Infection and Drug Resistance Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Peripheral Blood Levels of IL-27, IFABP, and DAO at Early Onset as Predictors of 28-Day Mortality in Enterogenic Sepsis Patients: A Single-Center, Prospective Pilot Study

Yin Ni[1,2], Renhua Sun[2], Bangchuan Hu[2], Jingquan Liu[2], Xiang-hong Yang[2], Jinzhu Wang[2]

[1]Hospital-Acquired Infection Control & Prevention and Health Care Department, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, 310014, People's Republic of China; [2]Emergency and Critical Care Center, Intensive Care Unit, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, 310014, People's Republic of China

Correspondence: Xiang-hong Yang; Jinzhu Wang, Email jyy623@163.com; linkimlin@163.com

Background: Currently, there is a lack of serum biomarkers that can accurately predict the short-term prognosis of enterogenic sepsis.

Methods: 99 patients with enterogenic sepsis were categorized based on their Acute Gastrointestinal Injury (AGI) grade on the third day of ICU admission into four groups: no AGI, AGI grade I, AGI grade II, and AGI (III+IV). Additionally, patients were classified into survival and death groups according to their 28-day clinical outcomes. Peripheral venous blood samples were collected to measure levels of interleukin (IL)-27, intestinal fatty acid-binding protein (IFABP), and diamine oxidase (DAO). Receiver operating characteristic (ROC) curves were generated to assess the ability of IL-27, IFABP, and DAO to predict the short-term prognosis of patients with enterogenic sepsis.

Results: On the third day, both the survival and death groups exhibited elevated serum levels of IL-27 and IFABP compared to the first day, while levels of DAO were lower than those observed on day one. Furthermore, a significant positive correlation was observed between IL-27 and both IFABP and DAO, with stronger correlations evident on day three compared to day one. As the Acute Gastrointestinal Injury (AGI) grading increased, levels of IL-27, IFABP, and DAO rose correspondingly, correlating with a gradual decrease in survival rates, all demonstrating statistical significance (all $P < 0.05$). The Area Under the Curve (AUC) values for IL-27, IFABP, and DAO on the third day, predicting short-term prognosis for intestinal sepsis patients, were 0.714, 0.772, and 0.724, respectively. Notably, these values surpassed those of the first day, with IFABP on the third day exhibiting the highest predictive capability.

Conclusion: IL-27, IFABP, and DAO levels measured on the third day of hospitalization can accurately predict the short-term prognosis of enterogenic sepsis.

Keywords: sepsis, enterogenic infection, interleukin-27, intestinal fatty acid-binding protein, diamine oxidase, short-term prognosis

Introduction

Sepsis claims millions of lives annually and remains the leading cause of death among ICU patients.[1,2] The intestines, critical organs in the human body, serve as the primary reservoir for bacteria and toxins, making them one of the main sources of infection leading to sepsis.[3,4] Intestinal damage can increase the permeability of the intestinal mucosal barrier, facilitating bacterial translocation into the bloodstream and precipitating sepsis.[5] Research indicates that patients with sepsis originating from the intestines are particularly prone to septic shock.[6] Studies have shown that the main pathogenic microorganisms causing enterogenic sepsis are Gram-negative bacteria, especially multi-drug resistant bacteria, which poses a serious challenge for anti-infection treatment. This not only consumes a lot of medical funds, but also greatly increases the case fatality rate of sepsis patients. Early identification of intestinal-origin sepsis patients at high risk for

Received: 19 September 2024
Accepted: 28 November 2024
Published: 7 December 2024

poor prognosis through specific markers and the implementation of targeted medical interventions can significantly improve outcomes and reduce mortality rates.

In recent years, some novel biomarkers have been gradually applied to the diagnosis of sepsis, which brings hope for early diagnosis of enterogenic sepsis. Interleukin-27 (IL-27) is a multifunctional cytokine with various immunomodulatory activities, exerting anti-inflammatory effects during infection and inflammatory responses.[7] Intestinal fatty acid-binding protein (IFABP) and diamine oxidase (DAO) are serum biomarkers indicative of intestinal mucosal barrier function, with their serum levels significantly increasing when intestinal function is impaired.[8,9] Current research on IFABP and DAO in critical care primarily addresses gastrointestinal dysfunction, particularly acute gastrointestinal injury (AGI).[10,11] However, there is a lack of studies on the changes and clinical significance of IL-27, IFABP, and DAO in the development and progression of enterogenic sepsis globally. To determine the predictive value of peripheral blood IL-27, IFABP, and DAO for the short-term prognosis of patients with enterogenic sepsis, we designed this single-center, prospective pilot study.

Materials and Methods

Clinical Data

The clinical data for this study were obtained from a subset of a prior multicenter, prospective, observational study conducted by our research team on sepsis, registered under number ChiCTR-OCS-13003824.[12] This study enrolled sepsis patients admitted to the Intensive Care Unit (ICU) at Zhejiang Provincial People's Hospital between March 2023 and August 2023. Inclusion criteria were as follows: (1) age $\geq$ 18 years; (2) meeting the enterogenic sepsis diagnostic criteria;[13,14] (3) ICU stay exceeding 72 hours; (4) consent for peripheral blood IL-27, IFABP, and DAO testing. Exclusion criteria were: (1) incomplete clinical data; (2) pregnancy or lactation; (3) history of autoimmune diseases, hematological disorders, or malignancies; (4) recent use of DAO inhibitors within the past month; (5) patients who discontinued treatment or were transferred to another facility during the study period. Patients were categorized into four groups based on the Acute Gastrointestinal Injury (AGI) classification on the third day of ICU admission (due to the limited number of grade IV cases, grades III and IV were combined), with criteria following the 2012 ESICM recommendations.[15] Outcome analysis at 28 days post-admission distinguished between survival and mortality groups. Refer to Figure 1 for detailed classification.

Research Methods

All patients received treatment according to the "2016 International Guidelines for the Management of Severe Sepsis and Septic Shock".

