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Heart-type fatty acid binding protein (H-FABP) as an early biomarker in sepsis-induced cardiomyopathy: a prospective observational study

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Abstract

Background Sepsis-induced cardiomyopathy (SICM) is a common and life-threatening complication of sepsis, significantly contributing to elevated mortality. This study aimed to identify crucial indicators for the prompt and early assessment of SICM.

Methods Patients diagnosed with sepsis or SICM within 24 h of intensive care unit (ICU) admission were enrolled in this prospective observational study. Patients were assigned to the training set, validation set and external test set. The primary endpoint was 7-day ICU mortality, and the secondary endpoint was 28-day ICU mortality. Three machine learning algorithms were utilized to identify relevant indicators for diagnosing SICM, incorporating 64 indicators including serum biomarkers associated with cardiac, renal, and liver function, lipid metabolism, coagulation, and inflammation. Internal and external validations were performed on the screening results. Patients were then stratified based on the cut-off value of the most diagnostically effective biomarker identified, and their prognostic outcomes were observed and analyzed.

Results A total of 270 patients were included in the training and validation set, and 52 patients were included in the external test set. Age, sex, and comorbidities did not significantly differ between the sepsis and SICM groups ($P > 0.05$). The support vector machine (SVM) algorithm identified six indicators with an accuracy of 84.5%, the random forest (RF) algorithm identified six indicators with an accuracy of 81.9%, and the logistic regression (LR) algorithm screened out seven indicators. Following rigorous selection, a diagnostic model for sepsis-induced cardiomyopathy was established based on heart-type fatty acid binding protein (H-FABP) (OR 1.308, 95% CI 1.170–1.462, $P < 0.001$) and retinol-binding protein (RBP) (OR 1.020, 95% CI 1.006–1.034, $P < 0.05$). H-FABP alone exhibited the highest diagnostic performance in both the internal (AUROC 0.689, $P < 0.05$) and external sets (AUROC 0.845, $P < 0.05$). Patients with SICM were further stratified based on an H-FABP diagnostic cut-off value of 8.335 ng/mL. Kaplan–Meier curve analysis demonstrated that elevated H-FABP levels at admission were associated with higher 7-day ICU mortality in patients with SICM ($P < 0.05$).

Conclusions This study revealed that H-FABP concentrations measured within 24 h of patient admission could serve as a crucial biomarker for the early and rapid diagnosis and short-term prognostic evaluation of SICM.

Keywords Heart-type fatty acid binding protein, Sepsis-induced cardiomyopathy, Biomarker, Machine learning

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Background

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, poses a significant challenge in clinical management due to its atypical clinical presentation and the difficulty in achieving timely diagnosis [1]. With mortality rates ranging from 15 to 20%, sepsis has emerged as a leading cause of death among critically ill patients [1, 2]. Sepsis-induced cardiac dysfunction, also known as sepsis-induced cardiomyopathy (SICM), has been a focal point of research. Its prevalence varies from 10 to 70% and is primarily characterized by left ventricular dilatation, normal or decreased filling pressures, reduced ventricular contractility, both left and right ventricular dysfunction, and diminished responsiveness to volume [3, 4]. Importantly, studies have shown that the mortality rate among patients with sepsis and myocardial injury is three times higher than among those without cardiovascular involvement [5].

The physiological abnormalities and pathophysiological mechanisms of sepsis-induced myocardial dysfunction remain uncertain. Currently, left ventricular systolic function is routinely evaluated by the left ventricular ejection fraction (LVEF) determined by echocardiography. However, LVEF and other ultrasonic assessments, while noninvasive, are largely susceptible to loading conditions, potentially limiting their utility as an indicator of left ventricular performance [6]. Moreover, not all primary healthcare facilities are equipped with echocardiography machines and trained personnel, presenting obstacles to its widespread adoption. Consequently, there is an urgent need for early, rapid and cost-effective methods to evaluate the condition of SICM.

Serum biomarkers, due to their simple and rapid detection, are widely used in clinical practice to evaluate patient conditions. This study aimed to identify key indicators from multiple biomarkers to facilitate the early and rapid diagnosis and prognostic evaluation of SICM, thereby aiding in the treatment of patients.

Methods

Study population

Patients who were diagnosed with sepsis or SICM within 24 h of admission to the intensive care unit (ICU) between January 2021 and May 2024 were enrolled in this prospective observational study (Fig. 1). The exclusion criteria were: (1) patients aged under 18 years, (2) ICU stay less than 24 h, and (3) withdrawal of treatment for any reason during hospitalization. Patients enrolled from Nanjing Medical University First Affiliated Hospital were assigned to the training and validation set, while patients from the Second Affiliated Hospital of Harbin Medical University were included in the external test set.

The definition of the SICM

The diagnostic criteria for sepsis-induced cardiomyopathy were as follows: (1) Sepsis was diagnosed according to the definition of sepsis-3 [1]. (2) Patients had no history of other pre-existing heart conditions, including acute coronary syndrome, chronic cardiac dysfunction, severe heart valve disease, severe arrhythmia, hypertensive heart disease, congenital heart disease, rheumatic heart disease, infective endocarditis, myocarditis, or any other form of cardiomyopathy (such as hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, or stress cardiomyopathy). (3) Patients exhibited an LVEF < 50% [6].

Preparation of blood samples and data collection

Demographic information, clinical data, blood samples, and echocardiographic measurements were obtained within 24 h of enrollment. Blood samples were centrifuged at 3000 × g for 5 min at 4 °C, and the upper layer of serum was collected and stored at -80 °C. The biomarkers involved in the study were systematically measured by the laboratory at the First Affiliated Hospital of Nanjing Medical University and the Second Affiliated Hospital of Harbin Medical University using blood samples from enrolled patients. The enzyme-linked immunosorbent assay (ELISA) kits were manufactured by Shanghai Enzyme-linked Biotechnology and Joinstar Biomedical Technology in China. Clinical data of patients were collected and recorded from the electronic monitoring system. The primary endpoint was 7-day ICU mortality, and the secondary endpoint was 28-day ICU mortality.

