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Original Article

Correlation of serum H-FABP, sTREM-1, and HMGB1 levels with severity and prognosis of sepsis

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Abstract: Objective: To investigate the correlation between serum levels of Heart-type fatty acid binding protein (H-FABP), Soluble Triggering Receptor Expressed on Myeloid Cells 1 (sTREM-1), and High mobility group box 1 protein (HMGB1) with disease severity, and their prognostic value in sepsis. Methods: A retrospective analysis was conducted using the clinical data from 86 sepsis patients admitted to West China Hospital of Sichuan University between June 2021 and December 2023, and these cases constituted the observation group. In addition, clinical data from 80 healthy individuals who underwent medical examinations at our hospital during the same period served as the control group. Serum levels of H-FABP, sTREM-1, and HMGB1 were measured in both groups. Based on disease severity, the patients were categorized into mild (n=42), severe (n=28), and shock (n=16) groups. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to assess the patients' condition. Follow-up evaluations showed that 60 patients survived and 26 died. Results: Serum levels of H-FABP, sTREM-1, and HMGB1 were significantly higher in the observation group compared to the control group (all $P<0.05$). Among the sepsis patients, the severe and shock groups exhibited significantly elevated levels of H-FABP, sTREM-1, and HMGB1 compared to the mild group, with the shock group showing the highest levels (all $P<0.05$). The levels of H-FABP, sTREM-1, and HMGB1 were positively correlated with APACHE II scores ($r=0.760$, $r=0.715$, $r=0.709$, all $P<0.001$). Furthermore, the levels of these biomarkers were significantly higher in patients who died than in survivors (all $P<0.05$). The AUCs of H-FABP, sTREM-1, and HMGB1 for predicting prognosis were 0.786, 0.790, and 0.781, respectively. Their combined prediction yielded an AUC of 0.834. Log-rank test showed that the survival time of patients with different expression levels of sTREM-1 (<856.50 pg/ml, ≥856.50 pg/ml) and HMGB1 (<395.80 ng/ml, ≥395.80 ng/ml) were significantly different ($P<0.05$). Conclusion: Serum levels of H-FABP, sTREM-1, and HMGB1 are elevated in sepsis patients and closely associated with the disease severity, making them valuable biomarkers for monitoring the severity of sepsis. Combined detection of serum H-FABP, sTREM-1, and HMGB1 shows promising prognostic value in sepsis, with lower levels of sTREM-1 and HMGB1 linked to improved survival.

Keywords: Sepsis, H-FABP, sTREM-1, HMGB1, prognostic value

Introduction

Sepsis is a systemic inflammatory response syndrome caused by infection and is one of the common critical conditions, with high morbidity and mortality rates [1, 2]. Despite significant advancements in understanding the pathophysiology of sepsis and improvements in treatment strategies, the mortality rate of sepsis remains high [3, 4]. Early identification of high-risk groups is crucial for the early assessment and treatment of sepsis, improving patient outcomes and increasing treatment success rates.

Heart-type fatty acid binding protein (H-FABP), a soluble protein, has a similar function to myoglobin but with lower molecular weight, and is mainly found in cytoplasm. H-FABP was initially used in coronary heart disease and acute myocardial infarction (AMI). In recent years, it has also been used as a marker for myocardial damage in sepsis [5, 6]. When myocardial cells are damaged, H-FABP is quickly released from the myocardial layer into the circulatory system, and its presence in serum can detect even minor myocardial injury, making it a highly sensitive indicator for AMI [7]. It has been shown that H-FABP level is related to the severity of sepsis, reflecting the cardiac function of sepsis patients and helping to evaluate disease progression [8].

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Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) is mainly produced by the proteolytic cleavage of triggering receptor expressed on myeloid cells 1 (TREM-1), which mainly exists in blood and urine. During bacterial or fungal infections, sTREM-1 is upregulated in neutrophils and mature monocytes and released into biological fluids. In sepsis, an increase in sTREM-1 level is associated with the severity of infection and the extent of the inflammatory response, making it a useful biomarker reflecting disease activity [9, 10].

High mobility group box 1 protein (HMGB1), commonly present in the nuclei of various immune cells, endothelial cells, and epithelial cells, is a member of the integrin family and a representative damage-related molecular pattern (DAMP) [11, 12]. HMGB1 can be actively or passively released from activated monocytes/macrophages and necrotic cells. In a physiological state, HMGB1 binds nuclear chromosomes to regulate biologic gene transcription, participate in cell replication, differentiation, and maturation, and can activate the innate immune system independently of foreign pathogens. In sepsis and septic shock, HMGB1 plays a dual role: On the one hand, it triggers inflammation by inducing the production and release of other inflammatory mediators and lead to vascular endothelial cell damage. On the other hand, HMGB1 responds to early inflammatory signals, initiating a cascade reaction that exacerbates multi-organ damage. HMGB1 levels are typically elevated in sepsis, reflecting the severity of the systemic inflammatory response. This makes HMGB1 an important biomarker for assessing the severity of sepsis and disease activity [13, 14].