Collection of Baseline Clinical Data

Baseline clinical data were collected, including gender, age, body mass index (BMI), medical history of chronic diseases, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, vasopressor usage proportion, heart rate (HR), mean arterial pressure (MAP), blood glucose levels, serum albumin (ALB), serum creatinine (Scr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), white blood cell count (WBC), hemoglobin (HGB), platelet count (PLT), C-reactive protein (CRP) levels, procalcitonin (PCT) levels, arterial lactate (Lac), sodium ions (Na+), potassium ions (K+), presence of acute kidney injury (AKI), receipt of continuous renal replacement therapy (CRRT), mechanical ventilation ratio, and the 28-day hospital outcome (survival or death).

Detection of Peripheral Blood IL-27, IFABP, and DAO Levels

Peripheral venous blood samples (5 mL) were collected from all patients on the first day of admission (immediately upon arrival) and on the third day of admission (at 5 a.m.) to measure IL-27, IFABP, and DAO levels. The blood samples were transferred by 2000 rpm centrifuge for 10 minutes and stored in the refrigerator at −80°C for detection. The concentrations of IL-27, IFABP, and DAO in peripheral blood were quantified using enzyme-linked immunosorbent assay (ELISA) kits, provided by Nanjing Jiancheng Bioengineering Institute, Nanjing, China. All detection tests were performed in strict

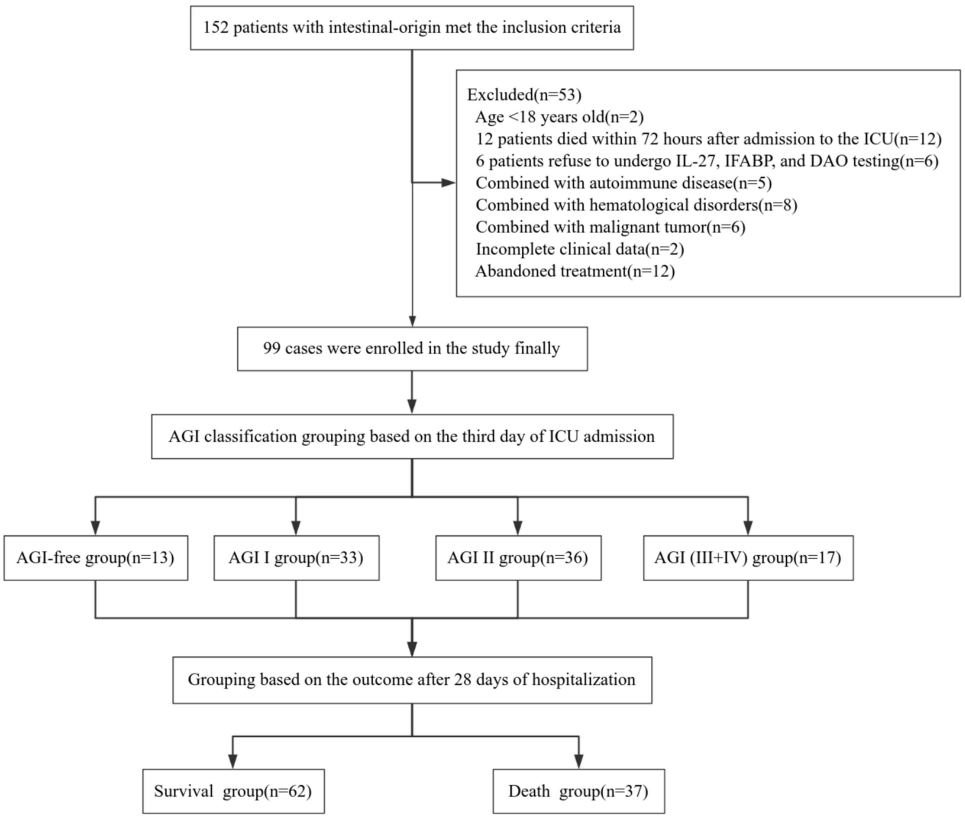

Figure 1 Research Flowchart.

accordance with the kit instructions, including dilution addition, washing, color development, and termination, and the corresponding IL-27, IFABP, andDAO levels were calculated according to the obtained optical density.

Comparison of Peripheral Blood IL-27, IFABP, and DAO Levels Between Survival and Death Groups

The levels of IL-27, IFABP, and DAO in peripheral blood were compared between the survival and death groups on the first and third days of admission. Additionally, the correlations among IL-27, IFABP, and DAO were analyzed for the same time points.

Comparison of Peripheral Blood IL-27, IFABP, and DAO Levels and 28-Day Hospital Survival Rates Among Different AGI Grading Groups

Peripheral blood levels of IL-27, IFABP, and DAO were measured on the third day after admission and compared between the two primary groups and among the four subgroups. Survival analysis was conducted using Kaplan-Meier curves to compare the 28-day hospital survival rates among the four subgroups.

Clinical Value of IL-27, IFABP, and DAO Levels on the First and Third Days of Admission in Predicting Short-Term Prognosis of Patients with Enterogenic Sepsis

The receiver operating characteristic (ROC) curve was employed to evaluate the clinical value of IL-27, IFABP, and DAO levels measured on the first and third days after admission for predicting the short-term prognosis of patients with enterogenic sepsis.

Statistical Methods

Statistical analyses were conducted using SPSS Version 24.0. Continuous variables were presented as means ± standard deviations, and comparisons between two groups were performed using *t*-tests if these data fit a normal distribution. If the data did not follow a normal distribution, used the M (Q_{25}, Q_{75}) for representation, and Mann–Whitney tests should

be used for inter-group comparison. One-way analysis of variance (ANOVA) was employed for comparisons among three or more groups. Categorical variables were expressed as numbers (percentages), and comparisons between groups were performed using the χ^2-test or Fisher's exact test. Survival analysis was conducted using Kaplan-Meier curves, correlation analysis was performed using Pearson's correlation coefficient, and the predictive value was assessed using receiver operating characteristic (ROC) curves. A P value of less than 0.05 was considered statistically significant.