Construction of the diagnostic model

A total of sixty-four indicators, including biomarkers related to cardiac, renal, and liver function, lipid metabolism, coagulation, and inflammation, were analyzed. Three machine learning classifiers—support vector machine (SVM), random forest (RF), and logistic regression (LR)—were employed to identify the most relevant biomarkers for the diagnosis of SICM. Subsequently, a diagnostic model based on multivariate logistic regression analysis was established, and both internal and external validations were conducted to assess the diagnostic performance of the model.

Echocardiography measurements

Echocardiographic examinations were conducted according to a standardized protocol based on guidelines from the American and European Society of Echocardiography

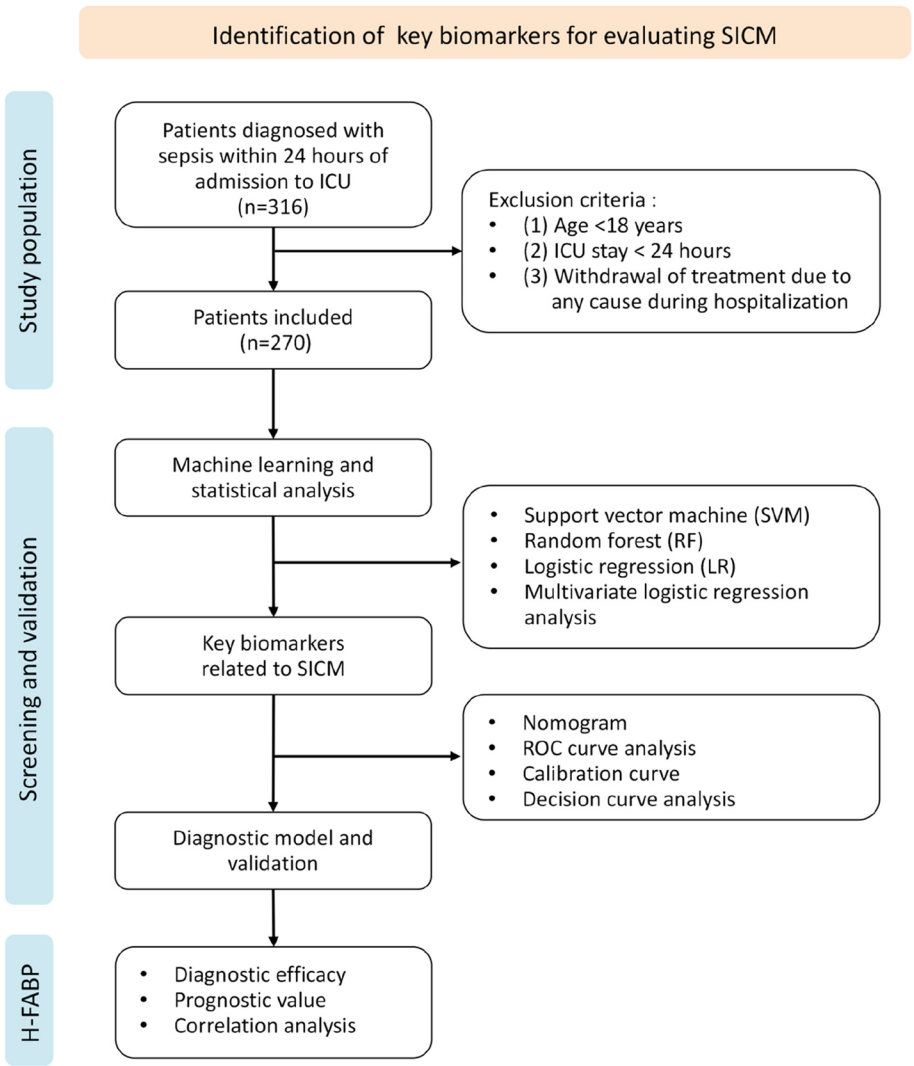

Fig. 1 Study flow chart

[7, 8]. All measurements were performed by experienced physicians proficient in echocardiography.

Statistical analysis

Data analysis and figure construction were performed using IBM SPSS Statistics 27 and R 4.4.1. Normally distributed continuous variables are presented as mean and standard deviation, while non-normally distributed continuous variables are presented as median and interquartile range. Group comparisons for normally distributed data were conducted using the independent sample t-test, whereas the Mann–Whitney U test was employed for non-normally distributed data. Categorical variables are presented as counts (percentages) and were analyzed using the chi-square test to determine significance. Three machine learning classifiers—SVM, RF, and LR—were utilized to identify indicators strongly associated with the diagnosis of sepsis-induced cardiomyopathy. A diagnostic model was constructed using multivariate logistic regression and tested for significance with a likelihood ratio test (forward: LR). The performance and clinical utility of the nomogram were evaluated using receiver operating characteristic (ROC) curve analysis, calibration curve analysis, and decision curve analysis (DCA). DeLong's test was used to compare differences between ROC curves. Spearman correlation analysis was conducted to assess the correlation between biomarkers and clinical indicators. Kaplan–Meier survival analysis was performed by the log-rank test. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

Results

Characteristics of the study population

This study included 316 patients admitted to the ICU of the First Affiliated Hospital of Nanjing Medical University. Forty-six patients were excluded according to our inclusion and exclusion criteria, and 270 patients were ultimately enrolled (Fig. 1). The patients were stratified into two groups: the sepsis group ($n=214$) and the SICM group ($n=56$), according to established definitions. There were no significant differences in age, sex, or comorbidities between the sepsis and SICM groups. Upon admission, cardiac biomarkers such as pro-B-type natriuretic peptide (pro-BNP), troponin T (TNT), and heart-type fatty acid binding protein (H-FABP) were significantly elevated in the SICM group compared to the sepsis group (2054.0 pg/mL vs. 672.8 pg/mL, $P<0.05$; 58.9 ng/L vs. 33.6 ng/L, $P<0.05$; 6.3 ng/mL vs. 4.7 ng/mL, $P<0.001$, respectively). Echocardiographic parameters, including stroke volume (SV) and LVEF, were significantly reduced in the SICM group compared to the sepsis group (41.7 mL vs. 54.4 mL, $P<0.05$; 43.2% vs. 64.2%, $P<0.001$, respectively; Table 1 and the complete data of the 64 indicators is shown in Table S1).