This study conducted a retrospective analysis of clinical data from sepsis patients treated at our institution. The aim of this study was to investigate the serum levels of H-FABP, sTREM-1, and HMGB1, explore their correlations with disease severity, and assess their prognostic value in sepsis patients.

Patients and methods

Ethical approval statement

This study was approved by the Ethics Committee of West China Hospital of Sichuan University. As it is a retrospective observational study, the clinical trial registration was exempted.

Patients

A retrospective analysis was conducted on the clinical data from 86 sepsis patients admitted to West China Hospital of Sichuan University between June 2021 and December 2023, and these cases constituted the observation group. Inclusion criteria: confirmed diagnosis of sepsis [15], Sequential Organ Failure Assessment (SOFA) score ≥2.0; and complete clinical documentation. Exclusion criteria: a history of organ transplantation; glucocorticoids use; presence of malignancy; or recent onset of acute infection. Additionally, 80 healthy individuals who underwent medical examinations at our hospital during the same period served as the control group. There were no significant differences in general demographic characteristics between the two groups (all P>0.05, **Table 1**).

Research methods

Serum levels of H-FABP, sTREM-1, and HMGB1 were measured as follows: A fasting venous blood sample of 10 ml was collected from each participant in the morning. The supernatant was carefully collected and stored in 2 ml clean, dry serum storage tubes, which were then frozen at -70°C until analysis. Enzyme-linked immunosorbent assays were used to quantify serum levels of H-FABP, sTREM-1, and HMGB1. H-FABP detection kit was purchased from Shanghai Baiyi Biotechnology Co., Ltd. (product number: by-B11179); STREM-1 test kit was purchased from Shanghai Bangjing Industrial Co., Ltd. (product number: BJ-E987883); HMGB1 detection kit was purchased from Shanghai Siger Biotechnology Co., Ltd. (product number: XG-E99197).

The severity of sepsis was categorized based on disease progression in accordance with established guidelines [16]. Mild sepsis: defined as systemic inflammatory response syndrome caused by confirmed or suspected infection; Severe sepsis: characterized by organ dysfunction and/or tissue hypoperfusion in the presence of sepsis; Septic shock: severe sepsis accompanied by irreversible hypotension that is unresponsive to treatment. According to these criteria, patients were categorized into mild group (n=42), severe group (n=28), and shock group (n=16). Patients were assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, with

Table 1. Comparison of general information between two groups

Group	Age (years)	Gender		BMI (kg/m^2)
		Male	Female	
Control group (n=80)	50.49±8.98	46	34	25.46±2.98
Observation group (n=86)	51.07±9.20	45	41	25.93±3.15
t/χ^2	0.411	0.448		0.986
P	0.682	0.503		0.326

Note: BMI: body mass index.