Results

Comparison of Baseline Clinical Data Between Survival and Death Groups

A total of 99 patients with intestinal sepsis were included in this study. Based on the 28-day hospital mortality outcome, patients were divided into a survival group (n=62) and a death group (n=37), resulting in a mortality rate of 37.4%. The heart rate (HR) in the death group was significantly higher than in the survival group, while the mean arterial pressure (MAP) was significantly lower in the death group compared to the survival group (both P<0.05). There were no statistically significant differences between the two groups concerning the proportion of male patients, age, BMI, history of chronic diseases, APACHE II score, SOFA score, use of vasoactive drugs, blood glucose levels, albumin (ALB), serum creatinine (Scr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), white blood cell count (WBC), hemoglobin (HGB), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), lactate (Lac), sodium (Na+), potassium (K+), incidence of acute kidney injury (AKI), and the proportion of patients receiving continuous renal replacement therapy (CRRT) and mechanical ventilation (all P>0.05). Details are provided in Table 1.

Comparison of IL-27, IFABP, and DAO Levels Between Survival and Non-Survival Groups

On the third day of admission, serum IL-27 and IFABP levels in both groups were elevated compared to the first day, whereas DAO levels were reduced. These alterations were more pronounced in the non-survival group, with statistically significant differences observed (all P < 0.05), as shown in Figure 2.

Table 1 Comparison of Baseline Clinical Data Between Survival and Death Groups

Characteristics	Survival Group (n=62)	Death Group (n=37)	*P value*
Demographic characteristics			
Percentage of males [n (%)]	45 (72.5)	26 (70.2)	0.805
Age (years old, $\bar{x} \pm s$)	60±19	66±18	0.094
BMI (kg/m^2, $\bar{x} \pm s$)	21.7±1.1	21.6±1.3	0.460
Chronic diseases [n (%)]			
Heart disease	1 (1.6)	3 (8.1)	0.112
Hypertension	25 (40.3)	19 (51.3)	0.285
Diabetes	6 (9.6)	8 (21.6)	0.099
COPD	5 (8.0)	3 (8.1)	0.994
Stroke	12 (19.3)	11 (29.7)	0.237
CKD	7 (11.2)	5 (13.5)	0.743
Severity at ICU admission			
APACHE II score (score, $\bar{x} \pm s$)	19±6	18±6	0.700
SOFA score (score, $\bar{x} \pm s$)	7±3	7±4	0.822
Use of vasoactive drugs[n (%)]	30 (48.3)	11 (29.7)	0.068
Vital signs			
HR [bpm, M(Q_{25},Q_{75})]	77 (67, 86)	86 (73, 100)	0.032
MAP (mmHg, $\bar{x} \pm s$)	74±16	66±11	0.013

(*Continued*)

Table 1 (Continued).

Characteristics	Survival Group (n=62)	Death Group (n=37)	*P value*
Laboratory examination at ICU admission			
Blood glucose (mmol/L, $\bar{x} \pm s$)	8.6±4.8	8.2±3.9	0.693
ALB (g/L, $\bar{x} \pm s$)	31.0±6.3	29.8±5.7	0.367
Scr[umol/L, M(Q_{25},Q_{75})]	103.4 (75.0, 144.3)	97.2 (74.7, 200.6)	0.739
ALT (U/L, $\bar{x} \pm s$)	167±412	141±372	0.753
AST (U/L, $\bar{x} \pm s$)	104±338	75±174	0.631
WBC (×10^9/L, $\bar{x} \pm s$)	14.6±7.1	13.4±6.2	0.403
HGB (g/L, $\bar{x} \pm s$)	110±27	105±29	0.322
PLT (×10^9/L, $\bar{x} \pm s$)	163±83	140±70	0.170
CRP[mg/L, M(Q_{25},Q_{75})]	72.7 (24.7, 118.7)	75.0 (20.2, 185.0)	0.600
PCT[ng/mL, M(Q_{25},Q_{75})]	0.43 (0.20, 3.40)	0.43 (0.26, 1.52)	0.519
Lac (mmol/L, $\bar{x} \pm s$)	2.2±1.4	1.8±1.1	0.101
Na^+(mmol/L, $\bar{x} \pm s$)	142±6	141±6	0.202
K^+(mmol/L, $\bar{x} \pm s$)	3.8±0.7	4.1±0.6	0.120
Incidence of AKI[n (%)]	16 (25.8)	7 (18.9)	0.432
Receiving CRRT[n (%)]	10 (16.1)	6 (16.2)	0.991
Mechanical ventilation [n (%)]	51 (82.2)	31 (83.7)	0.846

Notes: Additionally, 1 mmHg is approximately equal to 0.133 kPa.

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; HR, Heart Rate; MAP, Mean Arterial Pressure; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; ALB, serum albumin; Scr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count; CRP, C-reactive protein; PCT, procalcitonin; Lac, arterial blood lactate; Na+, sodium ion; K+, potassium ion; AKI, acute kidney injury; CRRT, continuous renal replacement therapy.

Correlation Analysis Between IL-27 and IFABP and DAO

On the third day of admission, a significant positive correlation was observed between IL-27 levels and those of IFABP and DAO. Notably, this correlation was more pronounced on the third day compared to the first day of admission. Refer to Figure 3 for the details.

Comparison of IL-27, IFABP, DAO Levels, and Survival Rates Among Different AGI Grades on the Third Day in ICU

Based on the Acute Gastrointestinal Injury (AGI) grades assessed on the third day of ICU admission, patients were categorized into the non-AGI group (n = 13), AGI I group (n = 33), AGI II group (n = 36), and AGI (III+IV) group (n = 17). As the AGI grade increased, the levels of IL-27, IFABP, and DAO also elevated, and the survival rate progressively declined, with all differences being statistically significant (all $P < 0.05$). For further details, refer to Figure 4.

Analysis of ROC Curves for IL-27, IFABP, and DAO in Predicting Short-Term Prognosis of Patients with Intestinal Sepsis

The area under the curve (AUC) values for IL-27, IFABP, and DAO on the third-day, predicting the short-term prognosis of patients with intestinal sepsis, were 0.714 (95% confidence interval [CI]: 0.603–0.824, P<0.001), 0.772 (95% CI: 0.672–0.871, P<0.001), and 0.724 (95% CI: 0.622–0.826, P<0.001), respectively. These values were all higher compared to those on the first day, with the third-day IFABP demonstrating the highest predictive value. When the third-day IL-27 level was ≥342.1 pg/L, the sensitivity, specificity, and Youden index for predicting short-term mortality were 0.811, 0.581, and 0.392, respectively. For third-day IFABP levels ≥8.2 mg/mL, the sensitivity, specificity, and Youden index were 0.784, 0.694, and 0.478, respectively. For third-day DAO levels ≥32.1 mIU/mL, the sensitivity, specificity, and Youden index were 0.757, 0.565, and 0.322, respectively. Refer to Table 2 and Figure 5.