Table 1 Clinical characteristics of the study population

Characteristics	Sepsis	SICM	*P* value
n	214	56	
Male sex, n (%)	151 (70.6)	41 (73.2)	0.822
Age (years)	65 (51, 77)	64 (56, 78)	0.571
Comorbidity, n (%)			
Pulmonary infection (%)	85 (39.7)	19 (33.9)	0.523
Abdominal infection (%)	27 (12.6)	5 (8.9)	0.597
Cerebral hemorrhage (%)	75 (35.0)	19 (33.9)	1.000
Renal insufficiency (%)	19 (8.9)	5 (8.9)	1.000
Operation (%)	56 (26.2)	13 (23.2)	0.78
APACHE II score	20 (15, 25)	18(16, 24)	0.225
WBC (×10^9/L)	9.2 (6.8, 13.3)	9.2 (6.4, 12.1)	0.725
NEUT (%)	82.1 (76.1, 87.5)	81.7 (75.3, 88.0)	0.946
LYMPH (×10^9/L)	0.8 (0.5, 1.2)	0.9 (0.5, 1.2)	0.928
PCT (ng/mL)	0.4 (0.1, 2.0)	0.5 (0.1, 2.1)	0.885
CRP (mg/L)	83.6 (33.9, 126.8)	63.4 (22.0, 99.6)	0.072
H-FABP (ng/mL)	4.7 (3.1, 6.7)	6.3 (4.2, 11.0)	< 0.001
Pro-BNP (pg/mL)	672.8 (181.3, 3224.2)	2054.0 (331.1, 7758.5)	0.014
TNT (ng/L)	33.6 (15.4, 86.2)	58.9 (22.9, 133.5)	0.007
CK-MB (ng/mL)	1.8 (1.0, 3.7)	2.1 (1.2, 3.0)	0.577
MYO (ng/mL)	142.8 (66.2, 442.4)	129.2 (83.5, 346.1)	0.931
LVEF (%)	64.2 (58.5, 72.7)	43.2 (33.1, 45.8)	< 0.001
SV (ml)	54.4 (39.9, 72.4)	41.7 (32.4, 64.4)	0.003
TAPSE (cm)	2.2 (0.7)	2.0 (0.7)	0.044
MAPSE (cm)	1.3 (1.1, 1.6)	1.2 (1.0, 1.4)	0.006
ALT (U/L)	23.0 (13.7, 52.9)	24.2 (13.9, 48.9)	0.732
AST (U/L)	33.8 (22.6, 61.4)	35.7 (23.6, 65.3)	0.566
ALP (U/L)	82.0 (62.2, 111.8)	82.0 (62.5, 120.0)	0.521
GGT (U/L)	38.4 (19.9, 79.9)	69.4 (27.2, 97.5)	0.017
TBIL (μmol/L)	12.7 (8.5, 19.1)	12.6 (8.8, 17.1)	0.872
Cr (μmol/L)	79.2 (57.2, 117.3)	84.4 (62.0, 178.5)	0.153
Urea (mmol/L)	9.0 (6.3, 15.2)	11.7 (7.5, 15.1)	0.143
RBP (mg/L)	23.8 (15.8, 33.0)	29.0 (19.2, 49.9)	0.007

WBC White blood cell count, *NEUT* Neutrophilic granulocyte, *LYMPH* Lymphocyte, *PCT* Procalcitonin, *CRP* C-reactive protein, *H-FABP* Heart-type fatty acid binding protein, *Pro-BNP* Pro-B-type natriuretic peptide, *TNT* Troponin T, *CK-MB* Creatine kinase-MB, *MYO* Myoglobin, *LVEF* Left ventricular ejection fraction, *SV* Stroke volume, *TAPSE* Tricuspid annular plane systolic excursion, *MAPSE* mitral annular plane systolic excursion, *ALT* Alanine aminotransferase, *AST* Aspartate transaminase, *ALP* Alkaline posphatase, *GGT* Gamma-glutamyltransferase, *TBIL* Total bilirubin, *Cr* Creatinine, *RBP* Retinol-binding protein

Screening indicators for the diagnosis of sepsis-induced cardiomyopathy

The SVM algorithm identified six indicators with an accuracy of 84.5% (Fig. 2A and Table S2). The RF algorithm identified six indicators with an accuracy of 81.9% (Fig. 2B and Table S2). The LR algorithm screened out seven indicators (Table 2). The intersection of the three algorithms was determined (Fig. 2C), and the resulting two indicators were subjected to multivariate logistic regression analysis. Finally, H-FABP (OR 1.308, 95% CI 1.170–1.462, $P<0.001$) and retinol-binding protein (RBP) (OR 1.020, 95% CI 1.006–1.034, $P<0.05$) were identified as the most relevant indicators for the diagnosis of SICM (Table 2).