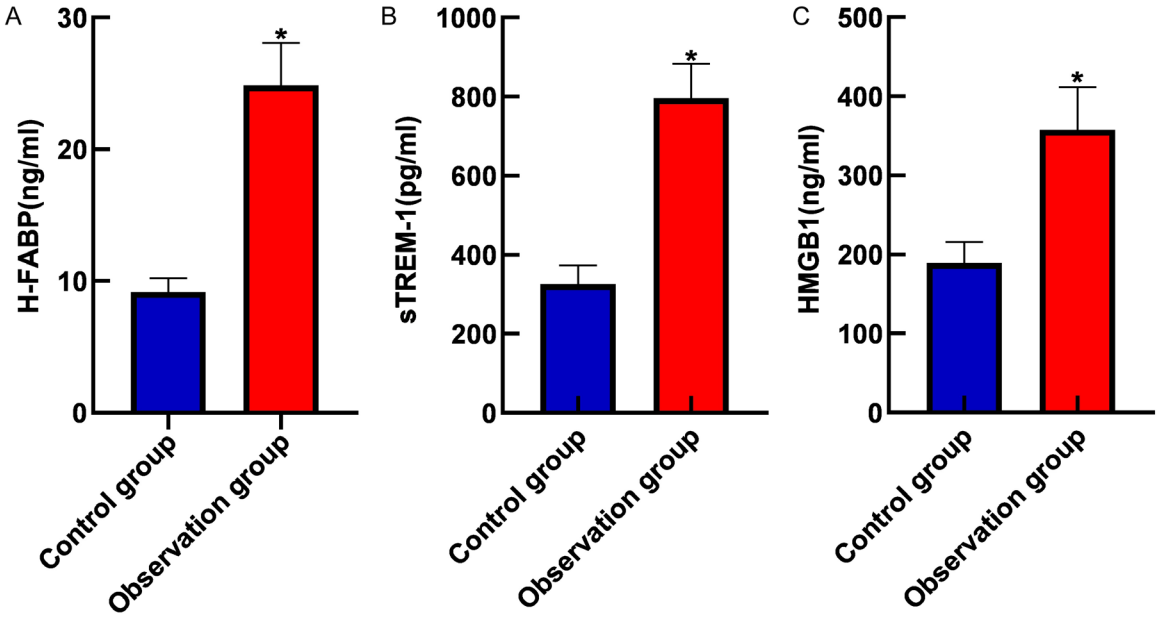

Figure 1. Comparison of serum H-FABP (A), sTREM-1 (B) and HMGB1 (C) levels between the two groups. Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein. *, P<0.05.

higher scores indicating more severe disease conditions.

Patients were followed up starting from admission on days 1, 3, and 5, and then weekly until day 28. Follow-up was conducted through outpatient visit and telephone contact. Based on these follow-up results, patients were categorized into survivors (n=60) and those who died (n=26).

Statistical methods

All data were analyzed using SPSS 22.0 statistical software, and GraphPad Prism 8 was used for graphical representation. Counted data were expressed as rates and compared using a chi-square test. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation and compared between groups using a T-test. Pearson correlation analysis was conducted to assess relationships between variables. ROC curve analysis was employed to evaluate the prognostic significance of serum levels of H-FABP, sTREM-1, and HMGB1 in sepsis patients. The Kaplan-Meier method was used to plot the survival curve, and a log-rank test was used to compare the survival time of sepsis patients with different levels of H-FABP, sTREM-1, and HMGB1. A *P*-value of less than 0.05 was considered significant.

Results

Comparison of serum levels of H-FABP, sTREM-1, and HMGB1 between the two groups

Compared to the control group, the observation group showed significantly elevated serum levels of H-FABP, sTREM-1, and HMGB1 (all P< 0.05), as shown in **Figure 1**.

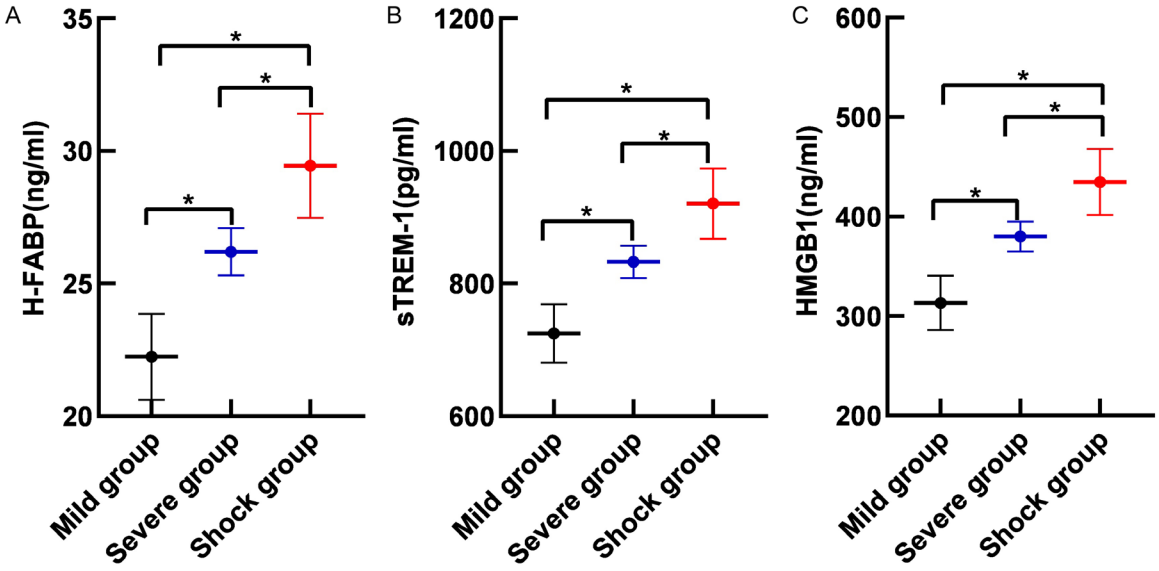

Figure 2. Comparison of serum H-FABP (A), sTREM-1 (B) and HMGB1 (C) levels in sepsis patients with different disease severity. Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein. *, P<0.05.