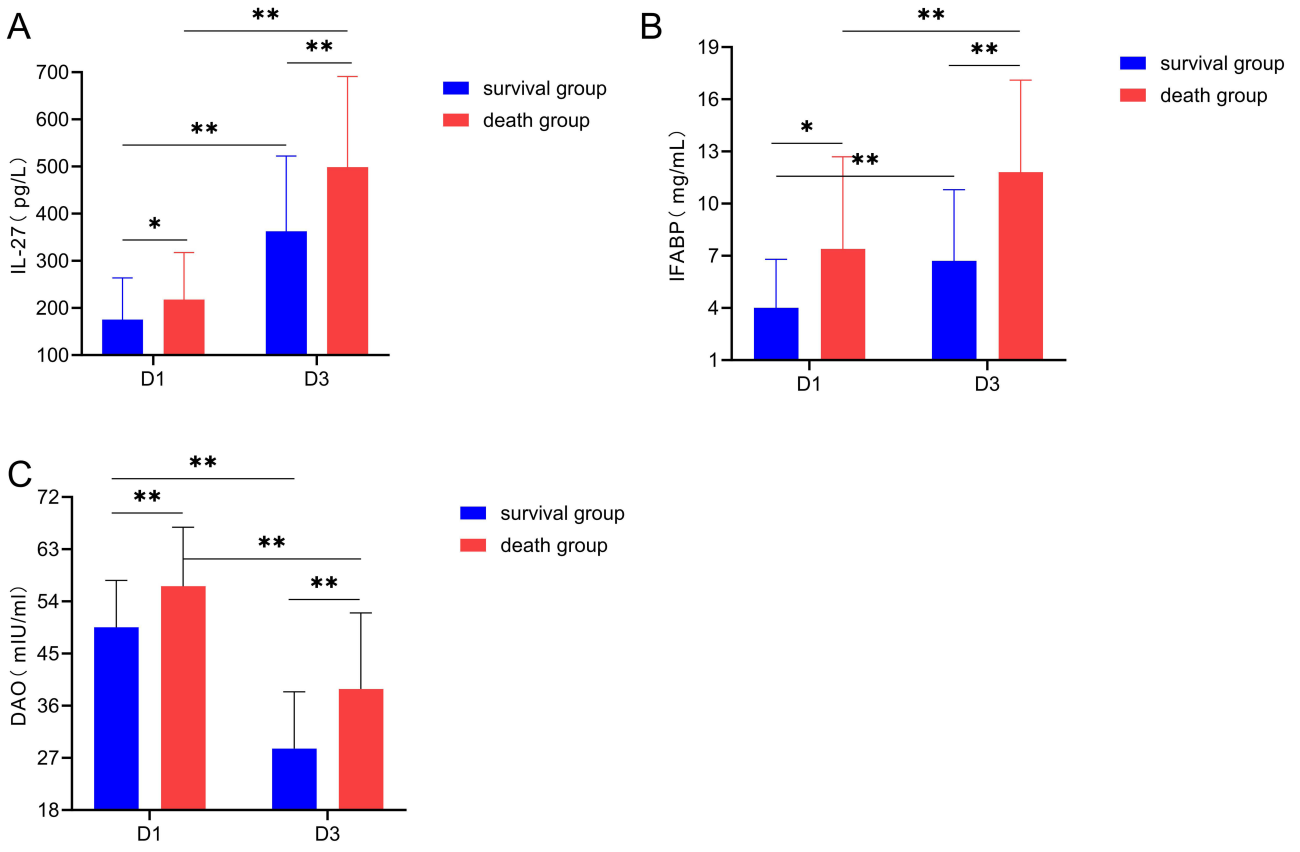

Figure 2 Comparison of IL-27 (**A**), IFABP (**B**), and DAO (**C**) levels between the survival and death groups. In the figure legend, (**A**) represents IL-27, (**B**) represents IFABP, and (**C**) represents DAO. Statistical significance is denoted by * for $P < 0.05$ and ** for $P < 0.001$, respectively.
Abbreviations: IL-27, interleukin-27; IFABP, intestinal fatty acid-binding protein; DAO, diamine oxidase.

Discussion

Since Border introduced the concept of intestinal-origin sepsis in 1987, there has been increasing research attention on this specific site of infection.[16] It is widely accepted that intestinal-origin sepsis encompasses two main concepts:[17] (1) sepsis resulting from identifiable intestinal infections, and (2) sepsis where no specific intestinal infection is evident, but damage to the intestinal mucosal barrier leads to increased permeability, bacterial translocation, and subsequent infection. The pathogenesis primarily involves the following factors:[18–20] (1) Disruption of intestinal microbiota: An imbalance in the normal intestinal flora results in the proliferation of harmful bacteria, which can translocate to extraintestinal tissues and organs, causing infection; (2) Impairment of intestinal mucosal barrier function: Pathological conditions such as infection and trauma can compromise the intestinal mucosal barrier, which normally protects the intestinal lumen by secreting mucus, thus allowing the translocation of intestinal flora and subsequent infection; (3) Impairment of the host's immune function: Reduced host immune function facilitates the translocation of toxins and bacteria within the intestine. Based on this premise, in clinical practice, cases presenting with typical signs of sepsis without a clear source of infection are often attributed to intestinal-origin sepsis.