Construction and validation of the diagnostic model for sepsis-induced cardiomyopathy

Patients were randomly divided into a training set and a validation set at a ratio of 6:4. A diagnostic nomogram model with two predictors was constructed (Fig. 3A). The area under the receiver operating characteristic curve (AUROC) of our diagnostic model, which was established by H-FABP and RBP was 0.722 (Fig. 3B). The calibration curve demonstrated good agreement between the predicted and actual probabilities of SICM (Fig. 3C). Decision curve analysis indicated a high net benefit and clinical decision effectiveness (Fig. 3D). The diagnostic performance of the model was further verified in the validation set (Fig. 3E-G).

Comparison of biomarkers and external validation

The ROC curve analysis revealed that the combined diagnostic performance of H-FABP and RBP for SICM (AUROC 0.697, $P<0.001$) was not significantly better than that of H-FABP (AUROC 0.689, $P<0.001$) alone (Fig. 4A, DeLong test, $P>0.05$). Given the excellent diagnostic performance of H-FABP, we further validated its diagnostic efficacy using an external test set of 52 patients from another center. Patients in the test set were selected based on the same inclusion and exclusion criteria, and the levels of H-FABP, as well as cardiac biomarkers pro-BNP and troponin I (TNI) were measured (Table 3). Notably, H-FABP exhibited the highest AUROC (AUROC 0.845, $P<0.05$) among these

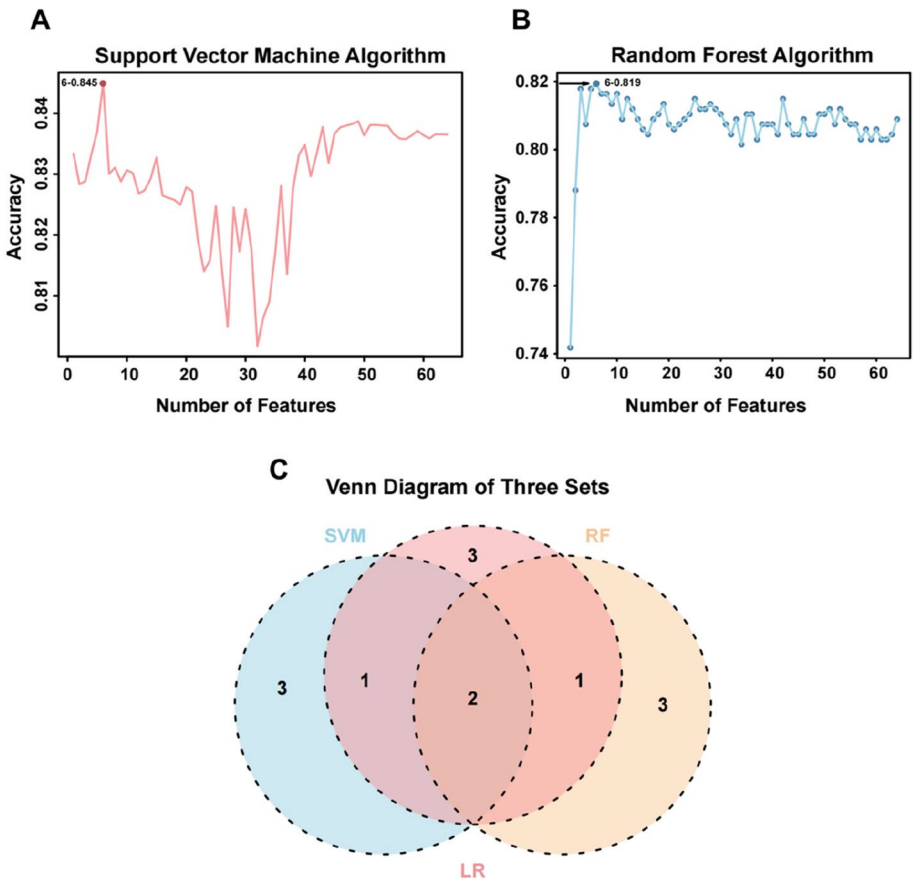

Fig. 2 Performance of machine learning algorithms. **A** and **B** are the results of the SVM and RF methods, respectively. **C** The Venn diagram illustrates the intersection of the results from the three machine learning algorithms

Table 2 Univariate and multivariate logistic regression analyses

Characteristics	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
APACHE II score	0.974	0.928-1.023	0.298			
WBC (×10^9/L)	0.981	0.924-1.041	0.523			
NEUT (%)	0.998	0.972-1.025	0.902			
LYMPH (×10^9/L)	0.950	0.612-1.475	0.82			
PCT (ng/mL)	0.999	0.983-1.015	0.876			
CRP (mg/L)	0.998	0.994-1.002	0.342			
H-FABP (ng/mL)	1.334	1.197-1.488	<0.001	1.308	1.170-1.462	<0.001
Pro-BNP (pg/mL)	1.000	1.000-1.000	0.004			
TNT (ng/L)	1.001	1.000-1.001	0.015			
CK-MB (ng/mL)	1.003	0.993-1.012	0.59			
MYO (ng/mL)	1.000	0.999-1.000	0.462			
ALT (U/L)	1.000	0.999-1.002	0.814			
AST (U/L)	1.001	1.000-1.001	0.204			
ALP (U/L)	1.003	1.000-1.006	0.048			
GGT (U/L)	1.004	1.001-1.007	0.013			
TBIL (μmol/L)	0.998	0.991-1.006	0.697			
Total Protein (g/L)	1.048	1.010-1.088	0.013			
Cr (μmol/L)	1.002	1.000-1.004	0.069			
Urea (mmol/L)	1.017	0.985-1.051	0.297			
RBP (mg/L)	1.024	1.010-1.037	<0.001	1.020	1.006-1.034	0.005

OR odds ratio, *CI* confidence interval

conventional biomarkers, indicating its novel and significant diagnostic efficacy for sepsis-induced cardiomyopathy (Fig. 4B).

