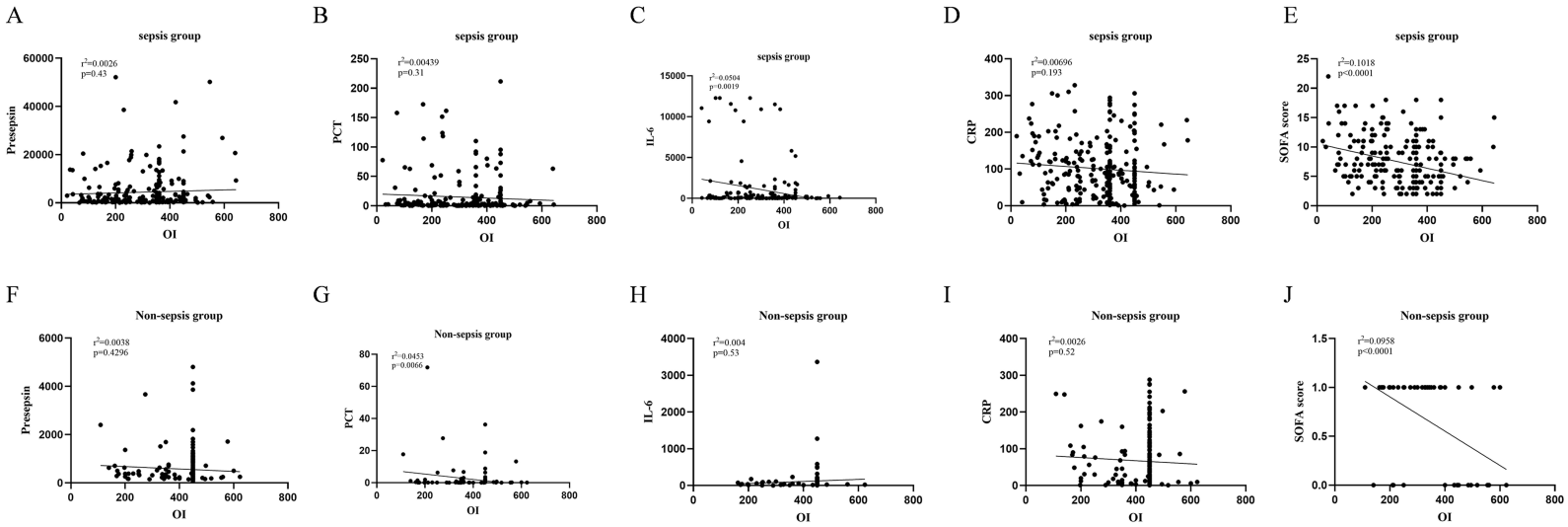

Figure 3 Correlation of OI with other commonly used laboratory infection indicators between the sepsis group and Non-sepsis group. (**A**–**E**) Correlation of OI with Presepsin(**A**), PCT(**B**), IL-6(**C**), CRP(**D**), SOFA score(**E**) in Sepsis group. (**F**–**J**) Correlation of HE4 with Presepsin(**F**), PCT(**G**), IL-6(**H**), CRP(**I**), SOFA score(**J**) in Non-sepsis group.

ROC Curve Analysis of Diagnostic Biomarkers

Diagnostic accuracy was assessed using ROC curve analysis conducted on the Deepwise & Beckman Coulter DxAI platform and GraphPad Prism. The individual biomarkers exhibited the following performance characteristics: Presepsin [AUC=0.821 (95% CI 0.781–0.861), cutoff=585.595 pg/mL, SEN=75.2%, SPE=73.9%], HE4 [0.803 (0.760–0.846), 247.965 pmol/L, 75.7%, 71.0%], OI [0.752 (0.704–0.800), 443.665 mmHg, 78.9%, 75.2%], PCT [0.816 (0.772–0.859), 0.625 ng/mL, 77.0%, 75.3%], CRP [0.659 (0.603–0.715), 40.84 mg/L, 75.9%, 54.0%], IL-6 [0.688 (0.627–0.750), 41.1 pg/mL, 69.7%, 58.8%], SOFA score [1.000 (1.000–1.000), 1.500, 100.0%, 100.0%])(Table 2 and Figure 4). The combined biomarker panel (PHO) demonstrated superior discriminative capacity (AUC=0.892 (95% CI 0.860–0.924), cutoff=0.45, sensitivity=88.6%, specificity=77.0%) compared to individual markers (Table 2 and Figure 4). MedCalc-derived comparison revealed statistically significant enhancements in AUC values for the combinatorial approach versus individual biomarkers (Presepsin, HE4, OI, PCT; all $P<0.05$), while no significant differential performance was observed between HE4 and Presepsin or OI (both $P>0.05$) (Table 3).