Comparison of serum levels of H-FABP, sTREM-1, and HMGB1 among sepsis patients of varying disease severity

The serum levels of H-FABP, sTREM-1, and HMGB1 were significantly higher in the severe and shock groups than those of the mild group, with the septic shock group exhibiting the highest levels (all P<0.05), as shown in **Figure 2**.

Correlation between serum H-FABP, sTREM-1, and HMGB1 levels and severity of sepsis

As shown in **Figure 3**, the serum levels of H-FABP, sTREM-1, and HMGB1 in sepsis patients were positively correlated with APACHE II scores (r=0.760, r=0.715, r=0.709, all P<0.001).

Comparison of serum levels of H-FABP, sTREM-1, and HMGB1 between sepsis patients with different outcomes

Compared to the sruvivors, patients who died exhibited significantly elevated serum levels of H-FABP, sTREM-1, and HMGB1 (all P<0.05, **Figure 4**).

Prognostic values of serum levels of H-FABP, sTREM-1, and HMGB1 in sepsis patients

ROC curve analysis revealed that serum H-FABP had an AUC of 0.786 (95% CI: 0.689-0.883), with an optimal cutoff value of 23.67 ng/ml and a Youden index of 0.512, yielding a sensitivity of 96.20% and specificity of 55.00% for predicting sepsis patient outcomes. Serum sTREM-1 showed an AUC of 0.790 (95% CI: 0.678-0.903), with an optimal cutoff value of 856.50 pg/ml and a Youden index of 0.532, achieving a sensitivity of 61.50% and specificity of 91.70%. Serum HMGB1 had an AUC of 0.781 (95% CI: 0.674-0.888), with an optimal cutoff value of 395.80 ng/ml and a Youden index of 0.494, showing a sensitivity of 57.70% and specificity of 91.70% for prognostic evaluation in sepsis patients. When combined, the three biomarkers yielded an AUC of 0.834 (95% CI: 0.739-0.930), with a Youden index of 0.549, sensitivity of 61.50%, and specificity of 93.40% for predicting patient outcome in sepsis. See **Table 2** and **Figure 5**.

Comparison of survival time of sepsis patients with different levels of H-FABP, sTREM-1, and HMGB1

Log-rank test showed that the survival time of patients with high and low expression levels of sTREM-1 (cut-off value at 856.50 pg/ml) and HMGB1 (cut-off value at 395.80 ng/ml) differed significantly (χ^2=5.576, 4.132, all P< 0.05). However, no significant difference was observed in the survival time of patients with high and low H-FABP expression levels (cut-off value at 23.67 ng/ml) (χ^2=3.234, P>0.05), as shown in **Figure 6**.