Patients with enterogenic sepsis often experience rapid disease progression, frequently developing septic shock in the early stages, which contributes to a high mortality rate. Research indicates that multiple inflammatory factors drive the progression of sepsis, initiating an inflammatory cascade that damages tissues and organs.[21] IL-27, a member of the IL-12 family, plays dual roles in both promoting and inhibiting inflammation by regulating T lymphocyte differentiation. It is closely linked to various infectious diseases such as pulmonary tuberculosis,[22] chronic enteritis,[23] and pneumonia.[24]

Fan et al[25] reported significantly elevated IL-27 levels in patients with sepsis-induced liver injury, correlating with traditional inflammatory markers such as CRP and PCT. This suggests IL-27 may play a role in the pathogenesis of sepsis-related liver damage. Similarly, Seman et al[26] found that IL-27 levels were abnormally high in the early stages of

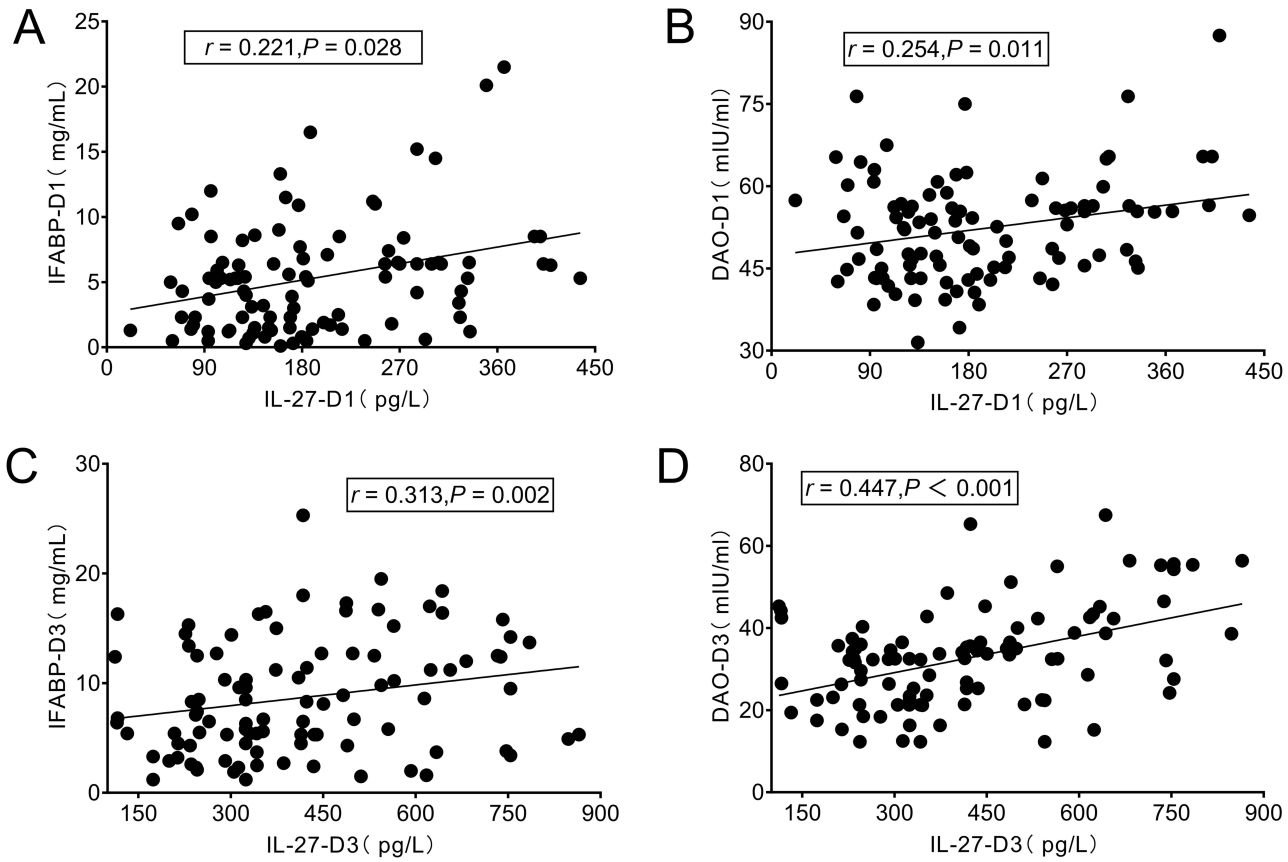

Figure 3 Correlation Analysis of IL-27 Levels with IFABP and DAO. Correlation analysis between IL-27 levels and IFABP on day 1 (**A**); Correlation analysis between IL-27 levels and DAO on day 1 (**B**); Correlation analysis between IL-27 levels and IFABP on day 3 (**C**); Correlation analysis between IL-27 levels and DAO on day 3 (**D**).
Abbreviations: IL-27, interleukin-27; IFABP, intestinal fatty acid-binding protein; DAO, diamine oxidase.

neonatal sepsis, which impaired bacterial control and enhanced inflammatory cytokine responses. They proposed that targeting IL-27 could be a novel therapeutic approach for neonatal sepsis.

Our study confirmed that IL-27 levels in peripheral blood are abnormally high in the early stages of adult enterogenic sepsis, with a more pronounced increase observed on the third day after admission. This persistent elevation of IL-27 is associated with a higher 28-day in-hospital mortality rate, providing new evidence supporting the potential for early anti-inflammatory treatment in sepsis patients.

IFABP is expressed in epithelial cells throughout the small intestine and colon. Upon intestinal damage, IFABP is released into the bloodstream in substantial quantities. Numerous studies have validated IFABP as a serum marker for diagnosing conditions such as mesenteric ischemia[27] and necrotizing enterocolitis.[28] In a study by Chen et al[29] involving 50 severe sepsis patients and 20 healthy individuals, it was observed that peripheral blood levels of IFABP in sepsis patients were markedly elevated compared to healthy individuals at 0, 1, and 3 days post-admission. Further correlation analysis revealed a significant positive correlation between IFABP levels and IL-6 (r=0.794, P<0.001), tumor necrosis factor-alpha (TNF-α) (r=0.878, P=0.010), and APACHE II scores (r=0.428, P<0.001) in severe sepsis patients. Tyszko et al[30] reported that IFABP levels were significantly higher in critically ill patients and could predict 28-day in-hospital mortality. Risk assessment utilizing IFABP and other intestinal markers aids in clinical decisions regarding the management of intestinal injury, imaging diagnostics, and potential surgical interventions. Diamine oxidase (DAO), an intracellular oxidase, is abundantly expressed throughout the intestine. Damage to the intestinal mucosa can result in increased DAO absorption into the bloodstream, serving as an indicator of intestinal functional impairment. Zhang et al[31] found that plasma levels of IFABP and DAO were significantly higher in patients with heat shock compared to