Prognostic Performance Analysis

The prognostic performance of Presepsin, HE4, OI, and PHO in sepsis patients was evaluated through a prospective 30-day survival follow-up conducted via telephone interviews. Among the 246 patients included, 134 patients (54.5%) survived the observation period. Significant intergroup differences ($P<0.05$) between survivors and non-survivors were observed for multiple parameters, including clinical characteristics (age, SOFA score), biomarkers (Presepsin, HE4, PCT, IL-6, CRP), hematological indices (NLR, RDW, PLT), and organ function markers (OI, AST, CHE, TBIL, UREA, CREA, PT, APTT, TT) (Table 4). ROC analysis demonstrated moderate prognostic performance for individual markers: Presepsin (AUC=0.652, 95% CI:0.586–0.725; cutoff=2389.77 pg/mL, SEN=54.5%, SPE=72.4%), HE4 (AUC=0.657, 95% CI:0.587–0.726; cutoff=711.13 pmol/L, SEN=67.0%, SPE=64.1%), and OI (AUC=0.649, 95% CI:0.583–0.720; cutoff=358.57 mmHg, SEN=65.2%, SPE=59.7%) (Figure 5). The combined PHO panel indicated enhanced predictive value (AUC=0.706, 95% CI:0.641–0.772; cutoff=0.514, SEN=54.5%, SPE=78.6%) (Table 5).

Discussion

Sepsis remains a critical global health burden, characterized by high mortality rates and substantial healthcare costs due to its complex pathophysiology involving dysregulated host responses to infection.[16] The clinical imperative for early detection of sepsis is underscored by the time-sensitive nature of effective intervention, yet current diagnostic paradigms, particularly microbial culture techniques (49.5% positivity rate in our cohort), remain constrained by suboptimal sensitivity (typically 40–60%) and protracted processing times.[17] To address these limitations, this study specifically aimed to investigate the clinical utility of a novel biomarker panel (Presepsin, HE4, Oxygenation Index) for both diagnosis and prognosis of sepsis in critically ill patients. This diagnostic vacuum has catalyzed interest in host-response biomarkers that capture immune dysregulation and end-organ damage, as conceptualized in the Sepsis-3 framework.[10]

Table 2 Diagnostic Performance of the Laboratory Infection Indicators in Subjects with Sepsis and Non-Sepsis Group

Variables	AUC (95% CI)	Youden Index	Cutoff	SEN (%)	SPE (%)
Presepsin	0.821(0.781–0.861)	0.491	585.595	75.2	73.9
HE4	0.803(0.760–0.846)	0.467	247.965	75.7	71.0
OI	0.752(0.704–0.800)	0.54	443.665	78.9	75.2
PCT	0.816(0.772–0.859)	0.523	0.625	77.0	75.3
CRP	0.659(0.603–0.715)	0.299	40.84	75.9	54.0
IL-6	0.688(0.627–0.750)	0.285	41.1	69.7	58.8
SOFA score	1.000(1.000–1.000)	1.000	1.500	100.0	100.0
HE4+Presepsin+OI	0.892(0.860–0.924)	0.656	0.45	88.6	77.0

Abbreviations: PCT, Procalcitonin; CRP, C-reactive protein; OI, oxygenation index; AUC, the area under the receiver operating characteristic curve; SEN, sensitivity; SPE, specificity.