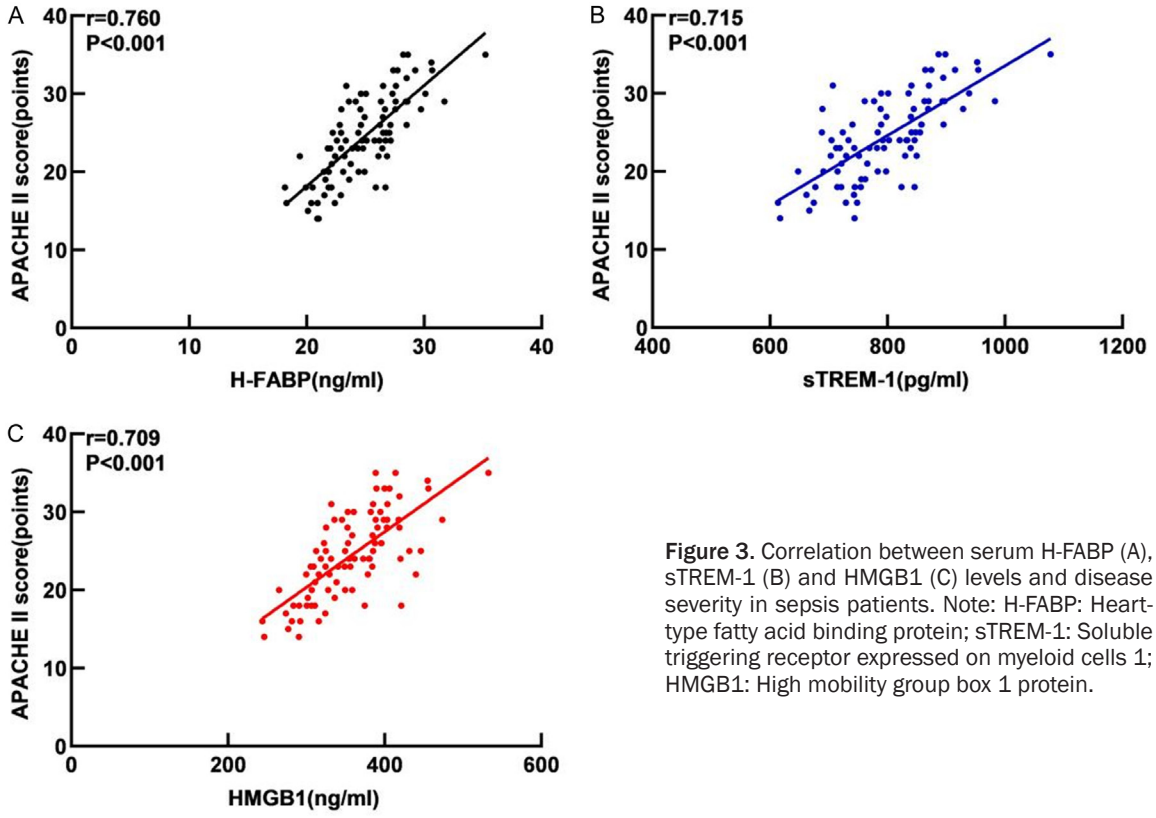

Figure 3. Correlation between serum H-FABP (A), sTREM-1 (B) and HMGB1 (C) levels and disease severity in sepsis patients. Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein.

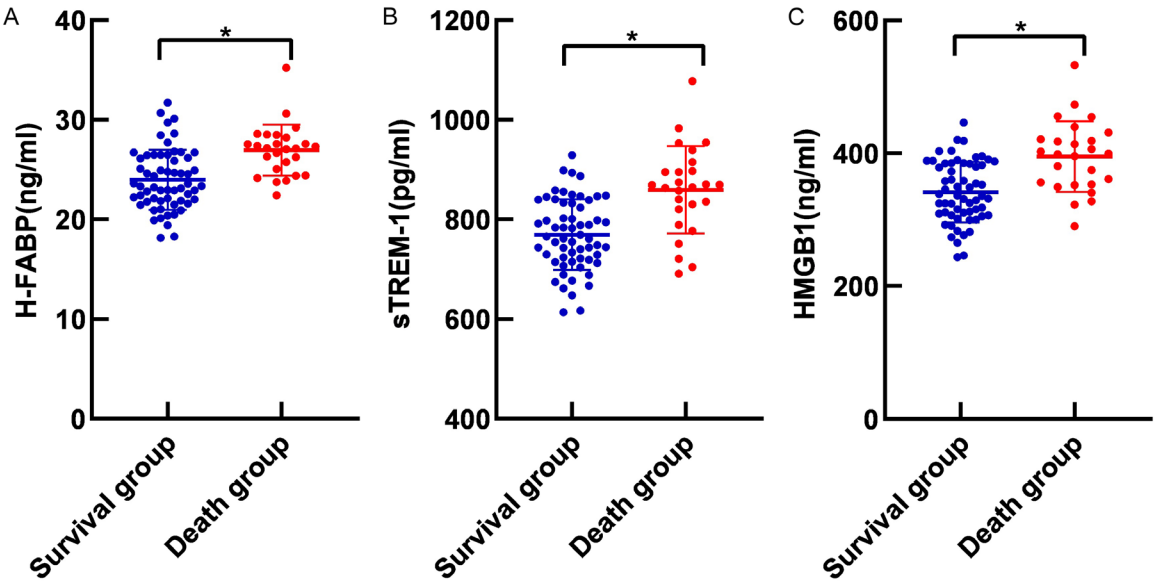

Figure 4. Serum H-FABP (A), sTREM-1 (B) and HMGB1 (C) levels in sepsis patients with different prognosis. Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein. *, P<0.05.

Discussion

Sepsis is characterized by acute onset, rapid disease progression, and high mortality rate. Its pathogenesis is complex, involving an imbalance in immune responses triggered by invading pathogens, leading to a pathologic syndrome marked by sustained excessive inflam-

Table 2. Prognostic values of serum H-FABP, sTREM-1 and HMGB1 levels in sepsis patients

Predictive index	AUC	95% CI	Youden index	Sensitivity (%)	Specificity (%)	Cut-off value
H-FABP	0.786	0.689-0.883	0.512	96.20	55.00	23.67 ng/ml
sTREM-1	0.790	0.678-0.903	0.532	61.50	91.70	856.50 pg/ml
HMGB1	0.781	0.674-0.888	0.494	57.70	91.70	395.80 ng/ml
Combined prediction	0.834	0.739-0.930	0.549	61.50	93.40	-

Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein.