Prognostic value of H-FABP in patients with sepsis-induced cardiomyopathy

Since the high diagnostic efficacy of H-FABP in SICM has been established, further analysis was continued to explore whether H-FABP levels measured within 24 h of patient admission could serve as an early prognostic biomarker for SICM. Accordingly, patients were stratified based on an H-FABP diagnostic cut-off value of 8.335 ng/mL, and their clinical outcomes were observed and recorded (Table 4). The *P*-value for comparing 7-day ICU mortality between patients in the high H-FABP group and those in the low H-FABP group was 0.013. The continuity correction (Yates' Correction for Continuity) was adopted to mitigate the potential bias of the Pearson chi-square test in small sample sizes, resulting in a *P*-value of 0.050. No significant difference was observed in 28-day ICU mortality between the two groups ($P > 0.05$). Kaplan–Meier curves were constructed using 7-day and 28-day survival outcomes as endpoints (Fig. 5). The results showed that patients with lower H-FABP levels exhibited significantly better 7-day survival outcomes than those with higher H-FABP levels ($P < 0.05$). However, no significant differences were observed in the 28-day survival outcomes.

Discussion

In this prospective observational study involving patients with sepsis and sepsis-induced cardiomyopathy, a diagnostic model containing H-FABP and RBP was established. Notably, H-FABP concentrations measured within 24 h of patient admission demonstrated significant diagnostic accuracy and short-term prognostic value for patients with SICM, offering crucial clinical insights into the early and rapid evaluation of SICM.

Sepsis is an inflammatory state, and inflammatory cell infiltration can be observed in all affected organs to some extent, which can lead to cardiotoxicity and cardiomyocyte injury, resulting in the release of H-FABP. In addition, in septic patients, the catabolism of glycogen and lipids can lead to a direct elevation in the concentration of free fatty acids, and simultaneously, lipid dysregulation and the liberation of free radicals may contribute significantly to the increase of H-FABP levels [9]. To further elucidate the clinical significance of H-FABP in sepsis, we conducted a correlation analysis between H-FABP and commonly used clinical indicators in 270 septic patients (see Fig. S1). The results demonstrated a significant

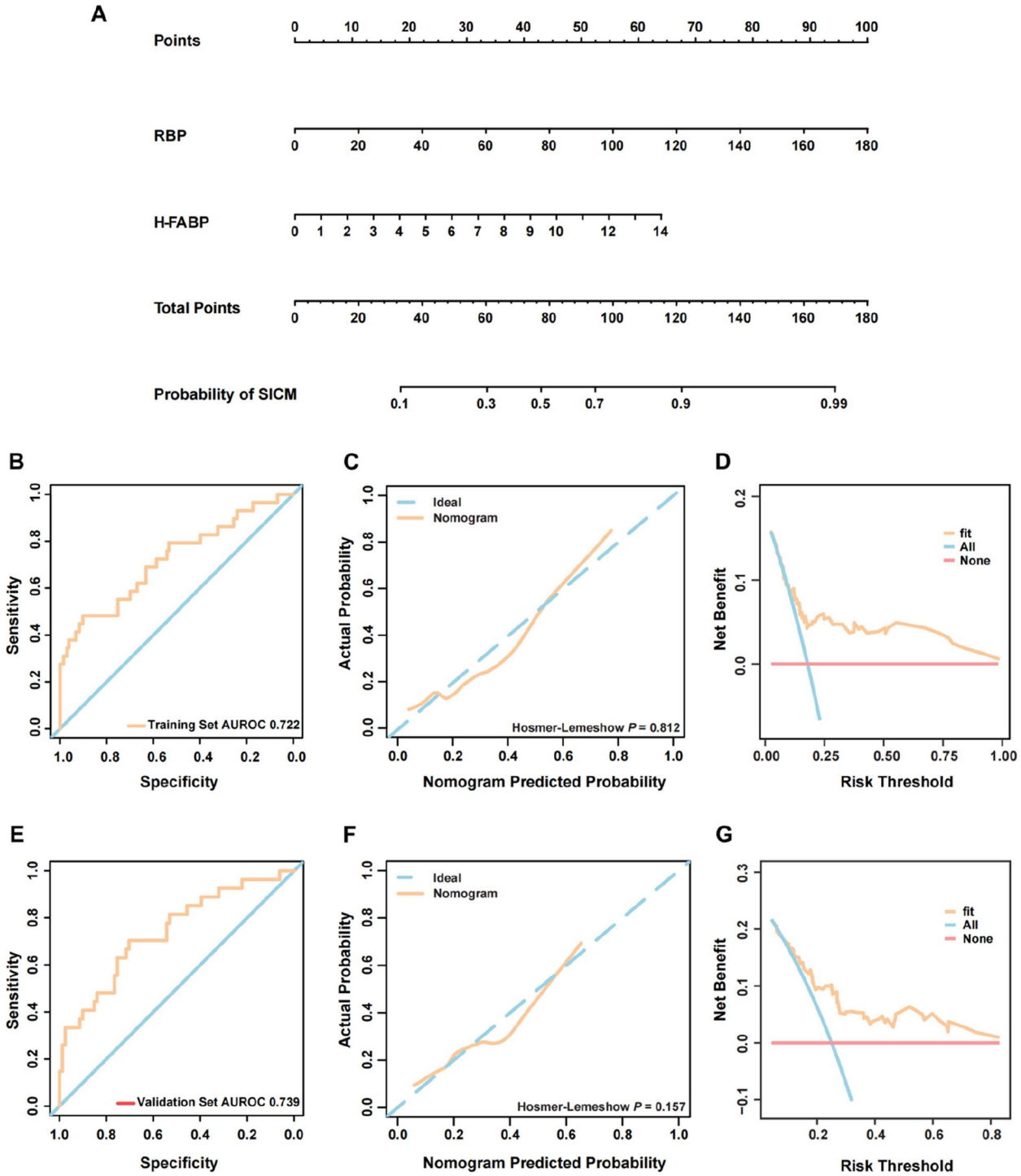

Fig. 3 Establishment and validation of a diagnostic model for SICM. **A** Nomogram of H-FABP and RBP for the prediction of SICM. Each indicator was assigned a corresponding score, and the "total points" were calculated by integrating the two indicators. **B**, **C** and **D** show the ROC curve, calibration curve and decision curve analysis of the model in the training set. The performance of the internal validation of the model in the validation set is shown in (**E**–**G**)