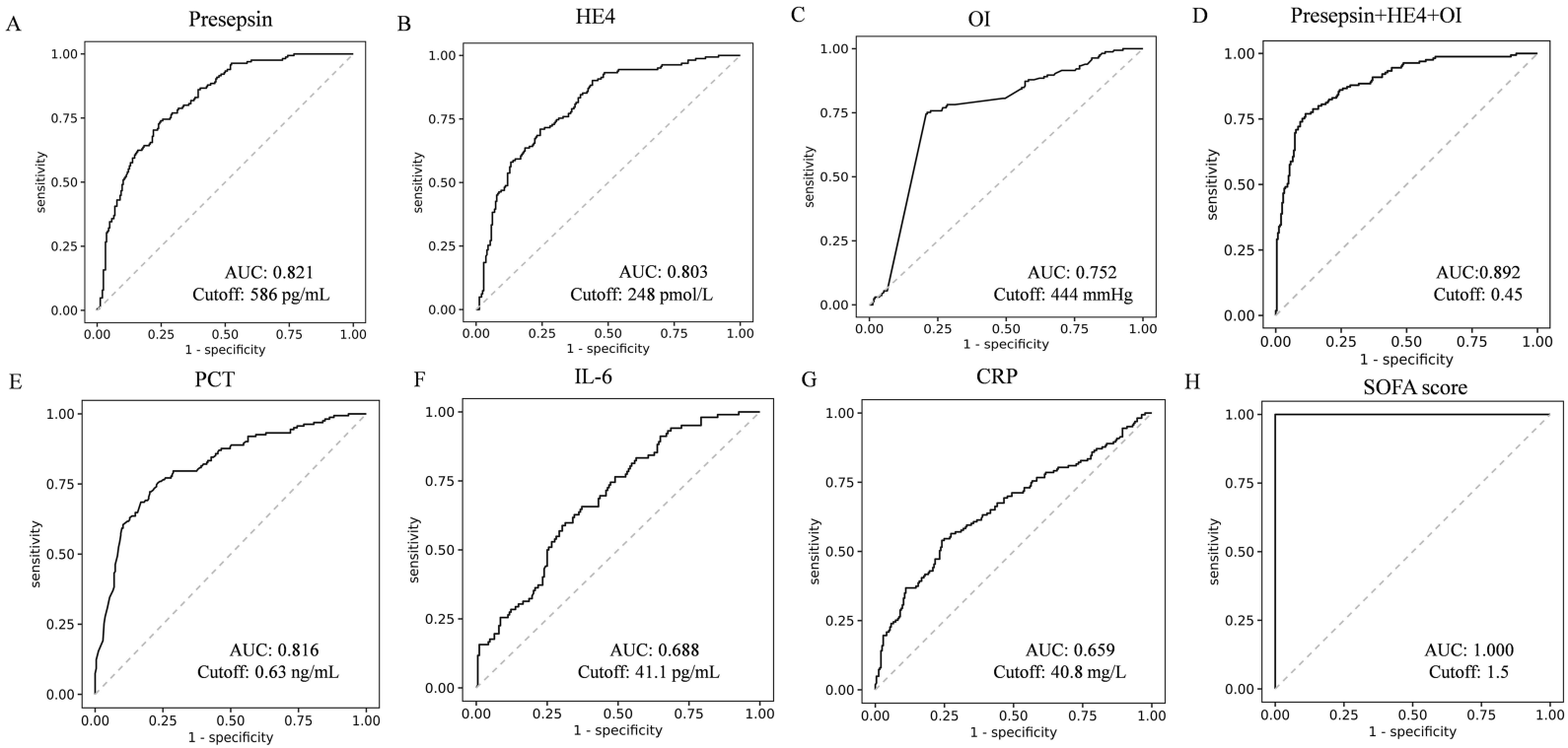

Figure 4 Diagnostic performance of the laboratory infection indicators in subjects with sepsis and Non-sepsis group. Diagnostic value of presepsin(**A**), HE4(**B**), OI(**C**), the combined Presepsin+HE4+OI(**D**), PCT(**E**), IL-6(**F**), CRP(**G**), SOFA score(**H**) in sepsis and Non-sepsis group.

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Table 3 Comparison of the AUC Areas of Presepsin, HE4, OI, and Presepsin+HE4+OI Combined Assays

Variables	Z-value	P-value
Combined indicator and Presepsin	4.095	<0.0001
Combined indicator and HE4	4.999	<0.0001
Combined indicator and OI	6.478	<0.0001
Combined indicator and PCT	3.624	0.0003
HE4 and Presepsin	1.128	0.2594
HE4 and OI	1.523	0.1278
Presepsin and OI	2.210	0.0271

Abbreviations: OI, oxygenation index; PCT, Procalcitonin.