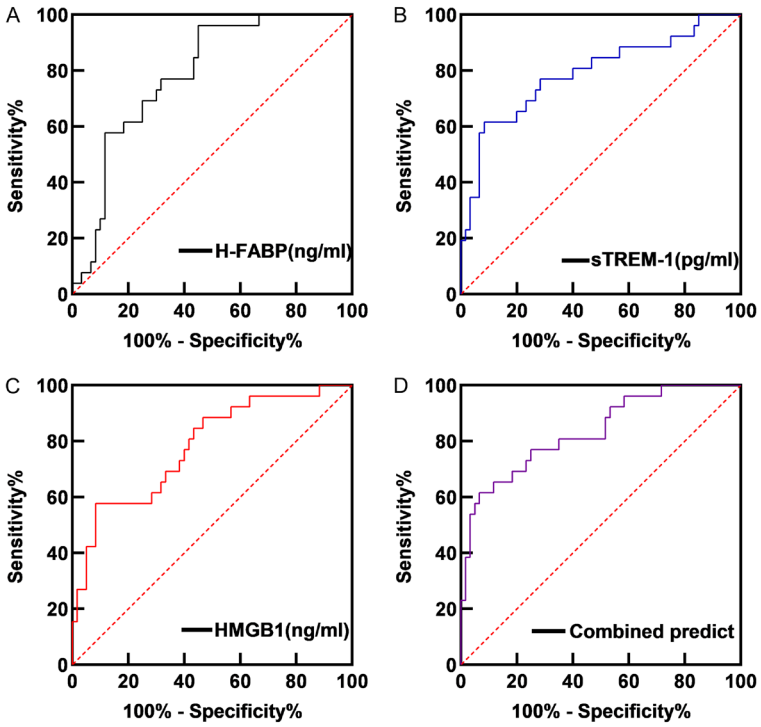

Figure 5. ROC curve of serum levels of H-FABP (A), sTREM-1 (B), HMGB1 (C) and Combined (D) in predicting the prognosis of sepsis patients. Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein.

Early immune dysregulation in sepsis may contribute to its challenging management and high clinical mortality rate [19, 20]. At present, most of the clinical diagnostic methods for sepsis patients have low specificity and show obvious shortcomings in assessing disease severity and treatment efficacy, failing to meet the current clinical needs [21, 22]. Early identification and diagnosis can reduce the likelihood of sepsis progressing to septic shock. Therefore, finding a diagnostic method with high sensitivity and specificity is crucial for improving the prognosis of sepsis. Commonly used indicators in clinical practice to assess the prognosis of sepsis patients include APACHE II score and SOFA score [23, 24]. Thus, this study utilized the APACHE II score to evaluate the severity of illness in sepsis patients.

mation and immune suppression. Sepsis exhibits complex changes in clinical progression, necessitating further investigation into its pathophysiologic mechanisms. Studies [17] show that during infection, the immune system is activated and imbalance in immune system regulation plays a key role in the occurrence, development, and prognosis of sepsis. Disruption of physiological homeostasis triggers the release of numerous pro-inflammatory cytokines, leading to a cascade of inflammatory responses [18]. This can result in severe dysfunction of multiple organ systems, such as cardiovascular, pulmonary, coagulation, and digestive systems, posing life-threatening risks.

H-FABP is a cytoplasmic protein abundant in myocardial cells, with specific immunological characteristics and molecular structure. It functions as a carrier for long-chain fatty acids in the cytoplasm, facilitating their entry into mitochondria for oxidation. When myocardial cells are damaged, H-FABP levels increase, as the body mobilizes fatty acids to supply energy, which then enter circulation through endothelial channels. Shortly after cellular damage, it is rapidly released from myocardial cells into circulation, leading to a rapid increase of H-FABP in the blood [25, 26]. Previous studies [27] have confirmed that most sepsis patients are accompanied by symptoms of myocardial inju-