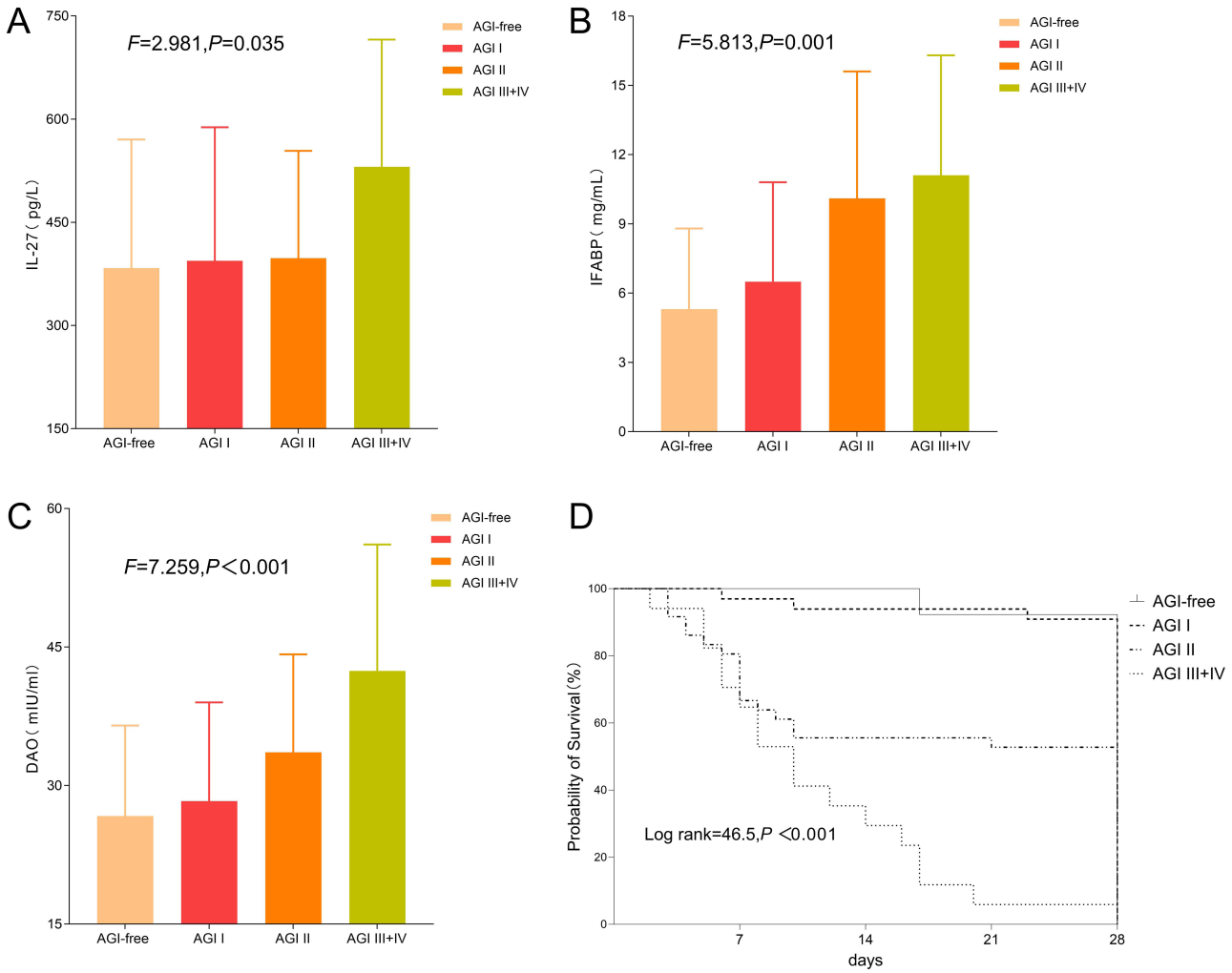

Figure 4 Shows the comparison of IL-27 (**A**), IFABP (**B**), DAO (**C**) levels, and survival rates among different AGI grading groups on the third day of ICU admission. The P value indicates statistically significant differences in these indicators between different AGI grading groups, as determined by one-way ANOVA. The Kaplan-Meier curve (**D**) illustrates the prediction of the 28-day in-hospital mortality risk for patients with enterogenic sepsis based on AGI grading on the third day of ICU admission. The P value indicates that the differences in survival rates between the different AGI grading groups are statistically significant, as shown by the Log rank test.
Abbreviations: IL-27, interleukin-27; IFABP, intestinal fatty acid-binding protein; DAO, diamine oxidase; AGI, acute gastrointestinal injury.

healthy controls (P<0.05), and these levels significantly decreased after treatment. This suggests that plasma IFABP and DAO levels can reflect the integrity of the intestinal mucosal barrier in heat shock patients and predict disease severity.

This study enrolled 99 patients diagnosed with sepsis of intestinal origin, with a 28-day in-hospital mortality rate of 37.4% (37/99). Dynamic monitoring of peripheral blood levels of IL-27, IFABP, and DAO was performed. On the

Table 2 The ROC Curve Analysis Results for IL-27, IFABP, and DAO in Predicting the Short-Term Prognosis of Patients with Intestinal-Origin Sepsis

Index	AUC	95% *CI*	*P* value	*Cut-off*	Sensitivity	Specificity	Youden Index
IL-27-D1 (pg/L)	0.617	0.502~0.733	0.051	123.2	0.838	0.323	0.161
IL-27-D3 (pg/L)	0.714	0.603~0.824	<0.001	342.1	0.811	0.581	0.392
IFABP-D1 (mg/mL)	0.693	0.580~0.806	0.001	3.9	0.757	0.516	0.273
IFABP-D3 (mg/mL)	0.772	0.672~0.871	<0.001	8.2	0.784	0.694	0.478
DAO-D1 (mIU/mL)	0.701	0.594~0.807	0.001	52.8	0.703	0.645	0.348
DAO-D3 (mIU/mL)	0.724	0.622~0.826	<0.001	32.1	0.757	0.565	0.322

Abbreviations: IL-27, Interleukin-27; IFABP, Intestinal Fatty Acid-Binding Protein; DAO, Diamine Oxidase; ROC, Receiver Operating Characteristic curve; AUC, Area Under the Curve; CI, Confidence Interval.