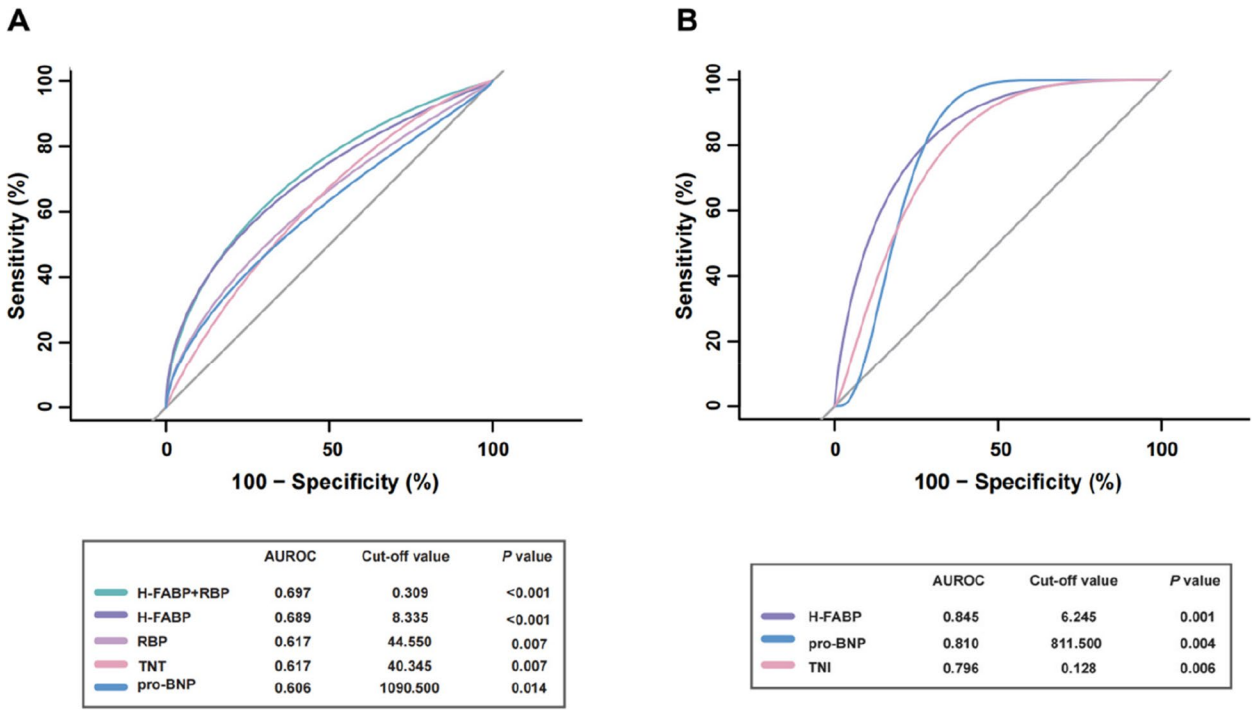

Fig. 4 ROC curve analysis of indicators related to the diagnosis of SICM. **A** ROC curve analysis of patients in the training set and validation set. **B** ROC curve analysis of patients in the external test set

Table 3 Clinical characteristics of the study population in the external test set

Characteristics	Sepsis	SICM	P value
n	43	9	
Male sex, n (%)	27 (62.8)	6 (66.7)	1.000
Age (years)	62 (10.8)	63 (17.7)	0.746
Comorbidity, n (%)			
Pulmonary infection	20 (46.5)	4 (44.4)	1.000
Abdominal infection	10 (23.3)	2 (22.2)	1.000
Cerebral hemorrhage	8 (18.6)	0 (0.0)	0.369
Renal insufficiency	12 (27.9)	2 (22.2)	1.000
Operation	4 (9.3)	1 (11.1)	1.000
WBC (×10^9/L)	13.1 (9.1, 15.8)	10.6 (7.9, 14.1)	0.282
NEUT (%)	87.6 (84.2, 91.8)	86.0 (69.9, 89.1)	0.266
LYMPH (×10^9/L)	1.0 (0.7, 1.4)	1.1 (0.9, 1.4)	0.570
PCT (ng/mL)	1.0 (0.1, 6.4)	0.2 (0.2, 0.3)	0.234
CRP (mg/L)	68.5 (15.6, 131.1)	35.9 (12.2, 70.8)	0.339
H-FABP (ng/mL)	4.8 (2.8, 6.3)	9.4 (7.8, 11.8)	0.001
pro-BNP (pg/mL)	500.0 (184.5, 2747.0)	5398.0 (2553.0, 10539.0)	0.004
TNI (μg/L)	0.0 (0.0, 0.1)	0.3 (0.1, 1.4)	0.006
LVEF (%)	64.6 (5.8)	36.6 (9.4)	<0.001
MAPSE (cm)	1.3 (1.2, 1.4)	0.9 (0.8, 1.2)	0.004
TAPSE (cm)	2.0 (0.5)	1.5 (0.7)	0.010
ALT (U/L)	11.0 (7.0, 27.5)	23.0 (14.0, 41.0)	0.127
AST (U/L)	35.0 (22.0, 59.5)	60.0 (24.0, 106.0)	0.537
TBil (μmol/L)	22.7 (11.3, 31.4)	19.5 (14.8, 22.7)	0.364
Cr (μmol/L)	99.0 (77.5, 147.5)	108.0 (91.0, 151.0)	0.562
Lac	1.6 (1.1, 2.3)	1.5 (1.3, 3.9)	0.513