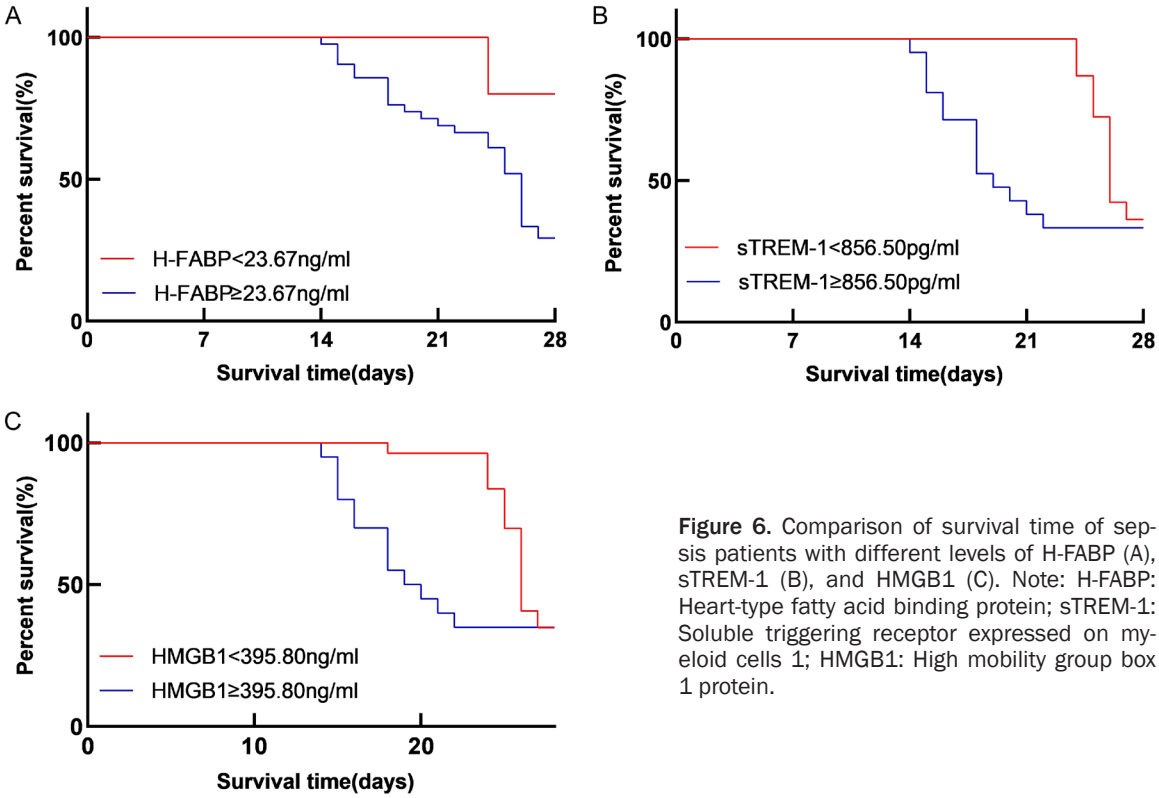

Figure 6. Comparison of survival time of sepsis patients with different levels of H-FABP (A), sTREM-1 (B), and HMGB1 (C). Note: H-FABP: Heart-type fatty acid binding protein; sTREM-1: Soluble triggering receptor expressed on myeloid cells 1; HMGB1: High mobility group box 1 protein.

ry, though there has been limited research specifically evaluating H-FABP levels to assess the severity of sepsis. The findings of this study demonstrate a significant elevation in serum H-FABP levels in sepsis patients, with H-FABP levels showing a significant positive correlation with APACHE II scores. This suggests that higher levels of H-FABP are associated with increased disease severity. Zhang et al. [28] reported that H-FABP, as a biomarker of myocardial injury and systemic inflammatory reaction, was significantly increased in sepsis patients, positively correlated with the severity of the disease. The analysis suggests that the extensive presence of H-FABP across multiple organs and tissues contributes to its role as a serum biomarker for assessing the severity of sepsis. Following myocardial cell damage, H-FABP is released into the bloodstream, resulting in an increased serum concentration of H-FABP. This underscores the utility of H-FABP as an indicator of sepsis severity.

TREM-1 is primarily expressed on the surface of mature neutrophils, monocytes, and macrophages, and plays a key role in promoting inflammation. TREM-1 is an important factor in triggering and inducing an inflammatory cascade reaction by promoting the production and release of inflammatory mediators [29, 30]. STREM-1 is one of the secretory subtypes of TREM-1, which is likely formed by hydrolyzing the extracellular segment of TREM-1 on the cell membrane by matrix metalloproteinases [31-33]. sTREM-1 exists as a soluble form of TREM-1. It has a deletion of three extracellular potential N-linked glycosylation sites, the transmembrane segment, and the intracellular segment, and is a splice variant of TREM-1 that is released into blood and body fluids during infection [34, 35]. Bellos et al. [36] found that the level of sTREM-1 was significantly increased in sepsis patients and closely related to the disease severity, which is consistent with the results in our study that an elevated sTREM-1 level in septic patients was positively correlated with APACHE II scores, suggesting that higher sTREM-1 levels are associated with greater disease severity. The analysis suggests that infection-induced upregulation of TREM-1 on cell surfaces, in synergy with Toll-like receptors, triggers and amplifies the production of inflammatory factors, consequently elevating sTREM-1 levels. Therefore, sTREM-1 serves as a useful serum biomarker for monitoring the severity of sepsis.