Table 4 Characteristics of Sepsis Group Patients According to 30-Day Mortality

Variables	Survivor (n=134)	Non-Survivor (n=112)	*P* value
Age (years)	58(47.25–70)	66(53–74)	0.031 [a]
Sex (male%)	64.9%	71.4%	0.277 [b]
Culture (positive%)	24.6%	26.8%	0.699 [b]
Infection site			
Lung	54.5%	57.1%	
Blood	24.6%	26.8%	
Abdominal cavity	24.6%	34.8%	
Urinary tract	14.2%	10.7%	
Biliary tract	3.7%	5.4%	
Skin soft tissue	16.4%	6.3%	
Others	5.2%	3.6%	
Multiple site (≥2)	37.3%	37.5%	
SOFA score	5(3–8)	8(5–11)	<0.001 [a]
GCS score	14(13–15)	14(9–15)	0.163 [a]
OI (mmHg)	360(281.88–450)	298.5(181.25–360)	<0.001 [a]
MAP (mmHg)	82.33(76.67–90.92)	80(71.34–90.84)	0.203 [a]
PCT (ng/mL)	1.41(0.41–6.16)	2.74(1.07–9.47)	0.002 [a]
Presepsin (pg/mL)	1016.39(469.51–2727.72)	2626.43(848.04–7708.80)	<0.001 [a]
HE4 (pmol/L)	416.33(181.18–1263.56)	1102.49(334.42–2335.66)	<0.001 [a]
IL-6(pg/mL)	76.98(21.18–223.13)	133.83(44.75–643.69)	0.011 [a]
CRP (mg/L)	82.31(24.56–127.49)	94.48(55.47–154.23)	0.02 [a]
WBC (×10^9/L)	9.86(6.76–14.26)	10.26(6.86–14.86)	0.749 [a]
NLR	10.2(5.53–17.41)	15.01(8.28–29.16)	0.001 [a]
Hb (g/L)	82.5(73.25–96.7)	79(71.5–91.25)	0.081 [a]
RDW	0.15(0.14–0.17)	0.16(0.15–0.18)	0.003 [a]
PLT (×10^9/L)	148.5(84.5–227.5)	107(49–181.25)	0.004 [a]
ALT (U/L)	24(13–42.75)	25(16–61)	0.313 [a]
AST (U/L)	31(22–54.25)	44(27–104)	0.003 [a]
ALP (U/L)	102.5(69.25–137.5)	98(70–176)	0.675 [a]
GGT (U/L)	63(35–113.5)	47.5(23–108)	0.085 [a]
CHE (U/L)	2989(2339–3872)	2557.5(1780.75–3571)	0.012 [a]
TBIL (μmol/L)	16.7(12.7–19.05)	22.8(12–50)	0.023 [a]
UREA (mmol/L)	9.8(5.83–14.58)	13.7(8.4–21.8)	<0.001 [a]
CREA (mmol/L)	85(51.25–171.75)	120(69–219)	0.029 [a]
PT (s)	15.3(14–16.75)	16(14.73–18.7)	0.001 [a]

(*Continued*)

Table 4 (Continued).

Variables	Survivor (n=134)	Non-Survivor (n=112)	*P* value
APTT (s)	42.3(35.3–50.9)	48.15(41.3–57.13)	<0.001 [a]
TT (s)	16.7(15.5–17.85)	17.25(16.10–18.7)	0.035 [a]
Fbg (g/L)	3.57(2.58–4.89)	2.97(2.13–4.43)	0.053 [a]
DD (mg/L)	3.76(2.37–6.85)	4.45(2.38–9.11))	0.286 [a]

Notes: Categorical and continuous variables are presented as frequency or median (IQR), respectively. Between-group differences in categorical and continuous variables are analyzed using Chi-squared test and Wilcoxon rank sum test, respectively. [a] Wilcoxon rank sum test; [b] Chi-squared test.
Abbreviations: OI, oxygenation index; PCT, Procalcitonin; MAP, mean arterial pressure; CRP, C-reactive protein; WBC, blood white cell; NLR, Neutrophils to Lymphocytes Ratio; RDW, red blood cell distribution width; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CHE, cholinesterase; TBIL, total bilirubin; UREA, urea nitrogen; CREA, creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; Fbg, fibrinogen; DD, D-dimer.

This study establishes robust clinical evidence for a novel tripartite biomarker panel (Presepsin, HE4, OI) addressing two critical unmet needs: (1) the lack of reliable early markers, and (2) the inability of single biomarkers to capture sepsis heterogeneity.

Presepsin, an LPS receptor, showed significant elevation in sepsis and septic shock patients compared to non-sepsis cases ($P<0.05$), exhibited quantifiable correlations with disease severity (SOFA score, CRP) and 30-day mortality. These findings align with prior studies,[10,11,18,19] and validate its role as a surrogate marker of innate immune activation.[18]

Similarly, HE4, a biomarker originally linked to ovarian cancer,[20,21] exhibited increased expression in sepsis patients ($P<0.05$), demonstrating progressive increases with disease severity and strong correlations with inflammatory markers CRP and and SOFA score. Its predictive capacity for mortality was comparable to established biomarkers. Notably, its association with 30-day mortality (AUC=0.706) suggests utility beyond diagnosis, potentially reflecting cumulative organ stress. Its correlation with inflammatory mediators suggests a potential nexus between metabolic stress and immune dysregulation,[22,23] warranting further investigation into its pathophysiological role.