TNI troponin I, *Lac* lactate

Table 4 Clinical characteristics of SICM patients grouped by H-FABP levels

Characteristics	Low H-FABP	High H-FABP	*P* value
n	33	23	
Male sex, n (%)	27 (81.8)	14 (60.9)	0.151
Age (years)	64 (21.1)	67 (16.0)	0.584
Comorbidity, n (%)			
Pulmonary infection (%)	11 (33.3)	8 (34.8)	1.000
Abdominal infection (%)	4 (12.1)	1 (4.3)	0.598
Cerebral hemorrhage (%)	16 (48.5)	3 (13.0)	0.014
Renal insufficiency (%)	1 (3.0)	4 (17.4)	0.168
Operation (%)	5 (15.2)	8 (34.8)	0.164
7-day ICU mortality (%)	0 (0.0)	4 (17.4)	0.050 (0.013) [1]
28-day ICU mortality (%)	7 (21.2)	10 (43.5)	0.137 (0.075) [1]
APACHEII	19.2 (5.8)	19.6 (6.8)	0.789
WBC (×10^9/L)	10.2 (4.4)	9.5 (4.1)	0.566
NEUT (%)	81.3 (74.7, 87.9)	82.4 (75.7, 87.6)	0.695
LYMPH (×10^9/L)	0.9 (0.5, 1.3)	0.7 (0.5, 1.1)	0.359
PCT (ng/mL)	0.4 (0.1, 2.2)	0.5 (0.2, 2.0)	0.449
CRP (mg/L)	83.6 (24.4, 124.0)	35.5 (21.1, 77.0)	0.076
Pro-BNP (pg/mL)	545.7 (131.5, 1990.0)	6021.0 (2784.0, 15,377.0)	< 0.001
TNT (ng/L)	29.6 (16.0, 83.6)	89.2 (50.1, 482.6)	0.001
CK-MB (ng/mL)	2.0 (1.2, 2.8)	2.4 (1.4, 3.9)	0.221
MYO (ng/mL)	116.9 (83.5, 314.5)	155.9 (83.6, 432.0)	0.400
LVEF (%)	44.2 (40.1, 47.0)	36.6 (28.5, 44.4)	0.008
SV (ml)	48.1 (36.1, 66.3)	36.5 (28.2, 42.9)	0.011
TAPSE (cm)	2.2 (0.7)	1.8 (0.6)	0.035
MAPSE (cm)	1.3 (0.3)	1.1 (0.3)	0.012
ALT (U/L)	34.4 (15.0, 48.3)	19.3 (8.4, 44.3)	0.360
AST (U/L)	36.9 (30.1, 59.9)	32.5 (23.5, 86.3)	0.816
ALP (U/L)	81.0 (61.0, 119.0)	83.0 (65.0, 114.0)	0.653
GGT (U/L)	54.8 (23.6, 101.0)	81.7 (38.8, 96.1)	0.489
TBIL (μmol/L)	12.6 (9.1, 17.1)	12.7 (8.0, 16.8)	0.842
Cr (μmol/L)	76.8 (53.7, 105.7)	128.6 (71.2, 228.9)	0.046
Urea (mmol/L)	8.9 (6.5, 14.9)	13.1 (9.8, 19.4)	0.073
RBP (mg/L)	22.4 (17.2, 40.1)	37.8 (25.2, 67.2)	0.004
Length of ICU stay (days)	14.0 (8.6, 20.0)	15.0 (6.0, 26.9)	0.809

[1] Pearson Chi-Square Test

correlation between H-FABP and both the diagnosis and prognosis of sepsis, suggesting its unique role in indicating the inflammatory state of sepsis. Further studies are required to clarify its potential clinical applications in SICM.

H-FABP is an essential member of the FABP family that participates in cellular fatty acid metabolism by reversibly binding and transporting long-chain polyunsaturated fatty acids from the cytoplasm to mitochondria. It is predominantly distributed in cardiomyocyte cytoplasm and plays a crucial role in the intracellular uptake and buffering of free fatty acids in cardiomyocytes [10]. Additionally, H-FABP contributes to cell growth and proliferation processes and can activate peroxisome proliferator-activated receptors (PPARs), which are pivotal in lipid metabolism and energy homeostasis [11, 12]. Compared to conventional biomarkers, such as myoglobin (MYO, 18 kDa) and TNT (37 kDa), H-FABP has a lower molecular weight (15 kDa), higher concentration, and superior stability in cardiomyocytes [13–17]. These characteristics enable H-FABP to traverse the cell membrane of ischemic cardiomyocytes and be released into the blood more rapidly than conventional myocardial biomarkers. In addition, studies have shown that H-FABP can identify early myocardial ischemia resulting from coronary artery spasm prior to the onset of apparent