HMGB1 is a DNA-binding protein primarily existing in the nucleus and plays a role in maintaining nucleosome integrity and promoting gene transcription. Beyond its role in regulating gene expression and cellular motility, HMGB1 also participates in modulating inflammatory and immune responses. It can be released into the extracellular matrix by granulocytes or necrotic cells and act as a chemotactic cytokine during infection, hypoxia, and ischemia-reperfusion, thereby promoting inflammatory response, aggravating septic shock, and increasing the risk of poor prognosis in affected patients [37]. HMGB1 can also polarize Th2 cells by regulating T cell activation, causing inflammatory factors to escape immune system monitoring [38]. Previous literature has shown that HMGB1 is associated with the development of encephalitis, arthritis, and sepsis, where it acts as a late inflammatory mediator [39]. HMGB1 exhibits potent pro-inflammatory activity and plays a crucial role as an inflammatory cytokine and important mediator in the process of inflammatory immune responses, closely linked to the occurrence of sepsis [40]. The pro-inflammatory function and characteristics of HMGB1 hold greater potential for clinical application than some early inflammatory mediators. Research indicates that HMGB1 is closely associated with inflammatory responses, mediating the release of various inflammatory mediators and cytokines [41]. Moreover, studies suggest that inhibiting HMGB1-induced inflammation can protect intestinal barrier integrity and alleviate gastrointestinal dysfunction in septic animals [42]. These findings propose HMGB1 as a novel therapeutic target for treating intestinal mucosal barrier damage in sepsis, positioning it as a potential therapeutic target in sepsis research models. In recent years, targeting HMGB1 has been recognized for its significant role in modulating the inflammatory cytokine profile and its correlation with sepsis prognosis. Qiang et al. [43] reported that increased HMGB1 level was closely related to the severity and prognosis of sepsis patients. HMGB1 can aggravate sepsis by promoting the release of inflammatory mediators, a mechanism also verified in our study, suggesting its use as a powerful biomarker for prognosis evaluation of sepsis. The findings of this study reveal significantly elevated serum levels of HMGB1 in septic patients, which correlate positively with APACHE II scores. This can be explained by HMGB1's dual role as a pro-inflammatory mediator that activates inflammation and promotes tissue repair. Following inflammation, injury, or stress, HMGB1 can be passively released from necrotic cells or actively secreted by activated inflammatory cells.

The ROC curve analysis in this study revealed that the AUCs of serum H-FABP, sTREM-1, and HMGB1 for predicting prognosis were 0.786, 0.790, and 0.781, respectively. When combined, these three biomarkers achieved an AUC of 0.834. These findings indicate that the combined assessment of these biomarkers significantly improves the prognostic evaluation compared to each single marker, highlighting their enhanced diagnostic value. The survival time of patients with sTREM-1≥856.50 pg/ml and HMGB1≥395.80 ng/ml was notably shorter than that of patients with sTREM-1<856.50 pg/ml and HMGB1<395.80 ng/ml. This indicates that patients with low levels of sTREM-1 and HMGB1 have better survival.

The limitations of this study are as follows: First, this was a single-center study, and the results may be influenced by regional factors and local healthcare conditions, which inevitably introduces limitations. Therefore, multi-center and multi-regional clinical studies are needed to further validate the findings. Second, as a retrospective study, the collected data may have inherent limitations. Prospective studies or randomized controlled trials are needed to better control confounding factors. Additionally, this study did not assess the dynamic changes in the observed indicators, so further large-scale experiments and dynamic observational studies are required. Lastly, the sample size of this study was relatively small,soexpanding the sample size is necessary to improve the accuracy of the research.

Conclusion

Serum levels of H-FABP, sTREM-1, and HMGB1 are consistently elevated in patients with sepsis, and these levels exhibit a close correlation with disease severity. Higher serum levels of H-FABP, sTREM-1, and HMGB1 are indicative of more severe disease, establishing them as critical serum biomarkers for monitoring the severity of sepsis. Finally, lower levels of sTREM-1 and HMGB1 predict longer survival of septic patients.

Disclosure of conflict of interest

None.

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