OI, reflecting sepsis-induced lung dysfunction,[15] was significantly reduced in patients and predictive of poor outcomes, consistent with previous research.[24,25] This aligns with the known pathophysiology of sepsis-associated ARDS, where impaired oxygenation exacerbates multi-organ failure.

Measuring multiple biomarkers at once may address limitations inherent to single biomarkers.[6] As our data showed that the combinatorial biomarker strategy achieved diagnostic accuracy (AUC=0.892) compared to individual markers (Presepsin AUC=0.821; HE4 AUC=0.803; OI AUC=0.752) and conventional inflammatory indicators (PCT, CRP, IL-6). This multi-biomarker achieved optimized performance characteristics with 88.6% sensitivity and 77.0% specificity at the

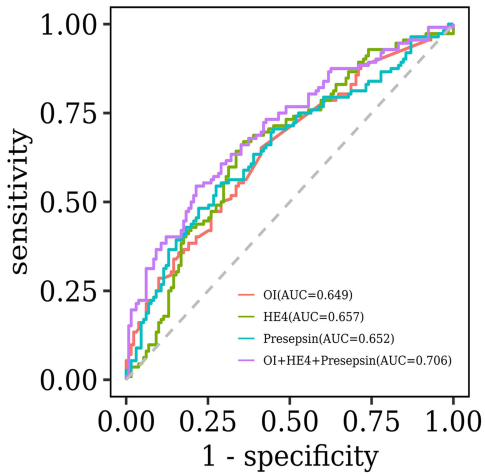

Figure 5 ROC curve analysis of the combined Presepsin+HE4+OI, HE4, Presepsin and OI in the prognosis of sepsis.

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Table 5 Prognostics Performance of the Laboratory Infection Indicators in Subjects with Survivors and Non-Survivors Group

Variables	AUC (95% CI)	Youden index	Cutoff	SEN (%)	SPE (%)
Presepsin+HE4+OI	0.706 (0.641–0.772)	0.331	0.514	54.5	78.6
HE4	0.657 (0.587–0.726)	0.311	711.13	67.0	64.1
Presepsin	0.655 (0.586–0.725)	0.269	2389.77	54.5	72.4
OI	0.652 (0.583–0.720)	0.249	358.57	65.2	59.7

Abbreviations: OI, oxygenation index. AUC, the area under the receiver operating characteristic curve; SEN, sensitivity; SPE, specificity.

determined cutoff value, representing a clinically meaningful improvement through simultaneous reduction of false-negative results (critical for early therapeutic intervention) and false positive outcomes (minimizing inappropriate antibiotic administration). Notably, the prognostic evaluation revealed sustained superiority of the panel (AUC = 0.706 for 30-day mortality prediction), with HE4 and Presepsin contributing predominantly to predictive capacity. This combinatorial biomarker strategy effectively complements conventional severity scores (eg, SOFA) by integrating quantitative laboratory parameters into clinical decision-making frameworks.[26]

Based on these findings, we propose two concrete clinical pathways for implementation: First, for early diagnosis of sepsis: The panel's high sensitivity (88.6%) and diagnostic accuracy (AUC=0.892) support its deployment as a complementary tool in emergency departments and ICUs. Integration into sepsis workups when culture results are pending or negative may reduce missed diagnoses during the critical golden window for targeted interventions. Second, enhancing the effect of dynamic risk stratification: Serial measurements of HE4 and Presepsin (key mortality predictors, AUC=0.706) should be adopted for monitoring high-risk patients. Rising trends could trigger preemptive care escalation before overt organ failure.

However, these conclusions warrant cautious interpretation: The single-center design may limit generalizability, potential confounding factors (eg, comorbidities or immunosuppressive therapies) remain unaddressed, and external validation across heterogeneous populations is pending. To address these limitations and advance clinical translation, we propose the following prioritized research agenda: Initial efforts should focus on conducting large-scale, multicenter prospective studies validating panel performance across diverse populations, implementing standardized pre-analytical protocols to ensure reproducibility. Concurrently, development of integrated point-of-care testing (POCT) systems enabling rapid biomarker triage at care initiation points warrants dedicated investigation. Finally, construction of dynamic AI models converting serial biomarker measurements into personalized risk forecasts represents a critical translational frontier. Collectively, these innovations could transform sepsis management from reactive protocols to preemptive precision medicine.

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Compliance with Ethical Standards

All experimental protocols in this study involving human subjects were performed in accordance with the ethical standards of the First Affiliated Hospital of Sun Yat-sen University and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (IRB No:2022-461).

Disclosure

The authors declare that there are no commercial or financial conflicts of interest for this work.

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