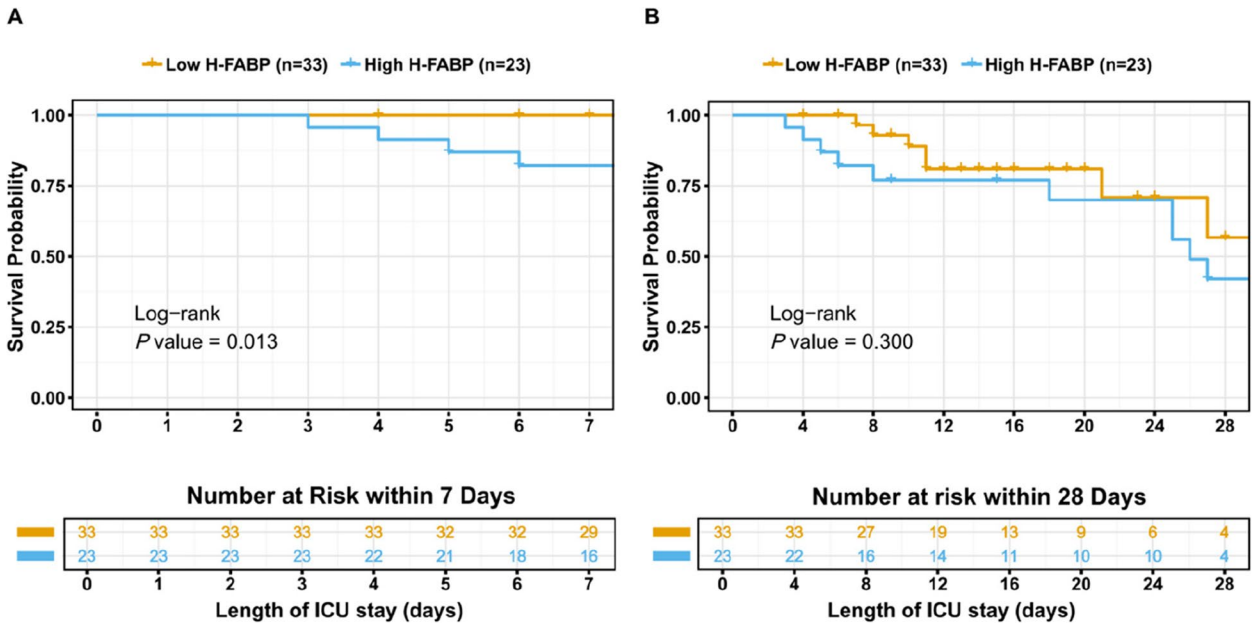

Fig. 5 Kaplan–Meier survival analysis of H-FABP in patients with sepsis-induced cardiomyopathy. The endpoint of the KM survival analysis in (**A**) corresponds to the survival outcome of patients on the 7th day of ICU stay, while in (**B**) it corresponds to the survival outcome of patients on the 28th day

cardiomyocyte necrosis, whereas troponin levels are typically not elevated in the blood at this stage [15]. Moreover, H-FABP has been shown to be associated with an increased risk of mortality and major cardiac events in patients with acute coronary syndromes, independent of other well-established clinical risk predictors and biomarkers [18, 19]. However, limited research has been conducted on its role in sepsis-induced cardiomyopathy.

Strengths and limitations of the study

To our knowledge, few studies employ machine learning algorithms to screen crucial indicators from clinical biomarkers for the diagnosis and evaluation of SICM. The combination of machine learning and statistical analysis enhances the rigor and accuracy of the screening results. Notably, H-FABP, an important intracellular fatty acid-binding protein that can be directly obtained from blood, is easy to detect, cost-effective, and has fewer operational requirements. Considering the high mortality of sepsis-induced cardiomyopathy, early diagnosis and prognostic evaluation based on H-FABP levels measured within the first 24 h of patient admission could significantly enhance treatment and improve clinical outcomes, underscoring the significance of this study.

However, this study has several limitations. First, the clinical data and samples were limited to the first 24 h after enrollment, and changes in H-FABP and other indicators were not monitored during the ICU stay. Second, further expansion of the sample size is necessary to better mitigate bias and more effectively establish the effects and underlying mechanisms of this valuable biomarker in sepsis-induced cardiomyopathy.

Conclusions

In conclusion, as an easily accessible serum biomarker, elevated levels of H-FABP measured within the initial 24 h of ICU admission can early suggest the diagnosis of sepsis-induced cardiomyopathy and indicate poor short-term prognosis, which provides crucial value for clinicians in evaluating the condition of SICM patients.

Abbreviations

ALP	Alkaline posphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUROC	Area under the receiver operating characteristic curve
CI	Confidence interval
CK-MB	Creatine kinase-MB
Cr	Creatinine
CRP	C-reactive protein
GGT	Gamma-glutamyltransferase
H-FABP	Heart-type fatty acid binding protein
LR	Logistic regression
LVEF	Left ventricular ejection fraction
LY	Lymphocyte
MAPSE	Mitral annular plane systolic excursion
MYO	Myoglobin
NEUT	Neutrophilic granulocyte
OR	Odds ratio
PCT	Procalcitonin
pro-BNP	Pro-B-type natriuretic peptide
RBP	Retinol-binding protein
RF	Random forest

SICM	Sepsis-induced cardiomyopathy
SV	Stroke volume
SVM	Support vector machine
TAPSE	Tricuspid annular plane systolic excursion
TBIL	Total bilirubin
TNT	Troponin T
WBC	White blood cell count

Supplementary Information

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Supplementary Material 1: Fig. S1. Correlation analysis between biomarkers and commonly used clinical indicators

Supplementary Material 2: Table S1.xls Clinical characteristics of the study population (complete version including 64 indicators). Table S2.xls Indicators identified by three machine learning algorithms

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Authors' contributions
XC and YH designed the study, interpreted the data and prepared the manuscript. YG, JW and JL conducted the experiments and collected the data. YM and QL assisted in preparing the manuscript. All the authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study received ethical approval and consent from the Institutional Review Boards (IRBs) of the First Affiliated Hospital of Nanjing Medical University (2020-SR-055 and 2022-SR-678) and the Second Affiliated Hospital of Harbin Medical University (2024GZRYS-228). Informed consent was obtained from all patients for the use of their personal data for scientific research.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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