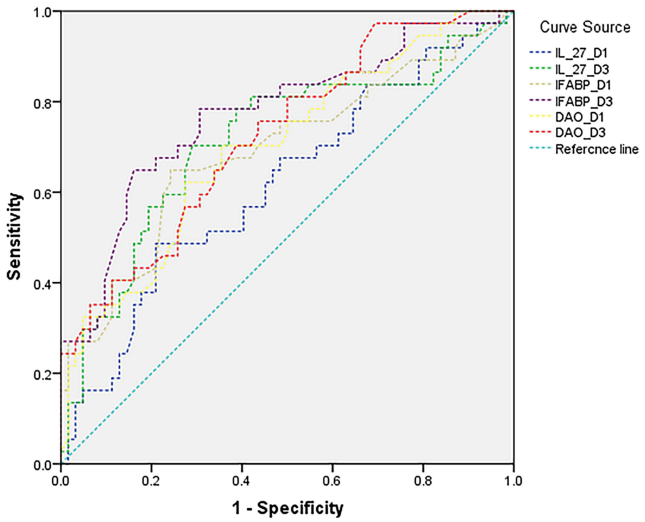

Figure 5 The ROC curve analysis for IL-27, IFABP, and DAO in predicting the short-term prognosis of patients with intestinal-origin sepsis.
Abbreviations: IL-27, interleukin-27; IFABP, intestinal fatty acid-binding protein; DAO, diamine oxidase.

third day, both the survival and non-survival groups exhibited significantly higher serum levels of IL-27 and IFABP compared to the first day, while DAO levels were significantly lower, especially in the non-survival group (all $P < 0.05$). A significant positive correlation was found between IL-27, IFABP, and DAO levels, with stronger correlations observed on the third day compared to the first day. Additionally, a comparison among patients with varying grades of Acute Gastrointestinal Injury (AGI) on the third day of ICU admission showed that as AGI grade increased, IL-27, IFABP, and DAO levels also increased, while the survival rate decreased, all with statistical significance (all $P < 0.05$).

These findings underscore the presence of a robust inflammatory response and damage to the intestinal mucosal barrier in patients with sepsis originating from the intestines. Furthermore, a correlation exists between the expression levels of IL-27, IFABP, and DAO in these patients, indicating their association with the severity of intestinal injury and short-term prognosis. Additional analysis using ROC curves revealed that on the third day, IL-27, IFABP, and DAO levels demonstrated superior predictive value for short-term prognosis compared to the first day, with IFABP on the third day exhibiting the highest predictive value.

This study confirmed that IL-27, IFABP and DAO are highly expressed in patients with enterogenous sepsis, and the mechanism may be closely related to inflammatory response syndrome and ischemia reperfusion in patients with enterogenous sepsis. However, the specific mechanism needs to be confirmed by further animal and clinical trials. Nevertheless, these biomarkers provide a new and viable approach for achieving early diagnosis of enteroborne sepsis.

This study has several limitations. Firstly, as a single-center study with a small sample size, it lacks both internal and external validation. As a result, this study may not obtain similar results in other hospitals or regions, which may lead to the popularization and application of the conclusions of this study. Secondly, the study focuses solely on assessing the short-term prognostic value of IL-27, IFABP, and DAO without conducting long-term follow-up, which reduces its clinical relevance. In future studies, we will conduct long-term follow-up of the patients and conduct a multi-center trial to increase the reliability of the research conclusions. Thirdly, the research investigates only the predictive capacity of IL-27, IFABP, and DAO for clinical outcomes, without exploring underlying mechanisms, leading to a lack of robust explanations for these outcomes. Future studies will address these shortcomings.

Conclusion

In summary, peripheral blood levels of IL-27, IFABP, and DAO can help to predict the short-term prognosis of intestinal sepsis, particularly on the third day after admission. Implementing dynamic monitoring in the early stages of intestinal sepsis facilitates the assessment of patients' short-term prognosis, enables timely adjustments to treatment strategies, and reduces mortality rates.

Data Sharing Statement

The data and materials can be obtained by contacting the corresponding author.

Ethics Statement

This study strictly adhered to the ethical principles outlined in the *Declaration of Helsinki* for human medical research and was approved by the Scientific Research and Clinical trial Ethics Committee of Zhejiang Provincial People's Hospital.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Acknowledgments

We would like to thank all the participants for their contributions to this study.

Author Contributions

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

Funding

This work was supported by the Natural Science Foundation of Zhejiang Province (TGD24H150002) and Medical and Health Research Project of Zhejiang Province(2023KY540).

Disclosure

The authors declare that there is no conflicts of interest regarding the publication of this paper.

References

1. Ackerman MH, Ahrens T, Kelly J, et al. Sepsis. *Crit Care Nurs Clin North Am*. 2021;33(4):407–418. doi:10.1016/j.cnc.2021.08.003
2. Spiegel R, Hockstein M, Waters J, et al. The survival of the surviving sepsis campaign. *Med Clin North Am*. 2022;106(6):1109–1117. doi:10.1016/j.mcna.2022.08.006
3. Adelman MW, Woodworth MH, Langelier C, et al. The gut microbiome's role in the development, maintenance, and outcomes of sepsis. *Crit Care*. 2020;24(1):278. doi:10.1186/s13054-020-02989-1
4. Klingensmith NJ, Coopersmith CM. Gut microbiome in sepsis. *Surg Infect*. 2023;24(3):250–257. doi:10.1089/sur.2022.420
5. Kullberg RFJ, Wiersinga WJ, Haak BW. Gut microbiota and sepsis: from pathogenesis to novel treatments. *Curr Opin Gastroenterol*. 2021;37(6):578–585. doi:10.1097/MOG.0000000000000781
6. Póvoa P, Coelho L, Dal-Pizzol F, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. *Intensive Care Med*. 2023;49(2):142–153. doi:10.1007/s00134-022-06956-y
7. Morrow KN, Coopersmith CM, Ford ML. IL-17, IL-27, and IL-33: a novel axis linked to immunological dysfunction during sepsis. *Front Immunol*. 2019;10:1982. doi:10.3389/fimmu.2019.01982
8. Blaser A, Padar M, Tang J, et al. Citrulline and intestinal fatty acid-binding protein as biomarkers for gastrointestinal dysfunction in the critically ill. *Anaesthesiol Intensive Ther*. 2019;51(3):230–239. doi:10.5114/ait.2019.86049
9. Shi L, Li Y, Liu Y, et al. Alterations of gut microbiota and cytokines in elevated serum diamine oxidase disorder. *Medicine*. 2022;101(50):e31966. doi:10.1097/MD.0000000000031966
10. Li H, Chen Y, Huo F, et al. Association between acute gastrointestinal injury and biomarkers of intestinal barrier function in critically ill patients. *BMC Gastroenterol*. 2017;17(1):45. doi:10.1186/s12876-017-0603-z
11. Liu M, Wang Y, Guan G, et al. Dietary supplementation of ancientino ameliorates dextran sodium sulfate-induced colitis by improving intestinal barrier function and reducing inflammation and oxidative stress. *Nutrients*. 2023;15(12):2798.
12. Hu B, Sun R, Wu A, et al. Severity of acute gastrointestinal injury grade is a predictor of all-cause mortality in critically ill patients: a multicenter, prospective, observational study. *Crit Care*. 2017;21(1):188. doi:10.1186/s13054-017-1780-4
13. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377. doi:10.1007/s00134-017-4683-6
14. Chen Y, Liao Y, Chen X, et al. Recognition and management of hemorrhaging in combination with emerging enterogenic sepsis during a hepatectomy: a case report. *BMC Anesthesiol*. 2023;23(1):186. doi:10.1186/s12871-023-02108-x

15. Reintam Blaser A, Malbrain ML, Starkopf J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. recommendations of the ESICM working group on abdominal problems. *Intensive Care Med*. 2012;38(3):384–394. doi:10.1007/s00134-011-2459-y
16. Deitch EA. Gut-origin sepsis: evolution of a concept. *Surgeon*. 2012;10(6):350–356. doi:10.1016/j.surge.2012.03.003
17. Chen P, Billiar T. Gut Microbiota and Multiple Organ Dysfunction Syndrome (MODS). *Adv Exp Med Biol*. 2020;1238:195–202.
18. Vaishnavi C. Translocation of gut flora and its role in sepsis. *Indian J Med Microbiol*. 2013;31(4):334–342. doi:10.4103/0255-0857.118870
19. Assimakopoulos SF, Triantos C, Thomopoulos K, et al. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. *Infection*. 2018;46(6):751–760. doi:10.1007/s15010-018-1178-5
20. Lu F, Inoue K, Kato J, et al. Functions and regulation of lipocalin-2 in gut-origin sepsis: a narrative review. *Crit Care*. 2019;23(1):269. doi:10.1186/s13054-019-2550-2
21. Font MD, Thyagarajan B, Khanna AK. Sepsis and septic shock - basics of diagnosis, pathophysiology and clinical decision making. *Med Clin North Am*. 2020;104(4):573–585. doi:10.1016/j.mcna.2020.02.011
22. Gollnick H, Barber J, Wilkinson RJ, et al. IL-27 inhibits anti- Mycobacterium tuberculosis innate immune activity of primary human macrophages. *Tuberculosis*. 2023;139:102326. doi:10.1016/j.tube.2023.102326
23. Nie M, Huang D, Chen G, et al. Bioadhesive microcarriers encapsulated with IL-27 high expressive MSC extracellular vesicles for inflammatory bowel disease treatment. *Adv Sci*. 2023;10(32):e2303349. doi:10.1002/advs.202303349
24. Xu Z, Wang XM, Cao P, et al. Serum IL-27 predicts the severity and prognosis in patients with community-acquired pneumonia: a prospective cohort study. *Int J Med Sci*. 2022;19(1):74–81. doi:10.7150/ijms.67028
25. Fan J, Zhang YC, Zheng DF, et al. IL-27 is elevated in sepsis with acute hepatic injury and promotes hepatic damage and inflammation in the CLP model. *Cytokine*. 2020;127:154936. doi:10.1016/j.cyto.2019.154936
26. Seman BG, Vance JK, Rawson TW, et al. Elevated Levels of Interleukin-27 in early life compromise protective immunity in a mouse model of gram-negative neonatal sepsis. *Infect Immun*. 2020;88(3). doi:10.1128/IAI.00828-19
27. Zenger S, Demir Piroğlu I, Çevik A, et al. The importance of serum intestinal fatty acid-binding protein for the early diagnosis of acute mesenteric ischemia. *Ulus Travma Acil Cerrahi Derg*. 2021;27(3):278–283. doi:10.14744/tjtes.2020.35823
28. Zafirovski A, Zafirovska M, Kuhelj D, et al. The impact of biomarkers on the early detection of acute mesenteric ischemia. *Biomedicines*. 2023;12(1):85. doi:10.3390/biomedicines12010085
29. Zhu C, Ding R, Sun Y, et al. Correlation of intestinal fatty acid binding protein and intestinal injury in severe sepsis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2014;26(6):420–424. doi:10.3760/cma.j.issn.2095-4352.2014.06.011
30. Tyszko M, Lipińska-Gediga M, Lemańska-Perek A, et al. Intestinal Fatty Acid Binding Protein (I-FABP) as a prognostic marker in critically Ill COVID-19 patients. *Pathogens*. 2022;11(12):1526. doi:10.3390/pathogens11121526
31. Zhang L, Fan X, Zhong Z, et al. Association of plasma diamine oxidase and intestinal fatty acid-binding protein with severity of disease in patient with heat stroke. *Am J Emerg Med*. 2015;33(7):867–871. doi:10.1016/j.ajem.2015.01.047